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REVIEW ARTICLE

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A practical algorithm for the treatment of mild-to-moderate atopic dermatitis (AD) in pediatric patients in Europe: expert recommendations

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ABSTRACT

Background: Atopic dermatitis (AD) is a chronic inflammatory skin condition, considered to be the most common cutaneous-related disease in children; early management in infancy with treatments of acceptable efficacy and safety has been recognized as important for outcomes.

Methods: An international panel of six European dermatologists and pediatric specialists was formed to discuss and develop a practical algorithm for the management of AD in pediatric patients in a European setting. The discussion combined a comprehensive review of published literature with clinical experience.

Results: Current guidelines recommend topical corticosteroids (TCS) as a first-line anti-inflammatory treatment for short-term AD flares, with specific recommendations for pediatric populations and sensitive areas of skin; however, due to the lack of long-term utility and associated side effects with TCS, there is a need for alternative treatments.

Conclusion: In this article, we propose an algorithm for a TCS-sparing treatment strategy, focusing on topical calcineurin inhibitors for the management of mild-to-moderate AD in infants and children, including AD of sensitive skin areas. This algorithm is intended as a supplementary tool to the current international and national evidence-based treatment guidelines, and to aid physicians who see and treat children with AD in their clinical practice.

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1. Introduction

Atopic dermatitis (AD) is a chronic, inflammatory skin disorder (1), characterized by great heterogeneity, with varying signs and symptoms, severity, extent, longitudinal course, and treatment responses (2). Key features of AD include a defect in the skin barrier (1), immune dysregulation, and inflammation. AD is recognized as a global issue, affecting up to 20% of children and approximately 3% of adults worldwide (3). The onset of AD occurs predominantly in childhood (3), with approximately 85% of patient cases beginning before the age of 5 years (4). It is the most common skin disease in pediatric patients (5) and its prevalence is on the rise (3). The impairment of quality of life caused by childhood AD (which affects all aspects of the lives of children and their families including physically, socially, and psychologically) is reported to be greater than or equal to other childhood diseases (e.g. asthma and diabetes) (6).

The clinical manifestation of AD is directly impacted by factors such as age, disease chronicity, ethnicity, presence of filaggrin mutation, immunoglobulin E levels and underlying molecular mechanisms (4). AD may be sub-classified into different subtypes, or phenotypes, based on its presentation (4). Each subtype has distinct underlying molecular mechanisms (endotypes); subtyping according to endotypes could provide a more precise and efficient method of AD classification compared with phenotype-based subtyping, and facilitate personalized and tailored treatment strategies for patients with AD (4). Currently, there are several novel endotype-based treatments for AD in various stages of clinical development (4), so we may witness a shift in the treatment paradigm moving forward. However, in current clinical practice, a "one-size-fits-all" approach is often used for treatment: emollients, topical corticosteroids (TCS), and topical calcineurin inhibitors (TCI) are used to treat mild-to-moderate AD, while other therapies, such as systemic treatments, are recommended for the management of severe forms of the disease (7).

In the pediatric population, TCS are recommended as first-line therapy for short-term treatment of acute flares (7), with many compounds and formulations of varying potency available (8). Although TCS have an important role in the management of AD (7,9), several limitations have been described with their use, including skin-related side effects and the risk of systemic adverse events (7–9). As such, potent TCS are unsuitable for long-term treatment on sensitive skin areas (e.g. the face) (9). In view of these limitations, alternatives to TCS are needed for long-term management of AD for infants and children, and AD of sensitive skin areas.

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Several treatment strategies for TCS sparing have been described in the literature, including optimized use of emollients (10), use of emollient 'plus' creams (11), avoidance of allergens (7), proactive treatment to prevent flare relapse (5), early utilization of TCI in specific clinical situations (5), new biologic drugs (5), restitution of the skin or gut microbiomes (12), and patient and parent, guardian, or carer education (13). Specifically for TCI, evidence has shown that they are as effective as TCS for the treatment of mild-to-moderate AD in pediatric patients with sensitive skin AD (14–17), thus offering a promising alternative as a steroid-sparing treatment.

The aim of the current article is to propose a practical TCS-sparing treatment approach for the management of infants and children with mild-to-moderate AD, including AD of sensitive skin areas, to guide daily clinical practice in Europe. The algorithm presented here is intended to supplement international and national evidence-based treatment guidelines.

2. Materials and methods

An international panel of six European dermatologists and pediatric specialists, from Germany, Italy, Poland, and Spain, was formed to discuss and develop a practical algorithm for the management of AD in pediatric patients in a European setting. The discussion combined a comprehensive review of published literature with clinical experience. Ethical approval was not required, as no interventional studies were conducted.

