




BRIEF REPORT

Practical Recommendations for the Topical Treatment of Atopic Dermatitis in South and East Asia

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ABSTRACT

Introduction: There is some evidence to suggest that the prevalence of atopic dermatitis (AD) in Asia is rising. We have therefore developed an algorithm for the topical treatment of AD throughout South and East Asia for use by primary care physicians, pediatricians and dermatologists.

Methods: Nine AD experts from South and East Asia and one from Europe developed the algorithm based upon treatment guidelines, relevant literature and local treatment practices.

The algorithm outlines current best practice for the use of emollients, topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI), with the intention of simplifying the treatment regimen of mild-to-moderate AD in South and East Asia.

Results: Patients with AD should bathe and cleanse affected skin to remove crusts and scales daily. Emollients should also be applied daily as a maintenance treatment. When selecting appropriate topical anti-inflammatory treatment for AD flares, several factors should be taken into consideration, including the patient's age, attitude to treatment options and site of AD lesions. Given the concerns regarding

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the risk of skin atrophy with use of TCS, a TCI should be used to treat AD lesions in sensitive skin areas: pimecrolimus is recommended for mild-to-moderate AD in these locations, while tacrolimus should be considered for moderate and severe cases. Either pimecrolimus or tacrolimus is recommended for flares in other, non-sensitive body locations. A proactive or intermittent maintenance treatment strategy involving regular emollient use and twice-weekly application of a TCI to previously affected areas is encouraged to reduce the risk of flares.

Conclusions: The algorithm proposed here is intended to simplify the topical treatment of mild-to-moderate AD in daily practice in South and East Asian countries.

Keywords: Algorithm; Atopic dermatitis; Pimecrolimus; South and East Asia; Tacrolimus

Key Summary Points

Atopic dermatitis (AD) is a chronic, relapsing, inflammatory skin disease that appears to be increasing in prevalence in Asia, indicating an urgent need for effective treatment strategies.

We have proposed a practical algorithm to simplify the topical treatment of mild-to-moderate AD in adult and pediatric patients in South and East Asian countries, with a focus on the role of topical calcineurin inhibitors (TCI).

The algorithm emphasizes the importance of sensitive skin areas and is intended for use in daily clinical practice by primary care physicians, pediatricians and dermatologists.

Pimecrolimus is recommended to treat mild-to-moderate AD affecting sensitive skin areas, while tacrolimus should be considered for moderate and severe cases; either pimecrolimus or tacrolimus is recommended for flares in other, non-sensitive body locations.

A proactive maintenance treatment strategy involving the twice-weekly application of a TCI and regular emollient use to previously affected areas may reduce the risk of a recurrence of disease flares.

DIGITAL FEATURES

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INTRODUCTION

Atopic dermatitis (AD) is a chronic, relapsing, inflammatory skin disease [1, 2], which is believed to exhibit distinct etiological differences between Caucasians and Asian races. For example, clinical studies have shown an increase in interleukin-17 (IL-17)-producing cells in Asian patients with AD and a predominance of the psoriasiform phenotype compared with Caucasian patients with AD [3]. The prevalence of AD varies across Asia. Children in Singapore have an AD prevalence of 20.6%, nearly twice that of Singaporean adults (11.1%) [4]. In Malaysia, the overall prevalence of childhood AD is 13.4%, and it is most common in Malays, males, children aged < 2 years, and those with an atopic background, such as asthma, hay fever, and family history of atopic diseases [5]. A study using Korean national statistics gathered from health insurance data reported that the prevalence of AD in 2008 ranged from 26.5% in 12- to 23-month-old infants to 2.4% in 18 year olds [6]. An investigation of trends over time (1990–2010) in international prevalence of AD suggests that AD is becoming more prevalent in East Asia [7]. However, the prevalence of AD in Singapore has plateaued at about one in five children when figures published in 2002 and 2018 are compared [4, 8].

The prevalence of AD varies between urban and rural areas, suggesting that environmental factors, such as air pollution, are significant contributors to the epidemiology of AD. Indeed, a recent study has shown that air pollutants found in urban areas, such as diesel exhaust particles, can trigger hyper-innervation and pruritus, leading to the development of AD [9, 10].

