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REVIEW

Pimecrolimus for the Treatment of Atopic Dermatitis in Infants: An Asian Perspective

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ABSTRACT

Atopic dermatitis (AD) is a common chronic, multisystem inflammatory skin disease in pediatric patients. There has been an increase in the incidence of AD in the pediatric population of the Asia–Pacific region. Studies have shown that genetic, epigenetic, environmental and cultural factors may lead to differences in the clinical manifestation and prevalence of AD between races. Early treatment of AD is necessary to prevent the atopic march leading to comorbidities such as asthma and allergic rhinitis. Topical corticosteroids (TCS) are used as first-line therapy for the treatment of AD, but their long-term usage poses a risk to the patient's health. Pimecrolimus (1%) is a topical calcineurin inhibitor (TCI) that is indicated for the treatment of mild to moderate AD. Pimecrolimus has no apparent increase in adverse events compared to TCS, and it causes less of a burning sensation than tacrolimus. The safety

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and efficacy of pimecrolimus has been established through various clinical trials; yet, in many Asian countries, the use of pimecrolimus in infants is still restricted due to safety concerns. Based on the available evidence, the expert panel recommends pimecrolimus in infants between 3 months and 2 years of age in the Asian population.

Keywords: Atopic dermatitis; Pimecrolimus; Infants; Asian population; Topical calcineurin inhibitor

Key Summary Points
The prevalence of atopic dermatitis (AD) has seen an increase in the Asia–Pacific region.
Topical corticosteroids are still used as the first line of therapy for the treatment of AD.
Pimecrolimus (1%) is a topical calcineurin inhibitor which can used as an alternative to steroid therapy.
Although the safety and efficacy of pimecrolimus has been established through various clinical trials, its use is still restricted in many Asian countries.
Existing post-marketing surveys and meta-analyses did not find an increasing risk of cancer with the long-term use of pimecrolimus.
Based on the available evidence, the expert panel recommends pimecrolimus in infants between 3 months and 2 years of age in the Asian population.

INTRODUCTION

Atopic dermatitis (AD) is one of the most common chronic, multisystem inflammatory skin diseases in pediatric patients. It affects the quality of life (QoL) of not only the patients but also their care givers [1]. Almost 20% of the global pediatric population, which is estimated to be about 230 million, are affected by AD [2, 3]. In the Asia–Pacific region, the prevalence of AD in the pediatric population is between < 5 and 10.1% [2]. The International Study of Asthma and Allergies in Childhood (ISAAC) Phase 3 has reported an increase in AD cases in the Asia–Pacific region [4].

AD is characterized by skin barrier and immune dysfunction, inflammation and an intense itch [5]. The majority of AD is mild to moderate, frequently affecting sensitive skin areas. The distribution and morphology of the lesions vary with age, and especially during infancy, sensitive skin areas, such as the face, neck and scalp, are affected. Studies have reported that genetic, epigenetic, environmental and cultural factors may lead to differences in the clinical manifestation and prevalence of AD between races [1]. AD is believed to exhibit a difference in etiology between Caucasians and Asian races. Evidence shows a predominantly higher number of interleukin 17 (IL-17)-producing cells in Asian patients with AD [6–8]. The occurrence of AD is often associated with the atopic march leading to comorbidities such as asthma and allergic rhinitis [9]. Apart from these comorbidities, AD also causes psychological disorders such as depression, anxiety and attention deficit hyperactivity disorder in the patients [10].

Early treatment of AD is essential to prevent worsening and the development of atopic comorbidities. The treatment paradigm for mild to moderate AD is based on emollients, topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI). Topical corticosteroids (TCS) are generally used as the first line treatment for AD [11]. Long-term use of TCS may cause local side effects such as skin infections, impairment of the epidermal barrier function and skin atrophy. Also, "corticosteroid phobia" is increasingly recognized as a significant factor contributing to poor TCS treatment adherence [6, 12].

Pimecrolimus (PIM) 1% is a TCI that is indicated for the treatment of mild to moderate AD [13]. The safety and efficacy of PIM in

Table 1 Overview of clinical studies evaluating the topical use of pimecrolimus in infants

