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ORIGINAL RESEARCH

Experts' Consensus on the Use of Pimecrolimus in Atopic Dermatitis in China: A TCS-Sparing Practical Approach

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ABSTRACT

Introduction: Atopic dermatitis (AD) is a chronic, pruritic, inflammatory skin disease with rising prevalence. Topical corticosteroids (TCS) are recommended as first-line therapy for patients with AD in China; however, corticophobia is a widespread concern, which can manifest as noncompliance: in a previous Chinese study, almost all parents whose children had AD were very concerned about the side effects of TCS and, as a result, nearly half did not use it in the event of recurrence. We propose a TCS-sparing treatment algorithm for the management of infants, children, adolescents, and adults with mild-to-moderate AD, to guide clinical practice in China.

Methods: A panel of eight experts in AD from China and one expert from Germany formed to develop a practical algorithm for the management of mild-to-moderate AD, focusing on pimecrolimus.

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Results: Irrespective of body location, all patients with mild AD (including acute flares) and infants with moderate AD should apply the topical calcineurin inhibitor (TCI) pimecrolimus twice daily to the affected area until symptoms disappear. For children, adolescents, and adults with moderate AD, pimecrolimus should be applied twice daily to sensitive skin areas, and a TCI (either pimecrolimus or tacrolimus) should be applied twice daily to other body locations. Short-term administration of TCS, followed by TCI twice daily, is recommended for most patients with moderate AD experiencing acute flares, regardless of lesion site. Emollients should be used regularly.
Conclusions: The algorithm presented intends to simplify treatment of AD in China and guide clinical decision-making.

Keywords: China; Consensus; Pimecrolimus

Key Summary Points

Why carry out this study?
Topical corticosteroids (TCS) are recommended as first-line therapy for patients with atopic dermatitis (AD) in China; however, corticophobia is a concern.
The aim of this article was to propose a practical TCS-sparing treatment algorithm for the management of infants, children, adolescents, and adults with mild-to-moderate AD, to guide daily clinical practice in China.
What was learned from the study?
All authors agreed on a TCS-sparing treatment algorithm for patients with mild-to-moderate AD, with a focus on pimecrolimus (and, when appropriate, tacrolimus) and emollient maintenance therapy
The algorithm presented here is intended to simplify the treatment of AD in daily practice in China.

INTRODUCTION

Atopic dermatitis (AD) is a chronic or chronically relapsing, pruritic, inflammatory skin disease [1, 2]. AD is one of the most common noncommunicable skin diseases, and is a global issue, with worldwide prevalence estimated at 15–20% in children (aged 6–14 years) and 1–3% in adults [3]. Prevalence is on the rise, notably in children [4]. Environmental aspects (e.g., air pollution) may influence the epidemiology of the disease, with the prevalence of AD in preschool children aged 3–6 years reportedly differing between urban and rural areas in China [5–7]. In addition, AD has a major impact on the quality of life (QoL) of patients and caregivers [8], who frequently experience depression, anxiety, suicidal ideation, and fatigue/insomnia [9–12].

The pathophysiology of AD is complex and is influenced by genetics [13], impairment of the epidermal barrier [13], the innate and acquired immune system [13], and the exposome (i.e., the sum of external factors an individual is exposed to), including the microbiome and pollution [14]. Due to the heterogeneous nature of the disease, it is characterized by various phenotypes and endotypes, based on and/or impacted by: age [15], disease severity [15, 16], chronicity (acute versus chronic) [15], epidermal barrier impairment (e.g., filaggrin [FLG] status: FLG^+ versus FLG^-) [15], immune dysregulation (e.g., immunoglobulin E status) [15], microbiome diversity [17], and environmental factors (e.g., air pollution) [5, 7, 18]. Etiological differences between European American, African American, and Asian patients (e.g., intrinsic versus extrinsic AD, immune polarization, epidermal thickness, genetic factors) also exist and influence the characterization of AD [15]. Stratification of AD by phenotypes and endotypes is therefore important for developing a patient-centric treatment strategy, distancing from the "one-size-fits-all" treatment model [15].

