ORIGINAL ARTICLE

A Comparative Study of Licochalcone A Moisturiser versus Topical Hydrocortisone in Treating Mild-to-Moderate Atopic Dermatitis

Leng Leng Tan, *AdvMDerm,* Nik Aimee Azizah Faheem, *MRCP,* Winn Hui Han, *MRCP,* Tharshne Shanmugam, *MBBS,* Su-Ming Wong, *AdvMDerm*

Division of Dermatology, Department of Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

Abstract

Background

Topical corticosteroids are the mainstay of treatment for patients with atopic dermatitis. However, adverse effects associated with long-term steroid use often limit its use. This interventional study compared the efficacy of a proprietary moisturiser containing licochalcone A, omega-6 fatty acids, and ceramide 3 against 1% hydrocortisone cream in treating patients with mild-to-moderate atopic dermatitis.

Methods

Patients with mild-to-moderate atopic dermatitis affecting either the cubital fossa or popliteal fossa symmetrically were given twice-daily applications of the moisturiser and hydrocortisone on opposite sides of the body and monitored for a total of three weeks in a non-randomised half body, double-blind study. Hydrocortisone was switched to aqueous cream after two weeks, whereas the application of the moisturiser continued until study completion. The assessment of SCORing Atopic Dermatitis (SCORAD) index and Dermatology Life Quality index was performed at baseline and every subsequent follow-up visit to measure patients' response to treatment.

Results

The licochalcone A (LA) moisturiser and 1% hydrocortisone (HC) cream both demonstrated significant reduction in sign and symptom scores after only 1 week of treatment (percentage of reduction in sign and symptom scores: 52.8% [LA] vs 58.5% [HC]). Further reduction in mean sign and symptom scores for both treatments was observed at week 2 (61.3% [LA] vs 56.8% [HC]) and also at week 3 when HC was switched to aqueous cream (70.5% [LA] vs 63.5% [HC→aqueous cream]) ($p<0.001$ vs baseline within the same treatment arm at weeks 1, 2 and 3). When comparing the mean difference in SCORAD index for both individual as well as total skin signs and symptoms between LA and HC (i.e. inter-arm comparison), there was no significant difference between the two treatments for all the assessed parameters. Patients reported improvements in itching, sleeplessness, and overall quality of life over the course of treatment.

Conclusion

The licochalcone A moisturiser can be considered as an effective steroid-sparing alternative to topical corticosteroids in managing mild-to-moderate atopic dermatitis.

Key words: *Atopic dermatitis; Eczema; Emollient; Licochalcone A; Omega-6 fatty acids; Ceramide 3*

Corresponding Author
Dr Tan Leng Leng
11, Jalan Teknologi,
PJU 5, Kota Damansara,
47810 Petaling Jaya, Selangor Darul Ehsan,
Malaysia
Email: tllktc@hotmail.com

Introduction

Atopic dermatitis (AD, also known as atopic eczema) is a chronic, recurring inflammatory skin condition. The prevalence of AD is most common in childhood with up to 90%

of children developing AD by the age of 5 years.[1] Although most children achieve disease resolution by adulthood, 10–30% of patients do not, and a smaller percentage develop symptoms as adults.[2] Classic signs and symptoms of AD include dry skin, itching, erythema, erosions, lichenification, oozing and crusting. As AD is often associated with elevated immunoglobulin E (IgE) levels, patients may also present with comorbid conditions related to IgE sensitisation such as asthma, allergic rhinitis, and food allergy. Therefore, AD imposes a substantial physical and psychological burden that can negatively impact the quality of life (QoL) of patients and their family.[3, 4]

The aetiology of AD remains unknown, but it has been postulated that the disease is caused by a complex interaction of genetic, immunological, and environmental factors that leads to altered epidermal barrier function.[5] Potential triggering factors that can worsen AD include aeroallergen (e.g. dust, pollen, animal dander), physical irritants (e.g. soaps, detergents, disinfectants), food, as well as patient and environmental factors (e.g. stress, pollution, heat).[6]

The management of AD relies on efficient control of flares by treating acute inflammatory symptoms and restoring skin barrier function. Currently, topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI) are the mainstay of treatment for disease flares, along with the use of moisturisers to improve skin hydration, maintain barrier integrity, and prevent new flare-ups.[6] Although TCS is associated with severe adverse effects (AEs) such as skin atrophy, telangiectasia and hypertrichosis, these AEs can be lessened when the duration and strength of TCS is used appropriately.[7] However, TCS is often underutilised owing to patients and/or their carers' steroid phobia, leading to poor treatment adherence and subsequent treatment failure.[8]

The aforesaid drawbacks have thus driven the search for effective steroid-sparing agents that could be used in the treatment of AD. This study compared the efficacy of a moisturiser containing licochalcone A, omega-6 fatty acids and ceramide 3 against 1% hydrocortisone cream for the treatment of mild-to-moderate AD in a small population of Malaysian patients.