Genetic factors may also influence the epidemiology of AD in Asia, as illustrated by mutations of the filaggrin gene in Chinese populations, which differ from those present in European populations [11, 12]. For example, the c.3321delA filaggrin gene mutation is associated with clinical phenotypes of AD in the Chinese Han population, but is absent from European populations [12].

The treatment paradigm for mild-to-moderate AD is based on emollients, topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI). Systemic immunosuppressive agents and phototherapy are typically reserved for more severe or refractory cases. However, slight geographical variations in prescribing practices exist across Asia. A survey of 255 dermatologists across Singapore, Malaysia, Indonesia, Thailand, Vietnam, and the Philippines found that most used mild-to-moderate potency TCS, but that there was a tendency in Vietnam and the Philippines to reserve TCS for severe cases in infants and children [13]. Similar variations were observed in the use of TCI [13].

Complementary and alternative medicines, such as herbal preparations, are used by many patients in China, Taiwan, and other Asian countries, either alone or in combination with licensed products [14, 15], although evidence-based data from randomized controlled trials are lacking [14, 16, 17], and the extent of their role in the management of AD in Asia is not clear. Integrative medicine (the combination of western medicine and Chinese medicine) may be useful in the treatment of AD but determining this will require collaboration between practitioners from each discipline [17].

AD often affects areas where the skin is thin and sensitive, such as skin flexures and the face. A naturally thin stratum corneum in these areas makes them prone to epidermal barrier dysfunction and transepidermal water loss, and

hence to the development of AD. Thinner skin is also more permeable to irritants, leading to more frequent flares, and is particularly vulnerable to steroid-induced atrophy [18]. Thin skin areas therefore require special consideration in the management of AD and may benefit from steroid-sparing treatment strategies.

Here we discuss steroid-sparing treatment strategies and also consider situations in which patients may benefit from steroid-sparing treatment, such as when they are reluctant to use TCS due to concerns over skin atrophy and other potential side effects. Such “corticophobia” is increasingly recognized as a significant factor contributing to poor TCS treatment adherence [19]. We also propose a practical algorithm for the topical treatment of mild-to-moderate AD in both adult and pediatric patients in daily clinical practice in South and East Asia. The algorithm has been structured for use by primary care physicians, pediatricians, and dermatologists. We aim to supplement, rather than replace, more detailed evidence-based international and national treatment guidelines, with a focus on the role of TCI in the treatment of mild-to-moderate AD.

METHODS

An international panel of nine experts in AD from Asian countries, including Hong Kong, Singapore, Malaysia, the Philippines, and Thailand, and one expert from Germany, was formed to develop an algorithm for the topical treatment of AD in daily clinical practice in South and East Asia. The panel included dermatologists and pediatric specialists. The first draft of the algorithm was proposed by one of the authors, Thomas Luger, which was then discussed with the other authors and adapted to South and East Asia based on their expertise, local knowledge, guidelines [20–26], and relevant literature. The first draft of the algorithm proposed by Professor Luger has also been adapted for the Middle East by a separate group of experts from the Middle East region [27].

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

Proposed Treatment Algorithm for Mild-to-Moderate AD in South and East Asia

The proposed new AD treatment algorithm, which emphasizes the importance of sensitive skin areas (applicable to both adult and pediatric patients), is outlined in Fig. 1.

Diagnosis and Initial Assessment of AD

The initial assessment of patients presenting with AD should take into account the patient's age and the site and severity of lesions (Fig. 1), since these factors may help determine the most appropriate treatment. Patient history may help to identify potential triggers (e.g., detergents, clothing, tobacco smoke, weather extremes, air pollution, food and environmental allergens) [28] that may precipitate the onset or flaring of AD.