3. Results

3.1. Treatments for mild-to-moderate atopic dermatitis

Management of AD, like other chronic illnesses, is life-long. In 2021, a European Expert Panel of dermatologists and pediatric allergologists concluded that the treatment of AD should be initiated as early as infancy to prevent worsening of the skin, prevent the development of atopic comorbidities, and decrease the significant burden of AD on both families and society (18). Mild-to-moderate AD is generally treated with emollients, TCS, and TCI (7), considering factors such as side effects, tachyphylaxis, adherence, long-term disease control, prevention of comorbidities, and cost (including indirect costs, such as costs of managing side effects and health-related quality of life) (18).

3.1.1. Emollients

Emollients are topical formulations with vehicle-type substances without active ingredients, and are considered the mainstay baseline therapy for AD (7). Recently, newer emollient "plus" creams containing active, non-pharmacological agents have emerged, which may also possess anti-pruritic and anti-inflammatory effects, depending on their composition (19).

3.1.2. Topical corticosteroids

In Europe, TCS are recommended as a first-line anti-inflammatory treatment, to be used for the treatment of short-term AD flares, with specific recommendations for pediatric populations and sensitive areas of skin (7). In children, low-to-moderate potency TCS should be used; higher potency TCS may be used for the treatment of short-term flares in adolescents and adults (7). Treatment of the face, especially the peri-orbital region, or other sensitive areas, should be restricted to use of low-to-moderate potency TCS (7). Treating sensitive areas, such as the face, with TCI whilst treating other affected body areas with TCS is also common practice (7).

Although TCS are effective at reducing symptoms associated with inflammation (7), their widespread use is associated with several adverse effects. In particular, TCS can contribute to the disruption of the skin barrier in AD, and prolonged use may lead to side effects such as skin atrophy, purpura, striae, tachyphylaxis, telangiectasia, hypertrichosis, acneiform or rosacea-like eruptions, and increased risk of skin infections (7–9). In addition, TCS have been linked with the possibility of systemic adverse events, such as hypothalamic-pituitary-adrenal axis suppression and, rarely, hyperglycemia, and linear growth suppression when used in children (9,20). The use of TCS in children is also limited by resistance amongst carers of children with AD, hampering treatment adherence (5). Therefore, alternatives to TCS for long-term management of AD in pediatric patients are needed.

3.1.3. Topical calcineurin inhibitors

The European guidelines for topical treatment of AD recommend use of TCI for treating AD in children and areas of sensitive skin (7). Two TCI are currently licensed in Europe for topical treatment of AD in children – pimecrolimus 1% cream and the 0.03% formulation of tacrolimus ointment (21,22). Tacrolimus ointment is approved for treatment of moderate-to-severe AD in children of 2 years and older (22). In contrast, pimecrolimus has been approved for the treatment of mild-to-moderate AD in infants aged ≥ 3 months in several global regions (18), including the recent approval in this age group in Europe, constituting the only topical calcineurin inhibitor to be approved in infants from 3 months of age by the European Medicines Agency (21).

Tacrolimus ointment has demonstrated long-term efficacy in children with moderate-to-severe AD, with adverse events such as skin burning and pruritus being transient and mostly of mild-to-moderate severity (23). In a Phase III trial of children aged 2–15 years with moderate-to-severe AD, across Europe and Canada, short-term use of tacrolimus ointment (0.03% and 0.1% formulations) was significantly more effective than 1% hydrocortisone acetate ointment ($p < 0.001$), with 0.1% tacrolimus more effective than 0.03% tacrolimus ($p = 0.006$) (24). Moreover, in a study of children aged 2–15 years with AD (mean study duration of 16.3 months), tacrolimus ointment showed notable improvement of disease severity (median Eczema Area and Severity Index score, median percent body surface area affected and median itch score) after 2 weeks of therapy, that was maintained throughout the study (23).

Pimecrolimus 1% cream has also demonstrated efficacy in infants with AD in both the short- and long-term (25,26). Treatment with pimecrolimus for the early signs and symptoms of AD improved long-term outcomes in infants (aged 3–23 months), and significantly reduced the incidence of flares compared with the control ($p < 0.001$): 67.6% of infants treated with pimecrolimus vs. 30.4% treated with control had no flares at 6 months and 56.9% vs. 28.3%, respectively, had no flares at 12 months (25). Moreover, pimecrolimus showed improvement of disease severity in infants (>80% improvement in median Eczema Area and Severity Index score) after 6-weeks versus vehicle control in a double-blind trial, and sustained efficacy and safety during a 20-week open-label follow-up phase (26).