The treatment of mild-to-moderate AD generally comprises emollients, topical corticosteroids (TCS), and topical calcineurin inhibitors (TCI) [19], with other therapies (e.g., systemic

immunosuppressive agents, phototherapy, biologics) recommended for the management of severe or refractory disease [20, 21]. Currently, there are geographical differences in the management of AD across Asia, owing in part to significant diversity within the region regarding treatment access, socioeconomic circumstances, and cultural beliefs [22]. A survey of 255 dermatologists across Southeast Asia (based in Indonesia, Malaysia, the Philippines, Singapore, Thailand, and Vietnam) found considerable variation in how familiar the respondents were with diagnostic criteria, as well as differences in how and when TCS and TCI were used [22]; this highlights the need for consensus on the optimal treatment regimen [22]. In addition, complementary and alternative medicines (e.g., herbal preparations) are widely used [23]. However, the availability of data from randomized trials in patients with AD is limited [23–25], and the level of use in the management of AD in Asia remains unclear.

TCS are recommended as first-line therapy for short-term treatment of acute flares when lesions are unresponsive to basic therapy (and as long-term therapy for the prevention of relapses) [19]. There are many considerations when selecting a TCS, including galenic formulation, potency, patient age, and area of the body to which medication will be applied [19]. Although TCS have an important role in the management of AD [26], they are associated with several limitations. Corticophobia (i.e., worries associated with use of TCS) is a major consideration due to its potential impact on treatment adherence, and is therefore a widespread concern [27, 28]. In a survey of 300 parents of children with AD conducted in China, 96% were very concerned about the side effects of TCS; as a result, 42% did not use TCS in the event of AD recurrence [27]. Elsewhere, a study of 200 patients with AD in the United Kingdom found that one-third of patients with concerns about TCS admitted to noncompliance with their TCS regimen [29]; similarly, a study of 208 patients with AD in France found that approximately 81% of respondents had fears about TCS and 36% reported nonadherence to their treatment [30].

In addition, use of TCS is associated with skin barrier impairment, skin atrophy, increased risk of skin infections, tachyphylaxis, and misuse/addiction [31, 32]. As such, TCS are not recommended for long-term management or the treatment of sensitive skin areas, which is notably an issue given the chronic nature of AD and the fact that the disease often affects sensitive skin areas (e.g., face, neck, and flexures) [1, 19]. Sensitive skin areas therefore require further consideration when it comes to therapeutic decision-making, and there is a need for TCS-sparing treatment strategies, based on different clinical manifestations (e.g., age, severity of disease).

TCI offer a valid alternative, as they have similar efficacy to low-to-mid potency TCS, and are not associated with the same limitations, such as skin barrier impairment and skin atrophy [33–35].

The aim of this article is to propose a practical TCS-sparing treatment algorithm for the management of infants, children, adolescents, and adults with mild-to-moderate AD, to guide daily clinical practice in China. The algorithm focuses on the role of TCI in the treatment of mild-to-moderate AD, incorporating a TCS-sparing approach, and identifying the role of pimecrolimus for sensitive skin areas. The algorithm has been structured so that primary care physicians (who regularly see patients with AD), as well as pediatricians and dermatologists, can use it. It is intended to support evidence-based treatment guidelines available at both the international and national level.

METHODS

A panel of eight experts in AD from China and one expert from Germany (including dermatologists and pediatricians) was established to discuss and create a practical algorithm for the management of AD in patients from China. Professor Zhao and Professor Luger developed the initial draft of the algorithm. This was reviewed and modified with the other authors according to relevant expertise, local knowledge, guidelines, and literature. Ethical approval

was not required since no interventional studies were carried out.

RESULTS

Clinical Evidence for the Treatment of Mild-to-Moderate AD

Assessment of Severity of AD

Initial assessment of patients presenting with AD should account for patient age, and the site and severity of lesions, as these factors help to inform optimal management. Several scales are available to measure the severity of AD: Severity Scoring of Atopic Dermatitis (SCORAD), Eczema Activity Severity Index (EASI), Investigator Global Assessment (IGA), Patient-Oriented Eczema Measure (POEM), Dermatology Life Quality Index (DLQI), visual analog scale (VAS), and numeric rating scale (NRS).