Study design	Number of subjects (*n*)	Age	Disease severity	Outcome	References
PIM (*n* = 1205) or TCS (*n* = 1213) for 5 years in randomized, OL, parallel-group study	2418	≥ 3- < 12 months	Mild to moderate	PIM had similar efficacy to TCS, and PIM was associated with a substantial corticosteroid-sparing effect	[14]
PIM (*n* = 129) or vehicle (*n* = 66) for 4 weeks in double-blind RCT, followed by OL treatment with PIM for 12 weeks, then 4-week follow-up without treatment	195	3–23 months	Mild to very severe	PIM 1% was well tolerated and effective in patients with mild to very severe atopic eczema, with rapid onset of action	[16, 17]
PIM (*n* = 204) or vehicle (*n* = 47) for 1 year in double-blind RCT, followed by 1-year OLE consisting of 76 patients who received PIM for 2 years	251	3–23 months	Mild to very severe	Treatment with PIM significantly reduced the incidence of flares and improved overall control of AD	[18, 19]
PIM (*n* = 123) or vehicle (*n* = 63) for 6 weeks in double-blind RCT, followed by 20 weeks of OLE with PIM	186	3–23 months	Mild to moderate	PIM was safe in infants with AD, showing rapid and sustained efficacy	[20]
PIM (*n* = 543) or vehicle (*n* = 544) for 3 years in double-blind RCT, followed by OLE including only patients without a diagnosis of asthma who were treated with PIM for 3 years or until the age of 6 years	1091	3–18 months	Mild to very severe	PIM was safe and effective in infants with mild to moderate AD	[21]

OL open-label, *RCT* randomized controlled trial, *OLE* open-label extension

infants has been established by many studies, including the 5-year PETITE study (Table 1) [14]. PIM (1%) is approved in Australia, New Zealand, Russia, Brazil, Israel, Canada and Europe for the treatment of AD in infants ≥ 3 months of age. Among the Asian countries, it is approved in India, Indonesia, the Philippines, Thailand and Taiwan [15].

In many of the Asian countries, the use of PIM in infants is still restricted due to safety concerns, even though the safety of PIM has been demonstrated in several randomized clinical trials, multiple publications and registries. Hence, there is a high need to have consensus guidance on the use of PIM in infants between 3 months and 2 years of age in the Asian

population. The aim of this article is to encourage the use of pimecrolimus in infants between 3 months and 2 years of age in the Asian population due to its safety profile. The expert panel also recommends that the labeling restrictions for this age group are no longer justified.

COMPLIANCE WITH ETHICS

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

EPIDEMIOLOGY OF AD IN THE ASIAN POPULATION

Studies show that the occurrence of AD is higher in the Asian region. Approximately 88% of the pediatric patients in Asia have mild to moderate AD. The ISAAC Phase 3 study showed that prevalence was higher (> 10%) in Thailand, Malaysia and South Korea and lower (< 5%) in Hong Kong, Pakistan, India, Syria, Iran, Oman and Vietnam [2]. In Japan, the prevalence of AD is almost 10.2% in the pediatric population [22]. The prevalence of AD in China is > 12%, with an average onset age of 0.86 ± 3.87 years [23]. In Taiwan, a prevalence rate of 22.4% was found in infants < 1 year old [24] and 16.93% in children younger than 2 years [25]. There is a prevalence rate of 3.4% in the Philippines, with 24% of the patients being infants < 1 year [26]. Singapore has an AD prevalence rate of 20.6% in children [27]. In Malaysia, 13.8% of infants < 2 years suffer from AD [28]. A systemic review of studies done on AD between 1990 and 2010 showed an increasing trend of AD cases in the Asian region [29].

ETIOLOGY OF AD IN THE ASIAN POPULATION

Studies have shown that there are genetic factors which influence different features of AD [30]. Mutations in genes involved in skin barrier function (FLG, FLG-2, SPINK5) and innate/adaptive immunity (IL-4, IL-13, DEFB1) affect the severity and occurrence of AD in different ethnic groups [31]. Asian patients with AD have more IL-17-producing cells [6–8]. The interleukin 19 (IL-19) level was also higher in the Asian population with AD. IL-19 increases IL-17's effect on keratinocytes, which play an important role in atopic skin inflammation [32]. There are also increased T_H17 frequencies in blood and acute lesions in Japanese patients with AD [33]. A mutation in the filaggrin (FLG) gene (c.3321delA) that is unique to the Asian population is found in AD patients in China, Japan and Korea [22]. FLG-null mutations (c.3321delA, c.6950_6957del8, p.S1515X, p.S2706X, p.Q2417X, p.E2422X, p.G323X) were found in 80% of AD patients in Singapore [34]. FLG encodes a key epidermal barrier protein, and mutations in this gene disrupt the skin barrier [35]. This increases epidermal permeability to environmental pollutants and allergens that are responsible for triggering immunologic responses leading to AD development [36]. The differential expression of inflammatory cytokines causes lichenified, well-demarcated and scaly lesions in Asians [7, 37]. East Asians are also characterized by low skin maturation and a weak skin barrier, resulting in increased skin sensitivity [38].