In a 5-year open-label study, pimecrolimus had similar efficacy to low- and medium potency TCS for the long-term management of mild-to-moderate AD in infants (aged 3–12 months), with more than 85% and 95% of patients who received pimecrolimus or TCS, respectively, achieving overall (pimecrolimus, 88.7%; TCS, 92.3%) and facial treatment success (pimecrolimus, 96.6%; TCS, 97.2%) (14). In

addition, a recent meta-analysis, which included data from 27 studies, found that among children the efficacy of pimecrolimus was similar to that of tacrolimus ointment and low- to medium-potency TCS, with a favorable safety profile (17). These studies suggest that pimecrolimus is as effective as low- and medium potency TCS and support the use of pimecrolimus as a first-line treatment of mild-to-moderate AD in pediatric patients. Further, it has been suggested that the good efficacy profile demonstrated by pimecrolimus can have a direct positive impact on the quality of life of parents or guardians of children with AD, further highlighting its value as a treatment for pediatric-onset AD (27).

TCI have also demonstrated efficacy in sensitive skin areas, such as the face and skin folds. In particular, pimecrolimus was effective in clearing or almost clearing facial AD in almost 50% of patients with head and neck AD intolerant of, or dependent on, TCS (46.5% vs. 16.2% in the control group) (28). In a 6-month open-label study, incorporation of pimecrolimus into patients' standard treatment regimens was well tolerated and improved facial AD lesions in approximately two-thirds of patients (29). Further, in a randomized study of patients aged 2–17 years, pimecrolimus was rated significantly higher for suitability for use on sensitive facial skin versus tacrolimus ointment (0.03% formulation) (30). Pimecrolimus tended to have a greater effect on the head/neck versus tacrolimus ointment (30).

Despite the lack of an established causal relationship, safety concerns were raised around a potential risk of malignancies, namely skin cancer and lymphoma, in patients treated with TCI (18). In January 2006, the United States (US) Food and Drug Administration added a boxed warning ('black box') to the labels of pimecrolimus and tacrolimus ointment to emphasize that their long-time safety had not been confirmed (9,18). Notably, a higher incidence of lymphoma has been described in patients with AD compared with matched controls, thus the possibility of a pediatric patient developing a malignancy later in life cannot be eliminated; nonetheless, use of TCI has not been associated with higher risk of cancer (7,18). Following a review of clinical trial data, post-marketing studies and epidemiological study evidence, the 2021 consensus paper on AD in infants by the European Expert Panel concluded that safety concerns regarding pimecrolimus were no longer valid, and that pimecrolimus offered an alternative of comparable efficacy and safety with TCS in infants aged ≥ 3 months (18). Furthermore, a systematic review and meta-analysis published in 2023 confirmed that, amongst individuals with AD, TCI did not increase the risk of cancer, supporting their use in the optimal treatment of patients with AD (31).

The current European guidelines recommend the use of TCI or TCS for both mild and moderate AD in children (7). While >75% of the guideline's authors recommended the use of TCS as anti-inflammatory agents, TCI were recommended by all of the guideline's authors in areas of the skin where atrophy may be an issue (7). The side effects listed in the guidelines are more severe for TCS than for TCI, including skin atrophy, hypertrichosis, and telangiectasia. In comparison, site reactions, such as tingling and burning, reported with TCI are transient and rarely lead to discontinuation of treatment (7,28,29). Additionally, monitoring of cutaneous side effects is recommended for patients on long-term potent TCS (7).

The TCS-sparing effects of TCI have been previously described in the literature; one study in pediatric patients found that almost 60% of patients who received pimecrolimus at the first sign of a flare did not need to receive TCS throughout the duration of the study (32). More recently, evidence supporting TCS sparing was published in a systematic literature review, which advocated for the use of steroid-sparing medications, such as TCI, as options of favorable safety profile with minimal adverse events for managing pediatric AD (15). However, more studies on treatment with TCI reported burning and pruritus compared with treatment with TCS, and it was recommended that these adverse events are considered when treating infants and children (15). Proactive therapy with twice-weekly applications of the TCI tacrolimus ointment can also reduce relapse flares and can be as effective as using a potent TCS (7).

3.1.4. Other topical treatments and interventions

Several other topical treatments have been approved for the management of AD in pediatric patients. For example, the topical Janus kinase (JAK) inhibitor, ruxolitinib has been approved in the US and delgocitinib has been approved in Japan (7). Other JAK inhibitors (e.g. brepocitinib, tofacitinib) are currently being investigated, but none have been approved for the treatment of AD in Europe (5,7). The phosphodiesterase-4 inhibitor, crisaborole, while approved for the treatment of mild-to-moderate AD in several countries, is not commercially available in Europe (5,7). Roflumilast, another phosphodiesterase-4 inhibitor has been approved in the US for the treatment of patients aged 6 years and older with mild-to-moderate AD (33) and tapinarof, an aryl hydrocarbon receptor agonist, has been approved in the US for the treatment of AD in adults and children aged 2 years and older (34). Other potential treatments, which are currently under investigation, include microbial products (*Roseomonas mucosa*, *Staphylococcus hominis* A9) (35).