Materials and Methods

Study design and patient population

This three-week, non-randomised half body, double-blind, interventional study was initiated to compare the efficacy of a cortisone-, fragrance-, colourant- and paraben-free moisturiser containing licochalcone A, omega-6 fatty acids and ceramide 3 (LA; Eucerin® Acute Care Cream) against that of 1% hydrocortisone (HC) in the treatment of mild-to-moderate AD. The active ingredients in LA were 0.025% licochalcone A, 12% omega-6 fatty acids, 0.05% ceramide 3, and 10% glycerin, while HC contained 1% cortisol (acetate salt of hydrocortisone).

The study was carried out at the dermatology clinic of University Malaya Medical Centre (UMMC), Kuala Lumpur, Malaysia between November 2018 and March 2019. Thirty patients aged between 1 and 80 years, who were diagnosed with mild-to-moderate AD based on the United Kingdom working party diagnostic criteria and the modified Hanifin and Rajka criteria, and not on any systemic or topical treatment, were enrolled in the study[9]; mild-to-moderate AD was defined by the SCOring Atopic Dermatitis (SCORAD) index score range of 1–50.[10] To qualify for study enrolment, patients were also required to have symmetrical involvement of skin lesions on both flexural area of the body (left and right cubital or popliteal fossa). Patients with skin infection and known allergies to any ingredients of the study interventions were excluded.

On recruitment, patients were given two white containers labelled A and B. The content of containers A and B was applied, twice-daily, on affected areas of the right and left sides of patients' bodies, respectively. The containers containing the topical agents were prepared and given to the patients by a doctor not involved in assessing the patients, while the post treatment

clinical outcome was assessed by a different dermatologist. Container A was filled with LA while container B was first filled with HC for two weeks, and then with a lipid-based topical formulation cream (AQ) for the remaining week of the study. The switch from HC to AQ was carried out to assess whether symptom control can be maintained by AQ (a non-active agent) once disease remission has been induced, without the knowledge of the patient and the investigators. Oral antihistamine, systemic steroid or immunosuppressant were not used by any of the patients during the study period. Patients were required to provide written consent and were free to withdraw from the study at any time.

Study assessments

Clinical outcome post treatment was documented by digital photography and assessed by a modified form of SCORAD.[10] The intensity of the disease (i.e. erythema, oedema, excoriation, lichenification, oozing/crusting, and dryness) was assessed on the right and left sides of patients' bodies and the corresponding scores were documented. Area of involvement and subjective symptoms were not included when assessing the right and left affected areas. Subjective symptoms, such as itch and sleeplessness, were assessed at each follow-up visit throughout the study duration (i.e. weeks 1, 2 and 3). QoL was assessed by Dermatology Life Quality Index (DLQI),[11] a patient-rated questionnaire comprising 10 questions concerning patients' perception of AD's impact on different aspects of their health-related QoL. Adverse events were recorded.

Statistical analysis

Continuous variables were presented as mean (standard deviation), while categorical variables were presented as frequencies and percentages. Changes in the SCORAD index of LA- and HC-treated areas were analysed by paired t-test. A p-value of <0.05 was considered statistically significant.

Ethics approval statement

This study was approved by the Medical Research Ethics Committee of University Malaya Medical Centre (approval number: 42866; 16 June 2018) and was conducted according to the principles of the Declaration of Helsinki.

Results

Patient characteristics

A total of 30 patients were enrolled in the study, with 73.3% being younger than 12 years of age and 83.3% have had AD for less than 10 years (mean duration: 8.35±9.2 years). Many of these patients have a family history of atopic diseases, particularly asthma (30%) and AD (30%), as well as a personal history of asthma (30%) and food allergy (30%) (**Table 1**).