There are variations in skin properties at the stratum corneum level across different ethnic groups [38]. Epidermal thickness is high in the Asian phenotype. In addition, demographic and socioeconomic factors, active and passive smoking, urbanization, diet, breastfeeding and time of solid food introduction, obesity and physical exercise, and environmental air pollutants are some of the conditions which affect the occurrence of AD (Fig. 1) [36].

IMPORTANCE OF EARLY TREATMENT OF AD IN INFANTS

AD is a chronic, relapsing skin disease which requires continuous treatment and compliance to control the symptoms [39]. Most (60%) childhood AD is remitted by adulthood. However, children with already persistent disease,

later onset, and/or more severe disease have increased persistence [40]. Early treatment at the first signs and symptoms in infants and children is necessary for long-term treatment of AD and to prevent comorbidity [41]. AD is the first step in the atopic march leading to allergic rhinitis, asthma and food allergy [9]. A systematic review of 66 studies confirmed a strong link between AD and food allergy [42]. AD increases skin permeability to allergens, bacteria and other bigger molecules due to the weakened skin barrier. This in turn increases sensitization due to increased IgE, leading to the atopic march [43]. A randomized study of 1091 infants (SAM study) with AD showed that IgE levels increased with AD severity [44]. Hence, early interventions to improve skin barrier function would subsequently prevent the atopic march.

ROLE OF PIMECROLIMUS IN THE MANAGEMENT OF AD IN INFANTS

Pharmacokinetic Profile of Pimecrolimus

PIM has negligible systemic bioavailability and a low potential for systemic side effects. In a study with guinea pigs as a model, it was seen that PIM in the blood was < 0.8% of the dermal bioavailability [45]. Permeation through the skin is lower for PIM compared to TCSs by a factor of 70–110 and lower by a factor of 9 compared to tacrolimus [46]. The primary reason for the low systemic bioavailability is that PIM is a highly lipophilic molecule. It has to pass through the horny layer (stratum corneum), which is lipid rich, to enter the lower epidermal layer, which is lipophobic. The lipid-rich horny layer slows down the permeation of PIM, resulting in a concentration gradient [47].

A 1-year study in five infants (5.7–11.9 months of age) who had moderate to severe AD treated with PIM (1%) showed very low levels of the drug (0–1.94 ng/ml) in the blood [48]. The distribution of blood levels of PIM was found to be similar in all age groups (3–23 months) for 1133 patients treated up to 2 years during the clinical development of PIM [49]. In a three-week multicenter study with 22 infants below 2 years of age with AD (10–92% of the body surface area affected at baseline), treatment with PIM (1%) did not show accumulation of the drug in the blood. The concentration of the drug remained below 0.5 ng/ml in 71% of the patients [17]. A study of 17 Japanese infants treated with PIM 1% b.i.d. for 3 weeks showed blood concentrations of < 0.5 ng/mL. Further, the concentration of PIM in blood did not increase with increasing treated body surface area [50]. A randomized

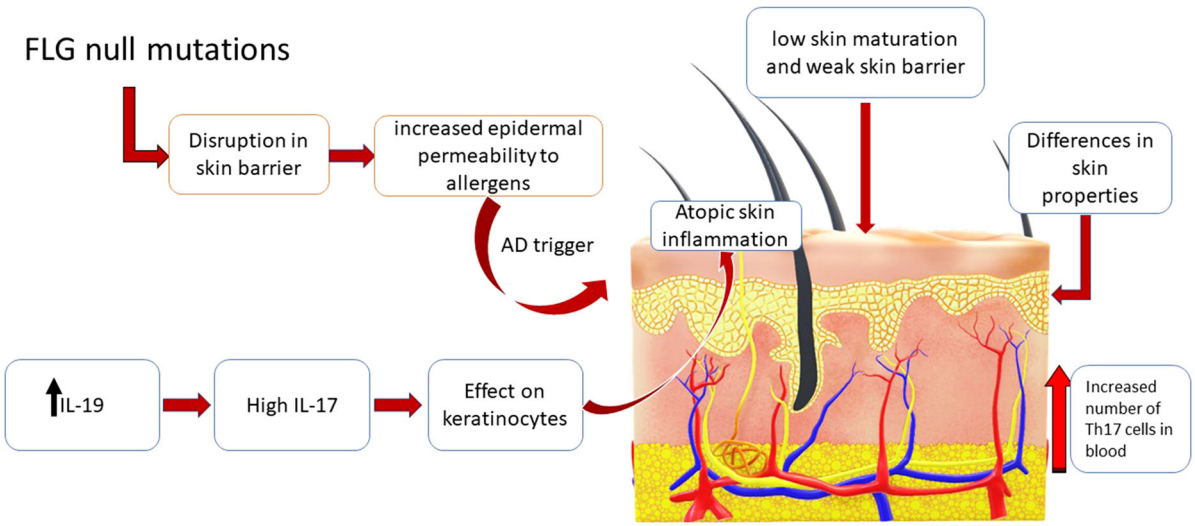

Fig. 1 Different causative factors of atopic dermatitis in the Asian population

study of 49 adolescents and adults treated with PIM b.i.d. or q.i.d. did not show a dose-dependent increase in PIM in blood over a period of 3 weeks [51].