Exploration for a potential food allergy may be an important aspect in the identification of triggers, particularly in infants and young children in whom reported rates of food allergy range from approximately one-third to two-thirds of children with AD [29]. Food allergens, including milk, eggs, soy, wheat, and peanuts, are among those commonly linked to exacerbation of AD [23]. If food allergy is suspected as a trigger, this should be investigated by measurement of immunoglobulin E (IgE) antibody levels and skin prick tests [23]. The diagnosis of food allergy should be confirmed by oral food challenge since eczematous reactions are often delayed and do not occur via the same mechanism as the immediate IgE-mediated response detected by a skin prick test [23]. Suspected allergens should be temporarily eliminated (e.g., for a period of 4–6 weeks) [23]; confirmed food allergies should be managed in partnership with a pediatric allergist. When the food containing the suspected allergen is gradually

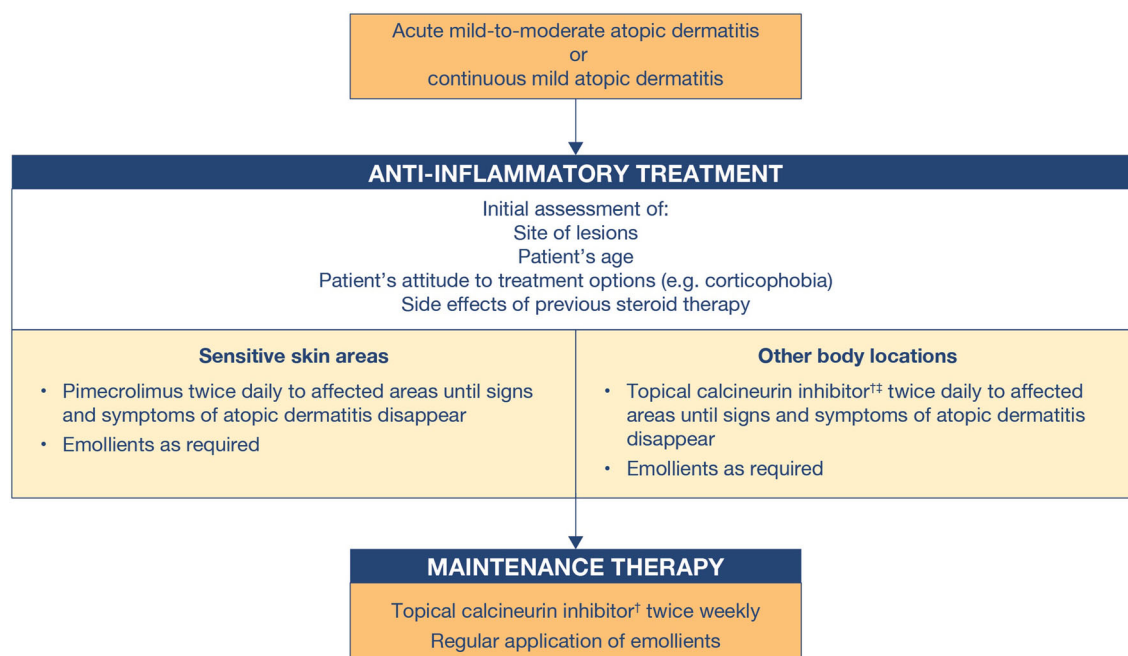


Fig. 1 Algorithm for the treatment of acute mild-to-moderate atopic dermatitis (AD) or continuous mild AD in children, adolescents, and adults in South and East Asia. Single dagger superscript (†) indicates topical calcineurin inhibitors (TCI): pimecrolimus 1% cream, or tacrolimus 0.1% (aged ≥ 16 years) or 0.03% (aged 2–15 years)

ointment; pimecrolimus is not indicated for severe AD and tacrolimus is not indicated for mild AD. Double dagger superscript (††) indicates use of topical corticosteroids (TCS) that should be reserved for severe disease flares, but brief treatment with TCS may be considered if inflammation persists despite treatment with TCI

reintroduced, the status of the patient's skin should be assessed before and 24 h after oral food challenge [29]. The initial evaluation of a patient presenting with AD may also include assessment of the impact of AD on the patient's quality of life, daily activities, sleep, and psychosocial wellbeing, and whether lesions appear infected.