Table 1. Patient demographics and characteristics

Characteristics	n (%)
Age	
1–6 years	12 (40.0)
7–12 years	10 (33.3)
>12 years	8 (26.7)
Gender	
Male	19 (63.3)
Female	11 (36.7)
Ethnicity	
Malay	21 (70.0)
Chinese	9 (30.0)
Family history	
Asthma	12 (40.0)
Food allergy	3 (10.0)
Drug allergy	2 (6.7)
Conjunctivitis	0 (0.0)
AD	9 (30.0)
Medical history	
Asthma	9 (30.0)
Food allergy	9 (30.0)
Drug allergy	1 (3.3)
Conjunctivitis	2 (6.7)

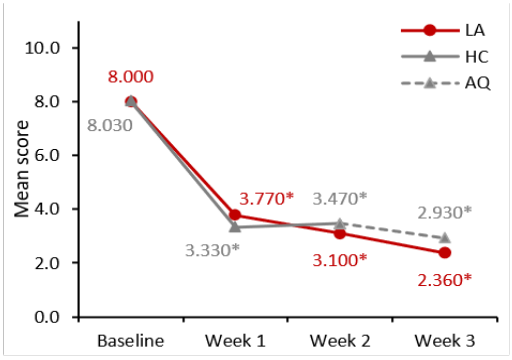
Changes in signs and symptoms associated with AD

Both LA and HC resulted in a progressive improvement of patients' mean SCORAD index for total skin signs and symptoms at each follow-up. Compared with the baseline values within the same treatment arm, both treatments showed comparable reduction in mean sign and symptom scores after one week of treatment

initiation (LA: 52.8% vs HC: 58.5% [percentage of reduction from baseline in mean SCORAD index]). At week 2, however, LA showed a greater reduction in mean sign and symptom scores compared with HC (LA: 61.3% vs HC: 56.8%), an observation that continued into week 3 of the study (LA: 70.5% vs HC→AQ: 63.5%). The mean differences between the baseline SCORAD index value and that calculated at subsequent follow-up visits were all significant ($p<0.001$ for both treatments) (**Figure 1**). Nonetheless, when comparing the mean difference in SCORAD index for total skin signs and symptoms between LA and HC (i.e. inter-arm comparison), there was no significant difference between the two treatments (LA vs HC at baseline, $p=0.972$; LA vs HC at week 1, $p=0.669$; LA vs HC at week 2, $p=0.701$; LA vs HC at week 3, $p=0.442$).

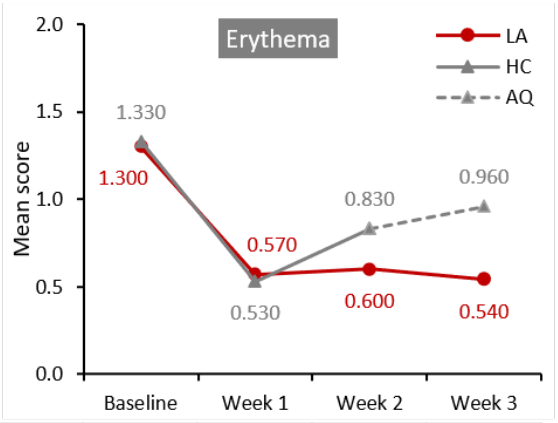
Additionally, when individual symptoms (i.e. erythema, oedema, crusting, excoriation, lichenification and dryness) were analysed separately, a comparison between LA and HC also showed no significant difference in SCORAD score reduction for all the assessed parameters (**Figure 2**). As such, LA was shown to be non-inferior to standard topical steroid therapy in resolving AD symptoms, especially skin erythema, oedema, crusting, excoriation, lichenification and dryness within the first week of treatment (**Figure 3**). Of note, one patient developed a flare-up of AD after the application of LA.

Figure 1. Mean SCORAD index for total skin signs and symptoms after three weeks of treatment with LA and HC

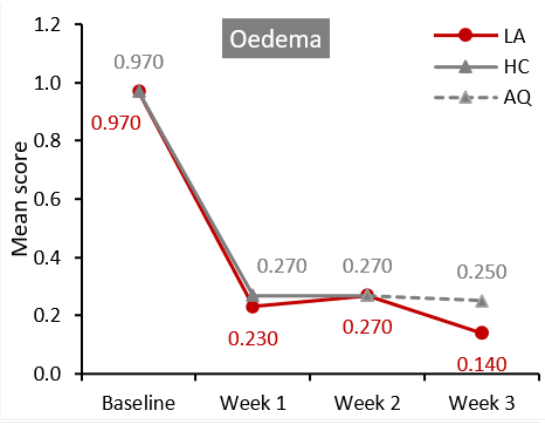


*p<0.001 vs baseline (within the same treatment arm). LA, licochalcone A formulation; HC, 1% hydrocortisone cream; AQ, aqueous cream