These measures can also be combined to further define the severity of AD (mild: SCORAD < 15, EASI < 6; moderate: SCORAD 15–50, EASI 6–23; severe: SCORAD > 50–103; EASI > 23–72), ahead of treatment selection [36].

Maintenance Treatment with Emollients

Emollients are the mainstay, basic, and maintenance therapy for AD [19, 37]. Traditionally, they have been defined as topical formulations with vehicle-type substances lacking active ingredients [19]. However, in recent years, emollient "plus" formulations have been developed: topical formulations with vehicle-type substances and additional active, non-medicated substances [19]. Emollients comprise a combination of several components including humectants (e.g., lactate, urea,and glycerin) that have water-attracting properties to promote water retention in the stratum corneum (SC), occludents (e.g., petrolatum) to reduce evaporation, and lipids that may supplement the diminished lipid component of the SC [19, 38, 39].

Emollients are recommended in various national and international treatment guidelines to assist physicians in the management of children, adolescents, and adult patients with mild-to-moderate AD [15, 39–42]. Emollients improve symptoms of AD through several mechanisms: reduced pruritus [43], preserved barrier lipid content [44, 45], decreased susceptibility to irritants [46], reduced transepidermal water loss (TEWL) [43], and moisturization and hydration of the skin [43, 46]. Emollient enhancement of the skin barrier from birth may therefore offer an effective AD prevention strategy [47]. Finally, emollients decrease the need for TCS, offering a TCS-sparing treatment approach [48–50].

Antiinflammatory Treatment

A number of pathophysiological mechanisms are implicated in AD and interplay between these leads to inflammatory responses involving T cells, chemokines, and cytokines, driving the development of AD [51].

Topical antiinflammatories, applied directly to the site of inflammation, are central to effective management of AD. The two predominant classes are TCS (numerous different agents with differing potencies and formulations) and TCI (pimecrolimus and tacrolimus) [19]. TCI available for the treatment of AD in Asia are summarized in Table 1 [19, 26, 52–54].

Proactive (i.e., preventative) and intermittent therapy have been recommended to prevent acute flares [67, 68]. Proactive therapy is a combination of long-term, low-dose antiinflammatory treatment with TCI applied two to three times weekly to areas of skin previously affected by AD. Alternatively, intermittent therapy with TCI involves the resumption of treatment at the first signs of a new flare, i.e., pruritus. However, there are no data from randomized controlled clinical trials conducted to date to indicate that proactive therapy provides greater benefit versus intermittent therapy. Additionally, clinical studies investigating adherence to proactive therapy in patients with myocardial infarction showed suboptimal long-term adherence [69].

TCI should be considered an alternative treatment to reduce the use of TCS, as they are not associated with the same side effects. Pimecrolimus 1% cream is approved for mild-to-moderate AD in adults and children aged ≥ 2 years in several countries [53];

Table 1 Topical calcineurin inhibitors used in the treatment of AD in Asia [19, 26, 52–54]

	Recommendation(s) for clinical use		Strength and formulation
Pimecrolimus	Management of mild-to-moderate acute flares, in particular those on sensitive skin, but also on other nonsensitive body locations		Infants aged ≥ 3 months to 2 years[a] [55–66]; children aged ≥ 2 years, adolescents, and adults [53]: 1% cream
Tacrolimus	Management of moderate-to-severe acute flares	Proactive use	Children aged ≥ 2 to 15 years [54]: 0.03% ointment
			Children aged ≥ 16 years and adults [54]: 0.1% ointment

AD atopic dermatitis, *TCI* topical calcineurin inhibitors
TCI may not be available across all countries in Asia. Pimecrolimus is not available in Japan
[a]Australia, Brazil, Canada, European Union, India, Indonesia, Israel, New Zealand, Philippines, Russia, Taiwan, and Thailand only

pimecrolimus is also approved in infants aged ≥ 3 months (Australia, Brazil, Canada, European Union, India, Indonesia, Israel, New Zealand, Philippines, Russia, Taiwan, and Thailand) [55–64].

Tacrolimus ointment is available in a 0.03% formulation, approved for the treatment of moderate-to-severe AD in patients aged 2–-15 years; a 0.1% formulation is licensed for use in patients aged ≥ 16 years [54].