Maintenance Treatment with Emollients

The cornerstone of AD management is regular use of emollients, with the aim to maintain skin hydration and reduce water loss due to epidermal barrier dysfunction [22, 23, 30]. An ideal emollient should contain a combination of occlusive agents to slow down water loss, humectants to increase capacity to withhold moisture, and lubricants to reduce friction against skin [31]. Many emollients are available, including aqueous lotions, water-in-oil or oil-in-water creams, and oil-based ointments [23]. There is no evidence for superiority of any one type of emollient over others [14, 31], therefore the choice of emollient may depend on local availability, cost, patient preference, and the physician's recommendation [31].

Selecting an appropriate emollient may involve an element of trial and error to identify the most suitable maintenance treatment for an individual patient. Preparations containing sodium lauryl sulphate are not recommended for regular use as emollients. Daily showers or baths with tepid or luke-warm water and soap-free washes or soap substitutes are recommended, especially to remove crusts or scales. A leave-on emollient should then be applied immediately after bathing to maintain hydration [14, 23]. In addition, if there are visible signs of inflammation, topical anti-inflammatory agents should be applied to the affected areas (see below) [22, 23].

Anti-inflammatory Treatment

The interplay of skin barrier defects, immune abnormalities, the microbiome, and environmental triggers appears to promote inflammatory responses involving T cells, chemokines,

and cytokines. These inflammatory responses lead to the characteristic pruritic flares of AD [1, 32–35]. Topical anti-inflammatory treatments are therefore an integral part of the management of AD and include two predominant classes: TCS (numerous different agents with a range of potencies) and TCI (tacrolimus and pimecrolimus). The topical anti-inflammatory agents available for the treatment of AD in Asia are summarized in Table 1 [22, 23, 36–49]. While these are often used to control acute flares, the value of proactive anti-inflammatory treatment during periods of remission to prevent recurrence of flares, is increasingly recognized [37].

TCS are regarded as first-line therapy for acute flares [2, 23] and play an important role in the management of AD in Asian patients when used appropriately [22]. Indeed, the recent Asian Academy of Dermatology and Venereology Expert Panel on Atopic Dermatitis recommend TCS use for flares uncontrolled by adequate skin care and moisturizers in Asian patients with AD [36]. However, TCI have similar efficacy to low-to-mid potency TCS overall [50], and may be considered as an alternative to TCS.

Two TCI were licensed since the early 2000s, namely tacrolimus and pimecrolimus. Tacrolimus ointment is available in a 0.03% formulation, approved for the treatment of moderate-to-severe AD in patients aged 2–15 years, and as a 0.1% formulation licensed for use in patients aged ≥ 16 years. Pimecrolimus 1% cream is licensed for the treatment of mild-to-moderate AD in adults and children aged ≥ 2 years, and in several countries pimecrolimus is also approved for infants aged ≥ 3 months (including Thailand [44], Indonesia [49] and the Philippines [47]). When TCI are not available, TCS should be used. Where use of TCI is not limited by their availability, we recommend taking multiple factors into consideration in the selection of TCS or TCI, such as patient attitude to treatment, site of AD lesions, and side effects of previous steroid treatment (discussed in detail in following subsections).

Table 1 Topical anti-inflammatory agents used in the treatment of AD in Asia [22, 23, 36–40]

Topical anti-inflammatory agents	Strength (%)	Formulation	Recommended usage
Topical calcineurin inhibitors			
Pimecrolimus	1 ^a	Cream	Control of mild-to-moderate acute flares on sensitive skin and other body areas Intermittent use on sensitive skin and other body areas
Tacrolimus	0.03 ^b , 0.1 ^c	Ointment	Control of moderate-to-severe acute flares on body areas other than face/flexures/other sensitive skin Proactive use on non-sensitive skin
Topical corticosteroids			
Class 7			
Dexamethasone	0.1	Cream	Control of mild acute flares on non-sensitive skin
Hydrocortisone	0.25, 0.5, 1	Cream/ointment/ lotion/solution	
Hydrocortisone acetate	0.5–1	Cream/ointment	
Class 6			
Fluocinolone acetonide	0.01	Cream/solution	Control of mild-to-moderate acute flares on non-sensitive skin
Desonide	0.05	Cream/gel/foam/ ointment	
Alclometasone dipropionate	0.05	Cream/ointment	
Class 5			
Hydrocortisone valerate	0.2	Cream/ointment	Control of mild-to-moderate acute flares on non-sensitive skin
Hydrocortisone probutate	0.1	Cream	
Hydrocortisone butyrate	0.1	Cream/ointment/solution	