Figure 2. Inter-arm comparison of disease intensity, as indicated by individual AD symptoms, after three weeks of treatment with LA and HC



p-value	0.900	0.881	0.311	0.219



p-value	1.000	0.823	1.000	0.371

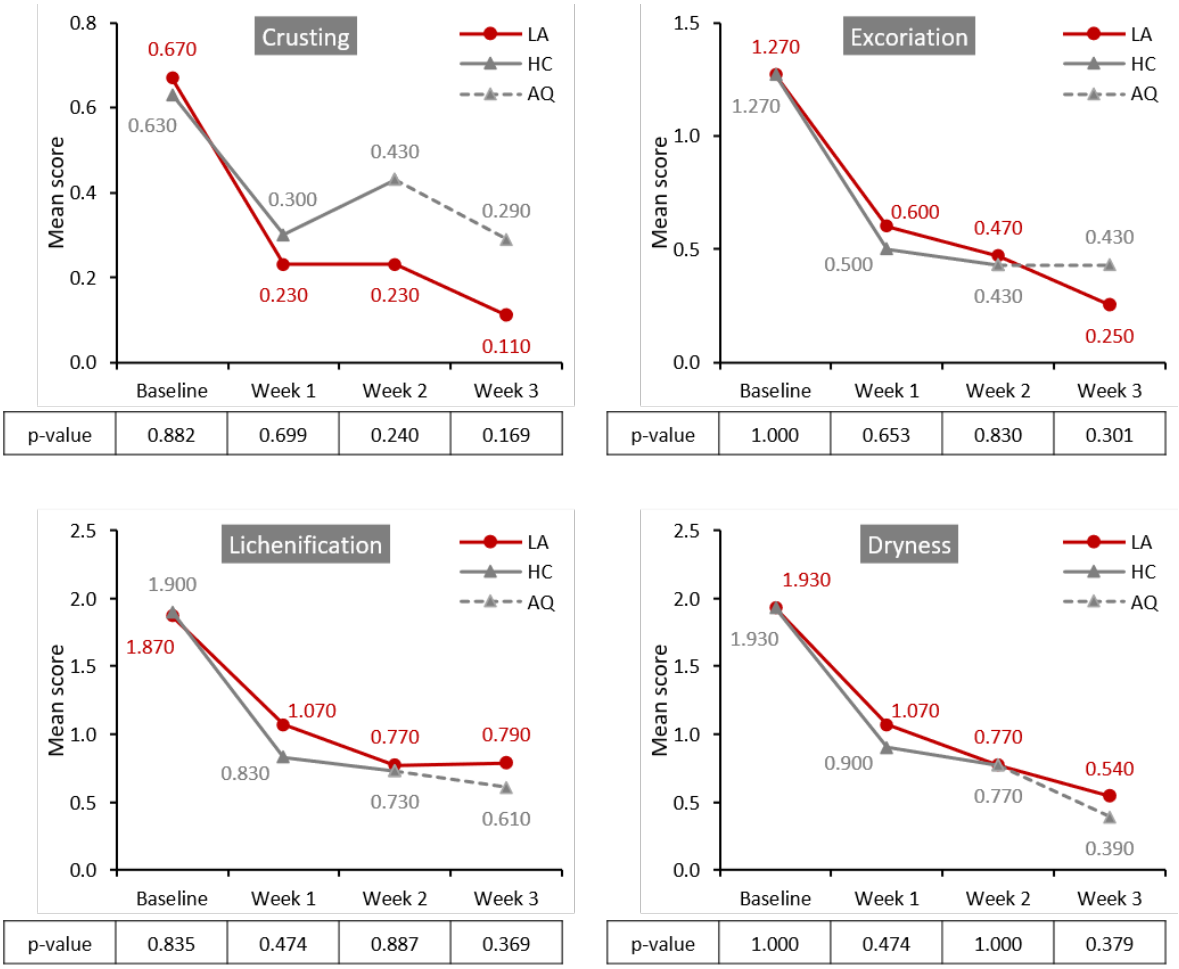
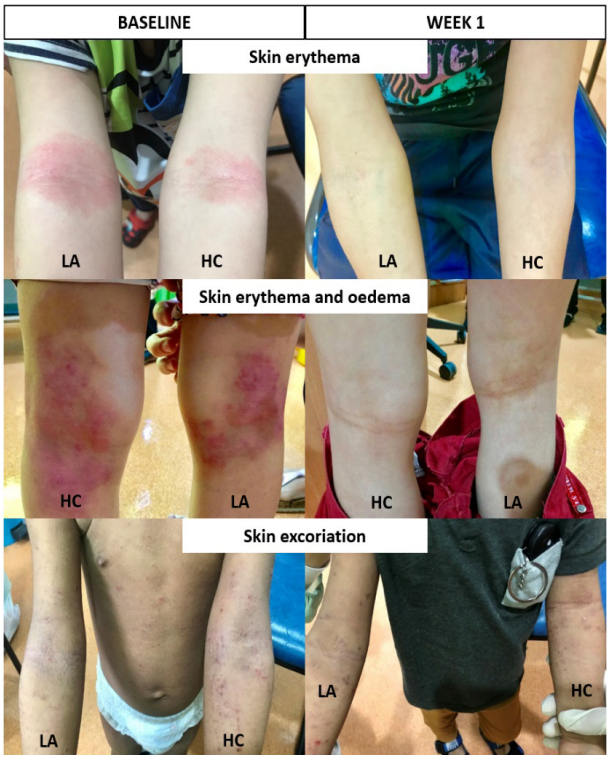
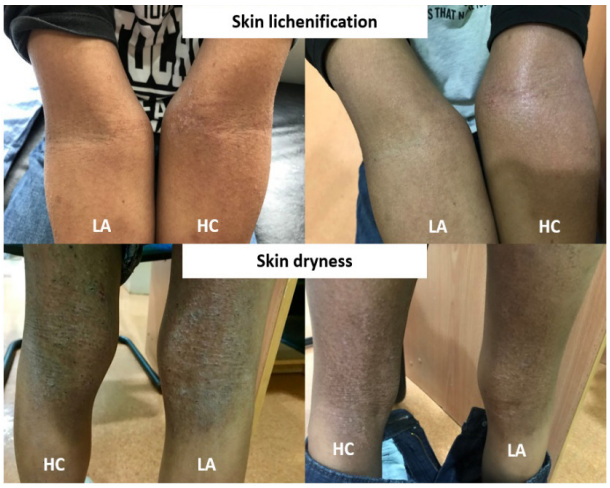