Efficacy of Pimecrolimus in Infants

A 6-month, open-label, multicenter study in 947 patients (≥ 3 months of age) with mild to severe AD treated with PIM (1%) showed that an improvement occurred within 1 week of treatment [52]. A 1-year, double-blind, controlled study was done in 251 infants (3–23 months of age) with PIM (1%). Treatment with PIM significantly modified the disease course in infants by reducing the incidence of flares and improving overall control of AD [19]. In a study conducted by Kaufmann et al., it was concluded that the mean Eczema Area and Severity Index (EASI) score decreased by 71.5% in the PIM group but increased by 19.4% in the vehicle group at the end of week 4. Patients who received PIM cream for 3 months showed a significant improvement in EASI score [16]. A 5-year study (PETITE study) with 2439 AD infants showed that PIM has similar efficacy in the treatment of AD to those of low- and mid-potency TCS [14]. PIM showed sustained long-term efficacy (12 months) in infants, with a high proportion of patients achieving treatment success (IGA 0 or 1) [19]. In a study with 713 AD patients, fewer of the patients using PIM required a TCS as rescue medication compared to the control (34.8% vs. 63.7%) [19]. PIM (1%) was also shown to achieve no to mild pruritus in 69.9% infants during a 6-week double-blind study in 186 infants with mild/moderate AD [20]. According to some studies in children, PIM is preferred over tacrolimus in sensitive skin areas because of its non-greasy appearance. This is of particular importance in countries with a hot and humid climate.

Safety of Pimecrolimus in Infants

PIM is safe and well tolerated for short- and long-term use. Patients treated with PIM had a lower susceptibility to bacterial and viral skin infections compared to TCS [53]. Topical treatment with PIM did not affect the density and function of epidermal Langerhans cells, contrary to topical corticosteroids and tacrolimus [54]. PIM is associated with initial burning (6.8–7.4% of pediatric patients; 6.8–10.4% of adults) at the application site, which is comparable to TCS (7.4% in the pediatric population; 3.1% in adults) and contrary to tacrolimus (47% of adults with tacrolimus 0.1%; 36–37% of the pediatric population and adults with tacrolimus 0.03%) [55]. However, this burning sensation is transient. The most common adverse events associated with the use of PIM in infants are nasopharyngitis, pyrexia, diarrhea, upper respiratory tract infection and cough, which are common childhood disorders (Table 2).

A 6-month, open-label, multicenter study in 947 patients showed that PIM (1%) was well tolerated, and no clinically unexpected adverse events were reported [52]. According to US post-marketing surveillance, tacrolimus was associated with Hodgkin lymphoma (HL) and cutaneous T-cell lymphoma (CTCL), which were found in 11 patients (95% CI) [58]. According to worldwide post-marketing surveillance, HL and CTCL were found in 19 patients and 61 patients receiving PIM treatments, respectively [58, 59]. There is no increased risk of cancer [e.g., lymphoma or non-melanoma skin carcinoma (NMSC) or melanoma skin carcinoma (MSC)] associated with exposure to TCI or TCS [60]. However, one study demonstrated an increased risk of lymphoma with high-potency TCS (high-potency TCS are mainly used to treat severe AD, and severe AD may have acted as a confounding factor here) [60]. In a nested case–control study of 293,253 patients with AD, it was found that the use of TCI such as PIM or tacrolimus did not pose an increased risk of lymphoma [61]. A systematic literature review done by Legendre et al. also did not find any significant relation between use of TCI and risk of cancer [60]. In a recent meta-analysis of 110 studies (including 52 randomized controlled trials), the odds ratio (OR) of any type of cancer risk associated with the use of TCI such as PIM or tacrolimus was compared with the control (no TCI). The study included almost 3.4 million patients. The absolute risk of any cancer upon TCI exposure was similar to that of the control (absolute risk

Table 2 Common adverse events (≥ 10% incidence) in infants treated with pimecrolimus (PIM) 1%

Number of patients treated with PIM 1%	Treatment duration	Adverse events	References
1205	260 weeks	Nasopharyngitis, pyrexia, diarrhea, upper respiratory tract infection and cough	[14]
947	24 weeks	Nasopharyngitis, upper respiratory tract infection	[52]
123	27 weeks	Pyrexia, upper respiratory tract infection, nasopharyngitis	[20]
267	6 weeks	Upper respiratory tract infection, nasopharyngitis	[56]
476	52 weeks	Nasopharyngitis, headache, bronchitis, influenza, cough, pyrexia	[57]
76	52 weeks	Pyrexia, upper respiratory tract infection, nasopharyngitis, rhinitis, cough, bronchitis, ear infection, teething	[18]

4.70 per 1000 with TCI vs. 4.56 per 1000 without), suggesting that TCI is safe [62]. There was no impact of topical PIM use on T and B cell function or vaccination response [14].