Table 1 continued

Topical anti-inflammatory agents	Strength (%)	Formulation	Recommended usage
Class 3–4			
Triamcinolone acetonide	0.1	Cream/ointment	Control of mild-to-moderate acute flares on non-sensitive skin
Mometasone furoate	0.1	Cream	
Fluticasone propionate	0.05	Cream/ointment	
Fluocinolone acetonide	0.025	Cream/ointment	
Betamethasone valerate	0.1	Cream/foam/lotion/ointment	
Class 2			
Triamcinolone acetonide	0.5	Cream/ointment	Control of moderate-to-severe acute flares on non-sensitive skin (limited duration of use: < 2 weeks)
Mometasone furoate	0.1	Ointment	
Fluocinonide	0.05	Cream/gel/ointment/solution	
Betamethasone dipropionate	0.05	Cream/foam/ointment/solution	
Amcinonide	0.1	Cream/lotion/ointment	
Class 1			
Diflorasone diacetate	0.05	Ointment	Control of severe acute flares on non-sensitive skin (limited duration of use: < 2 weeks)
Clobetasol propionate	0.05	Cream/foam/ointment	

Table is adapted from Chow et al. [36]. Some of the agents listed in table may not be available in all Asian countries

^a Infants aged 3 months to 2 years (Australia [41], Brazil [42], India [43], Indonesia [49], Israel [45], New Zealand [46], Philippines [47], Russia [48], Thailand [44] only; use in infants off-label elsewhere); children aged ≥ 2 years, adolescents, and adults. Pimecrolimus is not available for use in Japan

^b Children aged ≥ 2 years and adolescents aged < 16 years

^c Adolescents aged ≥ 16 years and adults

Patient Attitudes to Each Treatment Option

As mentioned above, corticophobia can compromise effective treatment with TCS because patients may fail to use their prescribed treatment or discontinue treatment prematurely to minimize steroid exposure [51–54]. While providing patients with accurate information regarding TCS may help alleviate concerns [55], TCI should also be considered in cases where

patients (or parents/caregivers of pediatric patients) express concerns regarding TCS use [56]. Conversely, some patients may be reluctant to use a TCI due to perceived safety concerns, since both tacrolimus and pimecrolimus carry a black box warning for risk of malignancy (e.g., lymphoma) [57, 58]. However, no causal relationship has been established, and as safety data accumulate, systematic reviews have not

found evidence of increased cancer risk [59, 60]. Indeed, the first Asian study to investigate the risk of malignancies with TCI in patients with AD found no association between pimecrolimus and tacrolimus use and overall development of malignancies [61]. Furthermore, a recent prospective, observational study of approximately 8000 children with AD who were treated with tacrolimus ointment for ≥ 6 weeks observed no incidence of lymphoma over a 10-year period [62]. The authors of the study concluded that there was no evidence to suggest that tacrolimus increased the long-term risk of cancer in children with AD [62]. A proactive approach by the clinician to openly discuss the content of the black box warning with the patient may help to reduce patient anxiety and subsequently help to improve TCI adherence [26, 63]. Nevertheless, misinformation and distrust of TCI and TCS persists in Asian populations [64].

In an observational study of the efficacy and safety of pimecrolimus 1% cream in patients with AD who were previously treated with TCS, patient satisfaction was higher with pimecrolimus than with TCS [65]. Approximately 60% of patients had no concerns about using pimecrolimus on sensitive skin compared with 10.1% for TCS [65]. In addition, more than 77% of patients felt that pimecrolimus improved their quality of life compared with less than 43% for TCS [65]. Similarly, in a 4-year follow-up study of children and adult patients with AD treated with 0.1% tacrolimus, 75% of patients and 76% of investigators expressed high satisfaction with the treatment [66]. In studies comparing tacrolimus 0.1% and TCS, efficacy results have favored tacrolimus although comparison of their impact on quality of life is less clear-cut [67, 68]. In a study comparing pimecrolimus 1% cream and tacrolimus 0.03% ointment in pediatric patients with AD, although efficacy was similar between treatments, a greater proportion of patients (or caregivers, in the case of pediatric patients unable to answer questions themselves) rated pimecrolimus as very good or excellent compared with tacrolimus for several aspects, including suitability for use on sensitive facial skin; non-sticky feel; ease of application; and ease of rub-in [69]. In the