Figure 3. Clinical response shown by patients with AD following treatment with AC and HC





Improvement in itching and sleeplessness

Patients reported reduced skin itching throughout the study for both treatments. LA afforded a greater mean score reduction throughout the study, with a mean difference

of 2.04±1.53 at week 1, 2.48±2.12 at week 2, and 2.84±2.06 at week 3. Meanwhile, HC showed a mean score reduction of 1.96±1.79, 2.37±2.02, and 2.64±2.16 at weeks 1, 2 and 3, respectively ($p<0.001$ vs baseline for all data points). Additionally, both treatments showed reduced mean score for sleeplessness over a period of three weeks. The application of either LA or HC resulted in a mean score reduction of 1.96±1.97 at week 1, 2.62±1.52 at week 2, and 3.26±2.05 at week 3 ($p<0.001$ vs baseline for all data points).

Improvement in overall quality of life

At baseline, 60% of patients felt that AD had a very large effect on their QoL (mean score: 13.00±4.06). However, after three weeks of treatment with either LA or HC, only 12% of the study participants reported the same degree of disease impact (mean DLQI score: 6.44±5.86; mean difference: -6.64±5.86), with close to half of the study population expressing small to no effect at all (48%). DLQI mean scores and the improvement in QoL throughout the study duration are shown in **Table 2** and **Table 3**, respectively.