DISCUSSION

AD requires long-term adherence to therapeutic management. Several factors such as the patient's age, attitude to treatment options, and site of AD lesions should be taken into consideration before selecting an appropriate treatment regime. Poor treatment adherence is seen in the case of TCS due their side effects and steroid phobia [6]. The European consensus has also recommended the use of PIM for infants ≥ 3 months of age [53]. The NICE guidelines (National Institute for Health and Care Excellence) recommends the use of TCI for moderate to severe AD [63]. Experts in South and South-East Asia also recommend the use of PIM in infants ≥ 3 months of age [15, 53].

Although some Asian countries have approved the use of PIM in infants ≥ 3 months, its use is still restricted in many countries due to the black box warning issued by the FDA [64]. However, there is a lack of scientific evidence suggesting a direct link between the use of TCI and an increased risk of malignancy [65]. In China, the guidelines recommend the use of PIM (1%) in children with mild to moderate AD [66]. In India, TCI (PIM 1% and tacrolimus 0.03%) are recommended as first-line therapies for the treatment of mild to moderate AD, with PIM 1% being preferred in children less than 2 years of age and on the face, flexures and genitalia [67]. The Korean Atopic Dermatitis Association (KADA) has recommended the use of tacrolimus (0.03%) and PIM (1%) in children older than 2 years for the management of AD, but they also mention that both of them can be safely used in children younger than 2 years, even in infants [40]. The Taiwanese Dermatological Association (TDA) and the Taiwan Academy of Pediatric Allergy, Asthma and Immunology (TAPAAI) recommend the use of TCI in children requiring long-term topical treatment, or the frequent use of mild TCS for AD in face and sensitive areas [68, 69].

The PETITE study, which was a pivotal study of PIM in pediatric patients with AD [14], used a unique real-world design in which TCS were used according to their label. The caregivers of infants randomized to treatment with PIM had ready access to short-term TCS as a rescue medication if AD flares could not be controlled with PIM. The PETITE study showed that the long-term usage of PIM is safe in infants and there is no drug accumulation in the blood [53]. The use of PIM is also economically viable, as there are longer symptom-free periods, reducing hospital visit costs.

CONSENSUS STATEMENT

The Asian Expert Panel concluded that the treatment of AD should be initiated as early as infancy, based on the clinical evidence. The authors recommend that regulatory authorities in Asian countries should remove the current boxed warnings (due to the lack of long-term safety data and the potential risk of the development of malignancies), as this will allow AD patients to have access to effective medications with comprehensively established safety profiles. Based on a review of the available evidence, the Asian experts suggest that labeling restrictions of PIM in infants aged 3 months and above are no longer justified, and it is an effective and safe treatment for long-term management of AD in infants.

CONCLUSION

Early treatment of AD is essential to prevent worsening, the development of atopic comorbidities and, most importantly, decrease the significant burden of AD on the entire family and society. The use of PIM has advantages such as a reduced risk for flares, a mean EASI reduction, long-term disease control and early treatment success. Post-marketing surveys have shown that there is no increased risk of cancer (e.g., lymphoma or non-melanoma skin carcinoma) associated with exposure to TCI or TCS. Many Asian countries have already approved the use of pimecrolimus for the treatment of AD in infants. Based on the available evidence, the expert panel recommends pimecrolimus in infants between 3 months and 2 years of age in the Asian population.

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Compliance with Ethics Guidlines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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REFERENCES

1. Huang J, Choo YJ, Smith HE, et al. Quality of life in atopic dermatitis in Asian countries: a systematic review. Arch Dermatol Res. 2021;314:445–62.

2. Tsai TF, Rajagopalan M, Chu CY, et al. Burden of atopic dermatitis in Asia. J Dermatol. 2019;46(10):825–34.

3. Laughter MR, Maymone MBC, Mashayekhi S, et al. The global burden of atopic dermatitis: lessons from the Global Burden of Disease Study 1990–2017. Br J Dermatol. 2021;184(2):304–9.

4. Suaini NHA, Tan CPT, Loo EXL, et al. Global differences in atopic dermatitis. Pediatr Allergy Immunol. 2021;32(1):23–33.