TCI in AD

Ethnicity (Caucasian versus non-Caucasian) had no effect on treatment outcomes with pimecrolimus in pediatric patients with AD [70]. Similarly, in an analysis of pooled data from studies conducted on adult and pediatric patients with AD in Asia, the efficacy and safety of tacrolimus was similar to that observed in studies in the USA, Europe, and Japan [71]. Hence, where data from studies not conducted specifically in Chinese patients are reported in this paper, results can be inferred to guide treatment practice in Chinese patients.

Steroid-Sparing Effects The steroid-sparing effects of pimecrolimus have been reported in numerous studies, irrespective of patient age and severity of disease [72–76]. In a 1-year, double-blind study in 251 infants (aged 3–-23 months) with AD, overall TCS use was substantially lower in patients receiving pimecrolimus versus conventional treatment (64% versus 35%, respectively) [72]. Pimecrolimus also reduced the need for rescue therapy with TCS in a study of 192 adults with moderate-to-severe AD; over a 24-week treatment period, TCS were used on 14% (95% confidence intervals [CI] 8.3, 21.1) and 37% (95% CI 30.4, 44.0) of days in the pimecrolimus versus control group, respectively ($p < 0.001$) [76]. Similarly, in a 26-week, randomized study in 543 patients (aged ≥ 18 years) with a history of mild-to-moderate AD, the mean number of TCS-free days was significantly higher in patients treated with pimecrolimus versus control (152 days versus 139 days; $p < 0.001$) at the first signs and/or symptoms of relapse/recurrence [74].

Rapid Relief from Pruritus Pruritus is a hallmark feature of AD that severely impacts QoL [77]; rapid relief is essential in the management of patients [78]. In a double-blind, vehicle-controlled, randomized study, 174 children and adolescents (aged 2–17 years) with mild-to-moderate AD and moderate-to-severe pruritus received twice-daily application of pimecrolimus or vehicle [78]. Median time to a ≥ 1 point improvement in pruritus score from baseline was significantly reduced in patients treated with pimecrolimus versus vehicle (48 versus 72 h, respectively; $p = 0.038$) [78]. In addition, significantly more patients achieved

complete resolution of pruritus by day 7 with pimecrolimus versus vehicle (37% versus 18%, respectively; $p = 0.008$) [78]. In infants with mild to very severe AD, rapid onset of action and no disease rebound after discontinuation was seen with pimecrolimus versus vehicle [79].

Reduction in pruritus has also been reported with tacrolimus. In a 6-week, multicenter, double-blind study in 317 patients aged 2–15 years with mild-to-moderate AD, pruritus scores were significantly lower in tacrolimus-treated patients versus vehicle-treated patients (2.1 versus 3.7, respectively; $p < 0.0001$) [80].

No Impairment of the Epidermal Barrier or Skin Atrophy A number of studies have reported the beneficial effects of pimecrolimus on the epidermal barrier. When applied to normal skin for 4 weeks, pimecrolimus did not cause skin atrophy, whereas significant epidermal thinning was reported with TCS [34]. Similar results were seen in an 8-week, investigator-blinded study in patients with mild-to-moderate AD comparing the effects of pimecrolimus and TCS on epidermal and dermal thickness [81]. Importantly, pimecrolimus was effective in patients with head and neck AD intolerant of, or dependent on, TCS [82]. Reversion of skin atrophy was also reported during TCS-free intervals [82]. In addition, after 3 weeks of twice-daily treatment with pimecrolimus or vehicle (one on each forearm) in patients with mild-to-moderate AD, there were significant improvements in skin hydration and TEWL with pimecrolimus versus vehicle [35]. Similarly, findings from a double-blind, randomized, placebo-controlled study in a combined group of patients with AD and healthy volunteers demonstrated that tacrolimus ointment, unlike TCS, did not cause skin atrophy [83].