Table 2. DLQI scoring of patients receiving either LA or HC over a period of 2 weeks

DLQI	Baseline n=27	Week 1 n=27	Week 2 n=27	Week 3 n=25
Mean score	13.00±4.06	8.74±5.16	7.00±4.48	6.44±5.86
Difference in mean score	-	-4.62±3.93	-6.00±4.67	-6.64±5.86

($p<0.001$ vs baseline)

Table 3. Impact of AD on QoL as measured by DLQI

Impact on QoL (DQLI Score)	Baseline n=30 (%)	Week 1 n=27 (%)	Week 2 n=28 (%)	Week 3 n=25 (%)
No effect at all (0–1)	-	2 (7.4)	4 (14.3)	6 (24.0)
Small effect (2–5)	-	6 (22.2)	8 (28.6)	6 (24.0)
Moderate effect (6–10)	10 (33.3)	7 (25.9)	8 (28.6)	9 (36.0)
Very large effect (11–20)	19 (63.3)	12 (40.0)	8 (29.6)	3 (12.0)
Extremely large effect (21–30)	1 (3.3)	-	-	1 (4.0)

Discussion

Patients in this study were mostly children of Malay ethnicity with atopic background and a family history of atopic disease, which matched the patient demographic of another cross-sectional study that reported the prevalence and management of AD in Malaysian children.[12] Incidentally, the same study also revealed that parents generally preferred TCS, specifically hydrocortisone, over nonprescription drugs in AD management. TCS and TCI, along with moisturisers, are the mainstay of treatment for AD in patients requiring pharmacological intervention. However, the side effects associated with the persistent use of corticosteroids limit its use. These risks, although mostly unfounded, have spurred efforts to seek alternative steroid-sparing anti-inflammatory topical agents for the management of AD.

This study demonstrated that the topical application of LA, a moisturiser containing licochalcone A, omega-6 fatty acids and ceramide 3, was an effective and safe therapy that is non-inferior to standard topical steroid therapy for the treatment of mild-to-moderate AD. These results were consistent with previous studies that demonstrated the efficacy of licochalcone A-based moisturisers, compared with 1% HC creams, in improving the clinical manifestations of AD.[13-16]

Licohalcone A is a flavonoid extracted from the Chinese liquorice root, *Glycyrrhiza inflata*. In vitro studies showed that licochalcone-A extracts exhibited potent antibacterial,[17] anti-inflammatory,[18] and immunomodulatory[19] activities. Clinical studies have also confirmed the efficacy of licochalcone A-containing formulation in reducing erythema[18] and skin irritations (i.e. dryness, itching, and burning sensation).[20] Additionally, LA also contains ceramide which improves skin barrier function and prevents transepidermal water loss in patients with AD.[21] Taken together, the findings from this study provide new evidence to support the efficacy of licochalcone A as an anti-inflammatory agent in the management of mild-to-moderate AD.

Itching is a major criterion of AD and is often worse at night, leading to a persistent itch-scratch cycle that can affect sleep and QoL. Given the

considerable impact of sleep insufficiency on mood, health, and development (particularly in growing children), achieving lasting itch relief with minimal treatment-related side effects is an important goal in the management of AD.[22, 23] The management of AD with either LA or HC can lead to considerable improvement in patients' overall QoL, as shown by the gradual reduction in mean DLQI scores throughout the study period.

Strengths and limitations

In this study, the side-by-side comparison of treatment efficacy in the same patient reduces the risk of potential errors that could be attributed to individual treatment response differences. However, we acknowledge that this study has a relatively small sample size and a short study period.

Conclusion

This study demonstrated that a proprietary moisturiser containing licochalcone A, omega-6 fatty acids and ceramide 3 as its active ingredients was non-inferior to 1% hydrocortisone cream in resolving symptoms associated with acute AD. Therefore, it may serve as a valuable steroid-sparing therapeutic alternative in the treatment of AD.

Conflict of Interest Declaration

The authors declare no conflict of interest.

Acknowledgement

Medical writing assistance was provided by MIMS Medica Sdn Bhd, and complied with Good Publication Practice 3 ethical guidelines (Battisti et al. *Ann Intern Med.* 2015; 163: 461–4). Medical writing assistance for this article has been funded by Beiersdorf (Malaysia) Sdn Bhd.