hot and humid climate of South and East Asia, the propensity to sweat from excessive heat is high and can be an aggravating factor for AD [70]. Therefore, certain product characteristics attributed to pimecrolimus, such as its non-sticky feel and ease of rub-in, should prove to be particularly beneficial. By contrast, ointments may be more occlusive and feel more greasy, especially when used in hot and humid conditions, trapping excess heat and sweat on the skin and potentially further exacerbating the risk of AD flares.

Site of AD Lesions

Sensitive skin areas, such as the face, neck, and skin flexures, are at particular risk of epidermal barrier impairment and skin atrophy with TCS treatment. Therefore, TCI are useful to treat patients with AD affecting these areas [14, 22]. In support of this approach, American and European guidelines for the treatment of AD recommend TCI, rather than TCS, as the preferred treatment for sensitive skin areas [25, 26].

The proactive treatment of sensitive skin areas involves long-term, low-dose intermittent topical anti-inflammatory therapy for previously affected areas with subclinical inflammation [71]. Patients experiencing frequent flares may require proactive anti-inflammatory treatment as an adjunct to continued use of emollients for maintenance treatment. Concerns regarding the side effects of TCS may be heightened if their prolonged use is required. In contrast, beneficial effects of TCI have been observed in long-term studies. Two early intervention studies of pimecrolimus (one in infants aged 3–23 months and one in children aged 2–17 years) have demonstrated a reduction in the incidence of flares with pimecrolimus compared with vehicle, as well as improved control of AD, over a period of 12 months [72, 73]. Furthermore, a 5-year study of ‘as needed’ treatment with pimecrolimus or TCS in infants with AD demonstrated that pimecrolimus had a similar efficacy to TCS and raised no safety concerns [74]. A non-comparative study of intermittent or continuous application of tacrolimus 0.1% ointment for up to 4 years (patients ≥ 2 years old) demonstrated sustained efficacy and a safety profile comparable with

those reported for shorter studies [66]. Long-term proactive treatment of AD in children with either pimecrolimus 1% cream (16-week study [75]) or tacrolimus 0.03% ointment (40-week study [76] and two 12-month assessments [77, 78]) has been found to delay flares and prevent relapses. Therefore, patients requiring proactive anti-inflammatory treatment and those for whom prolonged TCS use is not desired, may benefit from a TCI.

The authors of a recent systematic review of long-term efficacy and safety of both TCS and TCI for pediatric use concluded that TCI should be the standard-of-care maintenance therapy, with low-to-mid potency TCS used intermittently to control flares [60]. Twice-weekly application of TCI (rather than daily application) and regular emollient use is recommended for long-term maintenance therapy [22].

Side Effects of Previous Steroid Therapy

Patients who have experienced steroid-induced side effects when using corticosteroids for other pathologies are also candidates for treatment with TCI [25, 56].

Role of TCI

The use of tacrolimus has been evaluated in clinical trials involving Asian patients. Pooled analysis of data from several Asian studies found that the efficacy and safety of tacrolimus use in the Asian population was similar to that seen in European and US studies [79]. Similarly, ethnic origin has been found to have no effect on the efficacy of pimecrolimus, based on a pooled analysis of three pediatric studies comparing Caucasian and non-Caucasian (including Asian) subgroups [80]. In view of these findings, where results from studies not conducted specifically in Asian patients are reported in this paper, we believe that the results can be extrapolated to guide treatment practice in South and East Asia.