Long-Term Efficacy and Safety In the 5-year, open-label, randomized, PETITE study, long-term safety and efficacy of pimecrolimus and TCS were assessed in 2418 infants (aged $\geq$ 3 months to $\leq$ 12 months) with mild-to-moderate AD [84]. After 5 years, in both groups, > 85% of patients were cleared/almost cleared of overall AD and > 95% of patients cleared/almost cleared of facial AD. The profile and frequency of adverse events were similar in the two groups: there was no evidence for impairment of humoral or cell-mediated immunity in either group [84]. In a separate study in infants and young children with mild-to-severe AD, pimecrolimus treatment for up to 2 years was well tolerated and led to sustained improvements in disease [85].

Various noncomparative trials support the long-term efficacy and safety (up to 1–4 years of treatment) of tacrolimus 0.1% or 0.03% ointment in children, adolescents, and adults with moderate-to-severe AD [86–89].

Improvement of QoL Pimecrolimus improved the QoL of both patients' and caregivers' in various trials [76, 90–92]. In two trials reporting the effects of pimecrolimus in infants (aged 3 months to 2 years), children (aged 2–17 years), and parents, pimecrolimus significantly improved QoL versus control in all groups assessed [90].

Tacrolimus led to significant improvements in health-related QoL versus vehicle in children aged $\geq$ 2 years and adults with AD [93]. In addition, in Japanese patients with corticophobia ($n = 35$), following 12 weeks of treatment with tacrolimus ointment, overall QoL score significantly improved from baseline at the end of the study ($p < 0.001$) [94].

Reduction in AD Flares In previously mentioned studies, pimecrolimus cream was associated with significantly fewer AD flares versus vehicle in infants, children, adolescents, and adults with AD [72–76, 95].

Sensitive Skin Areas TCI have greater selectivity versus TCS in targeting cells involved in the inflammatory response at sites affected by AD [96]. As such, TCI (in particular, pimecrolimus) are preferred over TCS in sensitive skin areas [39], and are recommended by European guidelines for the treatment of facial lesions [19]. In terms of TCS, we recommend use for a short period, followed by TCI, in the treatment of acute flares of moderate AD on sensitive skin.

Tolerability and Acceptability The most common treatment-related adverse events with pimecrolimus are application site reactions, including feelings of warmth and/or burning, pruritus, and erythema/irritation [97]. In various trials, application site reactions following treatment with pimecrolimus were transient and/or mostly mild-to-moderate in severity [73–75, 98].

In two randomized studies of tacrolimus ointment (0.03% or 0.1%) versus vehicle, the most common adverse events with significantly greater incidence than in the vehicle group were sensation of skin burning, flu-like symptoms, and headache; symptoms generally resolved within the first few days of treatment [99]. However, in the authors' clinical experience, flu-like symptoms and headache have not commonly been reported with real-world application of tacrolimus.

In a 6-week, investigator-blinded study comparing pimecrolimus ($n = 71$) with tacrolimus ointment 0.03% ($n = 70$) in patients (aged 2–17 years) with moderate AD, incidence of erythema/irritation was less common (8% versus 19%; $p = 0.039$) and shorter duration (erythema/irritation lasting > 30 min: 0% versus 85%; $p < 0.001$) in pimecrolimus-treated versus tacrolimus-treated patients, respectively [100]. Warmth, stinging, and burning were similar between groups; however, adverse events lasting > 30 min were less common in the pimecrolimus group versus tacrolimus (0% versus 67%; $p < 0.001$) [100]. In addition, pimecrolimus was preferred to tacrolimus ointment across many product features (i.e., ease of application, suitability for face, nonsticky feel, ease of rub-in, and spreadability), with more patients rating ease of application as "excellent" or "very good" (76% versus 59%, respectively; $p < 0.02$) [100].

Langerhans cells (LCs) are specialized antigen-presenting cells in the epidermis with a pivotal role in cutaneous immune surveillance [101, 102]. In contrast to TCS, which led to depletion of LCs, pimecrolimus did not affect LCs in studies of murine epidermis, and healthy and atopic human skin [101–103]. Tacrolimus was shown to influence the maturation of LCs in vitro; however, in patients with AD, tacrolimus depleted inflammatory dendritic epidermal cells, with no apoptosis of LCs reported [104].