References

1. Lyons JJ, Milner JD, Stone KD. Atopic dermatitis in children: Clinical features, pathophysiology, and treatment. Immunol Allergy Clin North Am 2015;35:161-83.
2. Eichenfield LF, Tom WL, Chamlin SL, Feldman SR, Hanifin JM, Simpson EL et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. J Am Acad Dermatol 2014;70:338-51.
3. Lifschitz C. The impact of atopic dermatitis on quality of life. Ann Nutr Metab 2015;66 Suppl 1:34-40.
4. Na CH, Chung J, Simpson EL. Quality of life and disease impact of atopic dermatitis and psoriasis on children and their families. Children (Basel) 2019;6:133.
5. Thomsen SF. Atopic dermatitis: Natural history, diagnosis, and treatment. ISRN Allergy 2014;2014:354250.
6. MahTAS. Clinical Practice Guidelines: Management of Atopic Eczema 2018. Available at https://www.moh.gov.my/moh/resources/Penerbitan/CPG/Skin%20Condition/CPG%20Management%20of%20Atopic%20Eczema.pdf. Accessed on 8/1/2021.
7. Mooney E, Rademaker M, Dailey R, Daniel BS, Drummond C, Fischer G et al. Adverse effects of topical corticosteroids in paediatric eczema: Australasian consensus statement. Australas J Dermatol 2015;56:241-51.
8. Li AW, Yin ES, Antaya RJ. Topical corticosteroid phobia in atopic dermatitis: A systematic review. JAMA Dermatol 2017;153:1036-42.
9. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol (Stockh) 1980, 92(suppl): 44-7.
10. Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis. Dermatology. 1993;186:23-3.
11. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI) - a simple practical measure for routine clinical use. Clin Exp Dermatol 1994;19:210-6.
12. Goh YY, Keshavarzi F, Chew YL. Prevalence of atopic dermatitis and pattern of drug therapy in Malaysian children. Dermatitis 2018;29:151-61.
13. Angelova-Fischer I, Neufang G, Jung K, Fischer TW, Zillikens D. A randomized, investigator-blinded efficacy assessment study of stand-alone emollient use in mild to moderately severe atopic dermatitis flares. J Eur Acad Dermatol Venereol 2014;28 Suppl 3:9-15.
14. Udompataikul M, Srisatwaja W. Comparative trial of moisturizer containing licochalcone A vs. hydrocortisone lotion in the treatment of childhood atopic dermatitis: A pilot study. J Eur Acad Dermatol Venereol 2011;25:660-5.
15. Wananukul S, Chatproedprai S, Charutragulchai W. Randomized, double-blind, split-side comparison study of moisturizer containing licochalcone vs. 1% hydrocortisone in the treatment of infantile seborrhoeic dermatitis. J Eur Acad Dermatol Venereol 2012;26:894-7.
16. Wananukul S, Chatproedprai S, Chunharas A, Limpongsanuruk W, Singalavanija S, Nitiyarom R et al. Randomized, double-blind, split-side, comparison study of moisturizer containing licochalcone A and 1% hydrocortisone in the treatment of childhood atopic dermatitis. J Med Assoc Thai 2013;96:1135-42.
17. Tsukiyama R, Katsura H, Tokuriki N, Kobayashi M. Antibacterial activity of licochalcone A against spore-forming bacteria. Antimicrob Agents Chemother 2002;46:1226-30.
18. Kolbe L, Immeyer J, Batzer J, Wensorra U, tom Dieck K, Mundt C et al. Anti-inflammatory efficacy of Licochalcone A: correlation of clinical potency and in vitro effects. Arch Dermatol Res 2006;298:23-30.
19. Fontes LB, Dos Santos Dias D, de Carvalho LS, Mesquita HL, da Silva Reis L, Dias AT et al. Immunomodulatory effects of licochalcone A on experimental autoimmune encephalomyelitis. J Pharm Pharmacol 2014;66:886-94.
20. Broniarczyk-Dyła G, Prusińska-Bratoś M, Kmieć ML. Assessment of the influence of licochalcone on selected functional skin parameters in patients with impaired vasomotor disorders and rosacea. Post Dermatol Alergol 2011;28:241-47.
21. Chamlin SL, Kao J, Frieden IJ, Sheu MY, Fowler AJ, Fluhr JW et al. Ceramide-dominant barrier repair lipids alleviate childhood atopic dermatitis: Changes in barrier function provide a sensitive indicator of disease activity. J Am Acad Dermatol 2002;47:198-208.

22. Jeon C, Yan D, Nakamura M, Sekhon S, Bhutani T, Berger T et al. Frequency and management of sleep disturbance in adults with atopic dermatitis: A systematic review. Dermatol Ther (Heidelb) 2017;7:349-64.
23. Ramirez FD, Chen S, Langan SM, Prather AA, McCulloch CE, Kidd SA et al. Association of atopic dermatitis with sleep quality in children. JAMA Pediatr 2019;173:e190025.