5. Nakahara T, Kido-Nakahara M, Tsuji G, et al. Basics and recent advances in the pathophysiology of atopic dermatitis. J Dermatol. 2021;48(2):130–9.

6. Luk D, Hon KLE, Dizon MVC, et al. Practical recommendations for the topical treatment of atopic dermatitis in South and East Asia. Dermatol Ther (Heidelb). 2021;11(1):275–91.

7. Noda S, Suarez-Farinas M, Ungar B, et al. The Asian atopic dermatitis phenotype combines features of atopic dermatitis and psoriasis with increased TH17 polarization. J Allergy Clin Immunol. 2015;136(5):1254–64.

8. Chan TC, Sanyal RD, Pavel AB, et al. Atopic dermatitis in Chinese patients shows TH2/TH17 skewing with psoriasiform features. J Allergy Clin Immunol. 2018;142(3):1013–7.

9. Weinberg E. The allergic march. Contin Med Educ. 2010;28(2):64–68.

10. Kage P, Zarnowski J, Simon JC, et al. Atopic dermatitis and psychosocial comorbidities—what's new? Allergol Select. 2020;4:86–96.

11. Tier HL, Balogh EA, Bashyam AM, et al. Tolerability of and adherence to topical treatments in atopic dermatitis: a narrative review. Dermatol Ther (Heidelb). 2021;11(2):415–31.

12. Stalder JF, Aubert H, Anthoine E, et al. Topical corticosteroid phobia in atopic dermatitis: international feasibility study of the TOPICOP score. Allergy. 2017;72(11):1713–9.

13. Luger T, Boguniewicz M, Carr W, et al. Pimecrolimus in atopic dermatitis: consensus on safety and the need to allow use in infants. Pediatr Allergy Immunol. 2015;26(4):306–15.

14. Sigurgeirsson B, Boznanski A, Todd G, et al. Safety and efficacy of pimecrolimus in atopic dermatitis: a 5-year randomized trial. Pediatrics. 2015;135(4):597–606.

15. Rubel D, Thirumoorthy T, Soebaryo RW, et al. Consensus guidelines for the management of atopic dermatitis: an Asia-Pacific perspective. J Dermatol. 2013;40(3):160–71.

16. Kaufmann R, Folster-Holst R, Hoger P, et al. Onset of action of pimecrolimus cream 1% in the treatment of atopic eczema in infants. J Allergy Clin Immunol. 2004;114(5):1183–8.

17. Staab D, Pariser D, Gottlieb AB, et al. Low systemic absorption and good tolerability of pimecrolimus, administered as 1% cream (Elidel) in infants with atopic dermatitis—a multicenter, 3-week, open-label study. Pediatr Dermatol. 2005;22(5):465–71.

18. Papp KA, Werfel T, Folster-Holst R, et al. Long-term control of atopic dermatitis with pimecrolimus cream 1% in infants and young children: a two-year study. J Am Acad Dermatol. 2005;52(2):240–6.

19. Kapp A, Papp K, Bingham A, et al. Long-term management of atopic dermatitis in infants with topical pimecrolimus, a nonsteroid anti-inflammatory drug. J Allergy Clin Immunol. 2002;110(2):277–84.

20. Ho VC, Gupta A, Kaufmann R, et al. Safety and efficacy of nonsteroid pimecrolimus cream 1% in the treatment of atopic dermatitis in infants. J Pediatr. 2003;142(2):155–62.

21. Schneider L, Hanifin J, Boguniewicz M, et al. Study of the atopic march: development of atopic comorbidities. Pediatr Dermatol. 2016;33(4):388–98.

22. Cheng J, Wu JJ, Han G. Epidemiology and characterization of atopic dermatitis in East Asian populations: a systematic review. Dermatol Ther (Heidelb). 2021;11(3):707–17.

23. Guo Y, Li P, Tang J, et al. Prevalence of atopic dermatitis in Chinese children aged 1–7 ys. Sci Rep. 2016;6(1):29751.

24. Hwang CY, Chen YJ, Lin MW, et al. Prevalence of atopic dermatitis, allergic rhinitis and asthma in Taiwan: a national study 2000 to 2007. Acta Derm Venereol. 2010;90(6):589–94.

25. Cho Y-T, Hsieh W-T, Chan TC, et al. Prevalence of baseline comorbidities in patients with atopic dermatitis: a population-based cohort study in Taiwan. JAAD Int. 2020;1(1):50–8.

26. Lavadia AM, Cumagun AT, Palmero L, et al. The ABC topical management of atopic dermatitis in Philippines: expert recommendations. J Drugs Dermatol. 2021;20(1):84–7.