In terms of systemic effects, permeability of pimecrolimus through the skin is lower compared with tacrolimus (9–10 times slower), and much less than TCS (70–110 times slower) [104], decreasing the likelihood of transcutaneous resorption following topical administration, and leading to a reduced risk of systemic effects (e.g., hypothalamic–pituitary–adrenal axis suppression, Cushing's syndrome, femoral head osteonecrosis, and cataracts) [104]. This may be due, in part, to the higher lipophilicity of pimecrolimus (versus tacrolimus and TCS) [105].

Finally, long-term safety data illustrate no evidence that TCI cause skin malignancies and/or lymphomas [53, 106].

Other Treatments for Severe AD

The majority of cases of AD are mild to moderate in severity, although a subpopulation of patients suffer from severe eczematous skin lesions [36]. Tacrolimus is indicated for the treatment of moderate-to-severe AD [54]; there is some evidence supporting the use of pimecrolimus in this patient population [107]. However, several systemic immunosuppressive therapies are also recommended or under investigation in patients with moderate-to-severe or severe AD [20]. Dupilumab (anti-IL4Rα) [108–110] and cyclosporine A [111–113] are both approved treatments (although cyclosporine A is not approved by the Food and Drug Administration [FDA]), and methotrexate [114, 115], azathioprine [116], mycophenolate mofetil [117, 118], nemolizumab (anti-IL31Rα) [119], tralokinumab (anti-IL13) [120], and Janus kinase (JAK) 1/2 and JAK1/3 inhibitors (e.g., baricitinib [121], abrocitinib [122], tofacitinib [123]) have been investigated and have shown efficacy in this population of patients. Other biologics, such as tezepelumab (anti-thymic stromal lymphopoietin), are also under investigation in early-phase trials [124]. In addition, short-term use of systemic corticosteroids is noted in Asia-Pacific guidelines [125], and