The most common side effects with TCI therapy are transient local application site reactions, including erythema, pruritus, and stinging/burning sensations. In a comparative study of TCI use by patients aged 2–17 years, application site reactions were less common

and of shorter duration with pimecrolimus than with tacrolimus [26, 69]. At Day 4, the incidence of erythema/irritation with pimecrolimus was six out of 71 (8%) patients compared with 13 out of 70 (19%) patients with tacrolimus ($p = 0.039$) [69]. Furthermore, only six out of 71 (8%) patients experienced itching with pimecrolimus use in comparison with 14 out of 70 (20%) patients using tacrolimus ($p = 0.073$) [69]. Among those who experienced erythema/irritation, it was found that no patients using pimecrolimus experienced these symptoms for longer than 30 min, compared with 11 out of 13 (85%) patients applying tacrolimus ($p < 0.001$) [69]. Local burning may also occur less frequently in patients using pimecrolimus 1% cream, with 7.4% of pediatric patients and 10.4% of adults experiencing this side effect after applying the cream, compared with up to 36% of pediatric patients and 47% of adult patients applying tacrolimus ointment [81].

The potential for application site reactions should be discussed with patients (or parents/caregivers of pediatric patients) prior to the initiation of TCI treatment, and reassurance given that such reactions are transient. Offering this reassurance may reduce the likelihood of premature discontinuation if unexpected burning or stinging sensations occur. As discussed above, there remains no evidence for any causal relationship between TCI and malignancies, such as lymphoma [82].

Use of TCI on Sensitive Skin Areas

Those parts of the body where the skin is thinner than other areas are disproportionately affected by AD and therefore require special consideration in relation to AD management. TCS should be used with caution in sensitive skin areas, particularly in the peri-ocular region [22]. Despite TCS often being less expensive than TCI in most South and East Asian countries, TCI may be a more suitable treatment option than TCS for two important reasons, namely, a greater selectivity in targeting cells involved in the inflammatory response and a lower potential for transcutaneous resorption, as discussed in the following subsections

TCI Have Greater Selectivity than TCS in Terms of Targeting Cells Involved in the Inflammatory Response at Sites Affected by AD

Preclinical studies have shown that, unlike TCS and tacrolimus [83, 84], pimecrolimus does not affect epidermal Langerhans cells, which have an important role in cutaneous immunological responses [85, 86]. These findings have also been confirmed in a clinical study [87]. Analysis of skin biopsies from patients treated with pimecrolimus or betamethasone valerate (BMV) showed that pimecrolimus depleted T cells at sites of inflammation via the induction of apoptosis, but spared Langerhans cells, whereas BMV application depleted both Langerhans cells and T cells [87]. Both treatments also depleted dendritic epidermal cells in this study [87]. Tacrolimus depletes inflammatory dendritic epidermal cells with greater selectivity than TCS but also affects the immunophenotype of Langerhans cells [83, 84]. Pimecrolimus therefore has a more favorable balance of anti-inflammatory versus immunosuppressive activity compared with tacrolimus and TCS [88].

TCI Have Lower Potential for Transcutaneous Resorption than TCS

The beneficial property of TCI in terms of its lower potential for transcutaneous resorption is a particularly important consideration in thin skin areas because it reduces systemic exposure to topically applied medication. A comparison of the TCI revealed that pimecrolimus permeates the skin to a lesser extent than tacrolimus due to its greater lipophilicity and higher binding affinity for skin proteins [89, 90]. When pimecrolimus was compared with tacrolimus, the permeation of pimecrolimus through human skin was consistently lower by factors of 9–10, and in comparison with TCS the permeation was lower by factors of 70–110 [89]. While pimecrolimus possesses comparatively low exposure, it should be noted that patients treated with the highest concentration of tacrolimus (0.1%) experience low systemic exposure [91], and both TCI can be considered to be appropriate agents for situations requiring low permeability.

Given the mechanistic differences described above, we recommend pimecrolimus as the first-choice TCI for sensitive skin areas in mild-to-moderate disease; studies providing clinical evidence to support its use in special situations, such as facial AD, are summarized in Table 2 [69, 74, 92–95]. As pimecrolimus is not indicated for severe AD, we recommend tacrolimus for sensitive skin areas beyond moderate disease, as tacrolimus is recommended for use in moderate and severe disease; short-term treatment with TCS may also be appropriate, with a subsequent switch to a TCI when inflammation subsides. For AD in other parts of the body, the selection of a TCI can be determined by physician and patient preference.