27. Cheok S, Yee F, Song Ma JY, et al. Prevalence and descriptive epidemiology of atopic dermatitis and its impact on quality of life in Singapore. Br J Dermatol. 2018;178(1):276–7.

28. Goh YY, Keshavarzi F, Chew YL. Prevalence of atopic dermatitis and pattern of drug therapy in Malaysian children. Dermatitis. 2018;29(3):151–61.

29. Deckers IA, McLean S, Linssen S, et al. Investigating international time trends in the incidence and prevalence of atopic eczema 1990–2010: a systematic review of epidemiological studies. PLoS ONE. 2012;7(7):e39803.

30. Torrelo A. Atopic dermatitis in different skin types. What is to know? J Eur Acad Dermatol Venereol. 2014;28(Suppl 3):2–4.

31. Kaufman BP, Guttman-Yassky E, Alexis AF. Atopic dermatitis in diverse racial and ethnic groups—variations in epidemiology, genetics, clinical presentation and treatment. Exp Dermatol. 2018;27(4):340–57.

32. Czarnowicki T, He H, Krueger JG, et al. Atopic dermatitis endotypes and implications for targeted therapeutics. J Allergy Clin Immunol. 2019;143(1):1–11.

33. Koga C, Kabashima K, Shiraishi N, et al. Possible pathogenic role of Th17 cells for atopic dermatitis. J Invest Dermatol. 2008;128(11):2625–30.

34. Chen H, Common JE, Haines RL, et al. Wide spectrum of filaggrin-null mutations in atopic dermatitis highlights differences between Singaporean Chinese and European populations. Br J Dermatol. 2011;165(1):106–14.

35. Kawasaki H, Nagao K, Kubo A, et al. Altered stratum corneum barrier and enhanced percutaneous immune responses in filaggrin-null mice. J Allergy Clin Immunol. 2012;129(6):1538–46.

36. Ng YT, Chew FT. A systematic review and meta-analysis of risk factors associated with atopic dermatitis in Asia. World Allergy Organ J. 2020;13(11):100477.

37. Suarez-Farinas M, Dhingra N, Gittler J, et al. Intrinsic atopic dermatitis shows similar TH2 and higher TH17 immune activation compared with extrinsic atopic dermatitis. J Allergy Clin Immunol. 2013;132(2):361–70.

38. Muizzuddin N, Hellemans L, Van Overloop L, et al. Structural and functional differences in barrier properties of African American, Caucasian and East Asian skin. J Dermatol Sci. 2010;59(2):123–8.

39. Saeki H, Furue M, Furukawa F, et al. Guidelines for management of atopic dermatitis. J Dermatol. 2009;36(10):563–77.

40. Kim JE, Kim HJ, Lew BL, et al. Consensus guidelines for the treatment of atopic dermatitis in Korea (part I): general management and topical treatment. Ann Dermatol. 2015;27(5):563–77.

41. Huang A, Cho C, Leung DYM, et al. Atopic dermatitis: early treatment in children. Curr Treat Options Allergy. 2017;4(3):355–69.

42. Tsakok T, Marrs T, Mohsin M, et al. Does atopic dermatitis cause food allergy? A systematic review. J Allergy Clin Immunol. 2016;137(4):1071–8.

43. Dharmage SC, Lowe AJ, Matheson MC, et al. Atopic dermatitis and the atopic march revisited. Allergy. 2014;69(1):17–27.

44. Boguniewicz M, Schneider L, Leung D, et al. The allergic profile of infants in the SAM study: a large longitudinal study of development of asthma and allergies in patients with atopic dermatitis. J Allergy Clin Immunol. 2007;119(1):S209.

45. Gschwind HP, Waldmeier F, Zollinger M, et al. Pimecrolimus: skin disposition after topical administration in minipigs in vivo and in human skin in vitro. Eur J Pharm Sci. 2008;33(1):9–19.

46. Billich A, Aschauer H, Aszodi A, et al. Percutaneous absorption of drugs used in atopic eczema: pimecrolimus permeates less through skin than corticosteroids and tacrolimus. Int J Pharm. 2004;269(1):29–35.

47. Remitz A, De Pita O, Mota A, et al. Position statement: topical calcineurin inhibitors in atopic dermatitis. J Eur Acad Dermatol Venereol. 2018;32(12):2074–82.

48. Lakhanpaul M, Davies T, Allen BR, et al. Low systemic exposure in infants with atopic dermatitis in a 1-year pharmacokinetic study with pimecrolimus cream 1%. Exp Dermatol. 2006;15(2):138–41.

49. Paul C, Cork M, Rossi AB, et al. Safety and tolerability of 1% pimecrolimus cream among infants: experience with 1133 patients treated for up to 2 years. Pediatrics. 2006;117(1):e118–28.