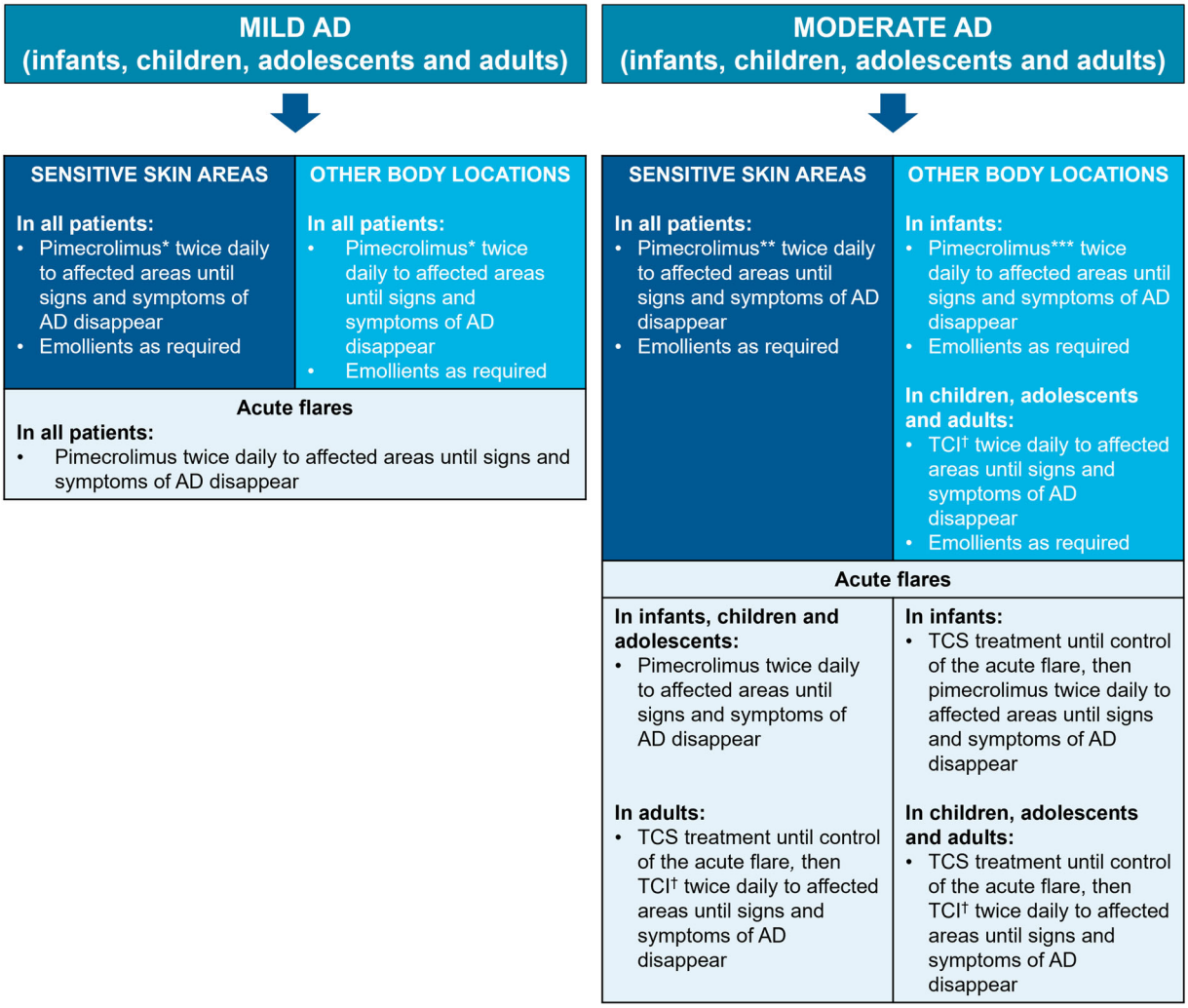

Fig. 1 Algorithm for the treatment of infants, children, adolescents, and adults with mild-to-moderate AD. *AD* atopic dermatitis, *EU* European Union, *TCI* topical calcineurin inhibitors, *TCS* topical corticosteroids. *Pimecrolimus 1% cream is indicated for mild-to-moderate AD (children aged ≥ 2 years, adolescents, and adults) [53] and for use in infants aged ≥ 3 months (Australia, Brazil, Canada, European Union, India, Indonesia, Israel, New Zealand, Philippines, Russia, Taiwan, and Thailand only) [55–66]. **Pimecrolimus is recommended in EU guidelines [19] in sensitive skin areas; evidence suggests patient preference for pimecrolimus versus tacrolimus [100]. ***Pimecrolimus is recommended in other body locations versus tacrolimus, as there is a body of evidence to support its efficacy and tolerability profile. †TCI: pimecrolimus 1% cream, or tacrolimus 0.1% (aged ≥ 16 years) or 0.03% (aged 2–15 years) ointment; pimecrolimus is indicated for mild-to-moderate AD, and tacrolimus is indicated for moderate-to-severe AD [53, 54]

occasionally used in China. Finally, phototherapy (e.g., narrow-band ultraviolet B) is recommended in European guidelines [19], and has resolved clinical disease in patients with moderate-to-severe AD [126]. However, patient age and affected body regions must be carefully considered before administering these therapies, and systemic treatment should be reserved for persistent, widespread AD that is unresponsive to other treatment [19, 125], or for patients with prolonged use of high-potency TCS [127]. Regardless of chosen therapy, this should be supplemented with local treatment with TCS and/or TCI [19, 20].

DISCUSSION

TCS-Sparing Treatment Algorithm for Mild-to-Moderate AD in China

Following discussions, all authors agreed on a TCS-sparing treatment algorithm for patients with mild-to-moderate AD, with a focus on pimecrolimus (and, when appropriate, tacrolimus) and emollient maintenance therapy in infants, children, adolescents, and adults (Fig. 1).

CONCLUSIONS

AD is one of the most common noncommunicable skin diseases, and a major issue globally and in China. Currently, there is a need for treatment approaches that reduce the use of TCS, owing to their association with corticophobia, adverse events and misuse, and lack of suitability for long-term treatment of AD. We recommend the use of emollients to prevent disease flares. We also recommend a TCS-sparing treatment strategy, focusing on the role of TCI (notably pimecrolimus 1% cream) in the management of infants, children, adolescents, and adults with mild-to-moderate AD. The algorithm presented here is intended to simplify the treatment of AD in daily practice in China.

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