Other Treatments

Crisaborole ointment, a phosphodiesterase-4 (PDE4) inhibitor, provides a novel steroid-sparing alternative to TCS or TCI for topical treatment of mild-to-moderate AD in patients aged ≥ 2 years [96]. However, it is currently only licensed in the USA and Canada, and its efficacy and safety has not been investigated in Asian patients; therefore its potential role in the management of AD in South and East Asia remains to be seen.

There have been many novel developments for the treatment of moderate-to-severe AD (e.g., biologics, such as dupilumab, and small molecules, including Janus kinase inhibitors and aryl hydrocarbon receptor-modifying agents) [97, 98].

CONCLUSIONS

Atopic dermatitis is a prevalent condition in Asia, particularly in urban areas, and effective treatment strategies are needed. We recommend pimecrolimus as the treatment of choice for mild-to-moderate AD affecting sensitive skin areas, with tacrolimus considered for moderate and severe cases. For other body locations, we recommend either pimecrolimus or tacrolimus, which are indicated for mild-to-moderate and moderate-to-severe AD, respectively.

Table 2 Evidence for efficacy of pimecrolimus in thin skin areas

First author of study, year, reference	Age of patients	<i>n</i>	Body area	Outcome
Sigurgeirsson B, 2015 (PETITE Study) [74]	Infants (3–12 months) followed to age 5–6 years	2418	Facial AD	Treatment success (facial IGA score 0 or 1) achieved by 61.0 and 61.8% of patients in pimecrolimus and TCS groups, respectively, after 3 weeks of treatment; 96.6 and 97.2% of patients, respectively, had IGA score 0 or 1 at end of 5-year study
Hoeger PH, 2009 [92]	2–11 years	200	Facial AD	IGA score 0 or 1 in 74.5% of patients in pimecrolimus group, vs. 51.0% in vehicle group ($p < 0.001$) at 6 weeks
Zuberbier T, 2008 [93]	2–17 years	140	Facial AD	Pimecrolimus delayed time to first flare (138 vs. 68 days; $p = 0.01$) and reduced need for TCS (11.7 vs. 20.7%; $p = 0.0024$) compared with vehicle 50% of pimecrolimus-treated patients free from facial AD flare over 24 weeks, vs. 37.5% in vehicle group ($p = 0.012$)
Kempers S, 2004 [69]	2–17 years	141	Head and neck	53.7% reduction in head/neck BSA affected with pimecrolimus vs. 34.9% reduction with tacrolimus
Lubbe J, 2006 (Prospective study in clinical practice) [94]	3 months to 81 years	947	Facial AD	65–80% of patients (varying across age groups) achieved facial IGA 0 or 1 after 24 weeks of pimecrolimus treatment Improvement more pronounced for facial IGA than whole body IGA (43–54% with IGA 0 or 1 at 24 weeks)
Murrell DF, 2007 [95]	≥ 12 years (adolescent/adult)	200	Facial AD	Facial IGA 0 or 1 in 46.5% of pimecrolimus-treated patients vs. 16.2% in vehicle group ($p < 0.001$) at 6 weeks
			Head and neck	≥ 60% change in head/neck EASI score in 50.5% of pimecrolimus-treated patients vs. 18.2% in vehicle group ($p < 0.001$) at 6 weeks
			Eyelids	44.6% of patients in pimecrolimus group vs 19.2% in vehicle group ($p < 0.001$) clear of eyelid dermatitis at 6 weeks

AD Atopic dermatitis, *BSA* body surface area, *EASI* Eczema Area and Severity Index, *IGA* Investigator Global Assessment (Score 0 = clear; 1 = almost clear), *TCS* topical corticosteroids

We also recommend a proactive maintenance treatment strategy involving the application of a TCI and emollients to previously affected areas. This maintenance therapy reduces the likelihood of disease flares occurring. All patients with AD should be encouraged to undertake general skin care measures, including the liberal and regular use of emollients on affected skin.

The algorithm presented here is intended to simplify the topical treatment of mild-to-moderate AD in daily practice in South and East Asian countries.

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