50. Eichenfield LF, Ho V, Matsunaga J, et al. Blood concentrations, tolerability and efficacy of pimecrolimus cream 1% in Japanese infants and children with atopic dermatitis. J Dermatol. 2007;34(4): 231–6.

51. Ling M, Gottlieb A, Pariser D, et al. A randomized study of the safety, absorption and efficacy of pimecrolimus cream 1% applied twice or four times daily in patients with atopic dermatitis. J Dermatolog Treat. 2005;16(3):142–8.

52. Lubbe J, Friedlander SF, Cribier B, et al. Safety, efficacy, and dosage of 1% pimecrolimus cream for the treatment of atopic dermatitis in daily practice. Am J Clin Dermatol. 2006;7(2):121–31.

53. Luger T, Augustin M, Lambert J, et al. Unmet medical needs in the treatment of atopic dermatitis in infants: an expert consensus on safety and efficacy of pimecrolimus. Pediatr Allergy Immunol. 2021;32(3):414–24.

54. Hoetzenecker W, Meingassner JG, Ecker R, et al. Corticosteroids but not pimecrolimus affect viability, maturation and immune function of murine epidermal Langerhans cells. J Invest Dermatol. 2004;122(3):673–84.

55. Reda AM, Elgendi A, Ebraheem AI, et al. A practical algorithm for topical treatment of atopic dermatitis in the Middle East emphasizing the importance of sensitive skin areas. J Dermatolog Treat. 2019;30(4): 366–73.

56. Langley RG, Eichenfield LF, Lucky AW, et al. Sustained efficacy and safety of pimecrolimus cream 1% when used long-term (up to 26 weeks) to treat children with atopic dermatitis. Pediatr Dermatol. 2008;25(3):301–7.

57. Wahn U, Bos JD, Goodfield M, et al. Efficacy and safety of pimecrolimus cream in the long-term management of atopic dermatitis in children. Pediatrics. 2002;110(1 Pt 1): e2.

58. Siegfried EC, Jaworski JC, Hebert AA. Topical calcineurin inhibitors and lymphoma risk: evidence update with implications for daily practice. Am J Clin Dermatol. 2013;14(3):163–78.

59. Paller AS, Folster-Holst R, Chen SC, et al. No evidence of increased cancer incidence in children using topical tacrolimus for atopic dermatitis. J Am Acad Dermatol. 2020;83(2):375–81.

60. Legendre L, Barnetche T, Mazereeuw-Hautier J, et al. Risk of lymphoma in patients with atopic dermatitis and the role of topical treatment: a systematic review and meta-analysis. J Am Acad Dermatol. 2015;72(6):992–1002.

61. Arellano FM, Wentworth CE, Arana A, et al. Risk of lymphoma following exposure to calcineurin inhibitors and topical steroids in patients with atopic dermatitis. J Invest Dermatol. 2007;127(4):808–16.

62. Devasenapathy N, Chu A, Wong M, et al. Cancer risk with topical calcineurin inhibitors, pimecrolimus and tacrolimus, for atopic dermatitis: a systematic review and meta-analysis. Lancet Child Adolesc Health. 2023;7(1):13–25.

63. National Collaborating Centre for Women's and Children's Health. Atopic eczema in children: management of atopic eczema in children from birth up to the age of 12 years. London: RCOG Press; 2007.

64. Ring J, Mohrenschlager M, Henkel V. The US FDA "black box" warning for topical calcineurin inhibitors: an ongoing controversy. Drug Saf. 2008;31(3): 185–98.

65. Thaci D, Salgo R. Malignancy concerns of topical calcineurin inhibitors for atopic dermatitis: facts and controversies. Clin Dermatol. 2010;28(1):52–6.

66. Yao X, Song Z-Q, Li W, et al. Guidelines for diagnosis and treatment of atopic dermatitis in China (2020). Int J Dermatol Venereol. 2021;4(1):1–9.

67. Rajagopalan M, De A, Godse K, et al. Guidelines on management of atopic dermatitis in India: an evidence-based review and an expert consensus. Indian J Dermatol. 2019;64(3):166–81.

68. Chan TC, Wu NL, Wong LS, et al. Taiwanese Dermatological Association consensus for the management of atopic dermatitis: a 2020 update. J Formos Med Assoc. 2021;120(1 Pt 2):429–42.

69. Yao TC, Wang IJ, Sun HL, et al. Taiwan guidelines for the diagnosis and management of pediatric atopic dermatitis: consensus statement of the Taiwan Academy of Pediatric Allergy, Asthma and Immunology. J Microbiol Immunol Infect. 2022;55: 561–72.