Education around the efficacy and safety of available topical treatments for AD for all individuals involved in the care of children with skin disorders, in particular pediatricians and family physicians, who regularly see and treat infants and children, is fundamental in the management of AD in order to address any concerns (e.g. potential side effects of treatments), encourage treatment of AD early in the disease course, reduce the negative impact on health-related quality of life, and improve adherence (6).

3.2. Topical corticosteroid-sparing algorithm

Following author discussions, we recommend TCS-sparing treatment algorithms for pediatric patients with mild-to-moderate AD (Figures 1 and 2). The aim of the algorithms is to simplify the

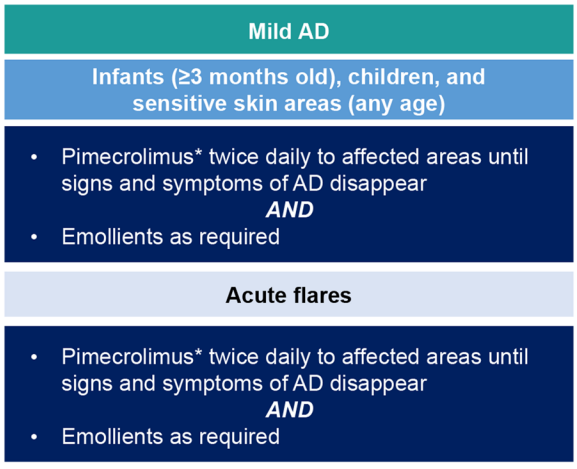

Figure 1. Algorithm for the treatment of mild AD in infants and children, and for mild AD of sensitive skin areas.
Acute flare is defined as a clinically significant worsening of signs and symptoms of AD requiring therapeutic intervention (6).
*Pimecrolimus 1% cream is indicated for treatment of mild-to-moderate AD in infants aged ≥ 3 months (21). AD, atopic dermatitis.

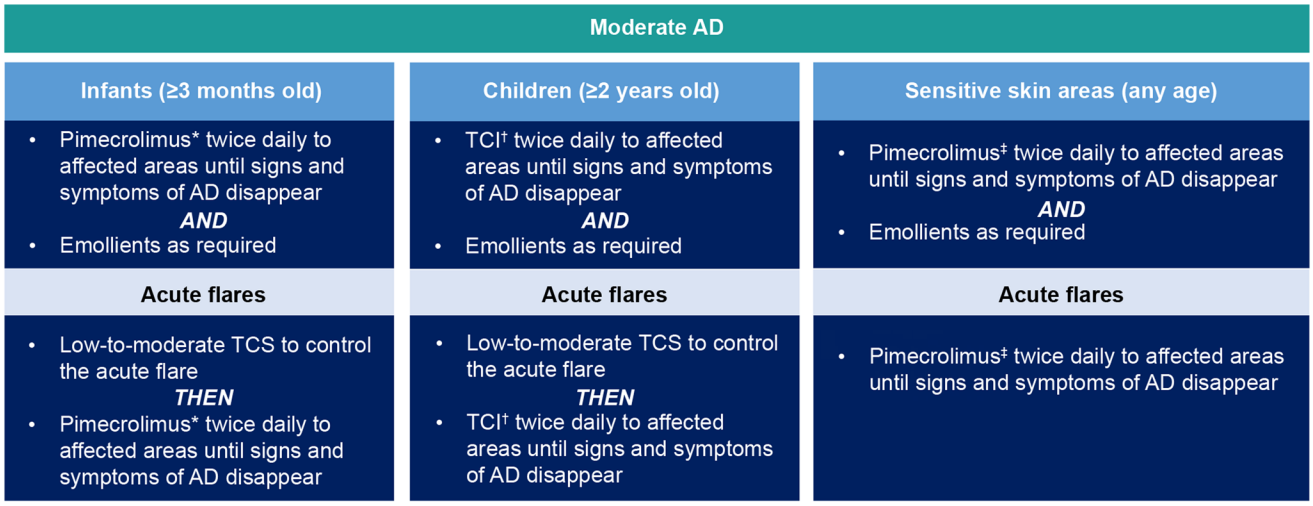

Figure 2. Algorithm for the treatment of moderate AD in infants and children, and for moderate AD of sensitive skin areas.
Acute flare is defined as a clinically significant worsening of signs and symptoms of AD requiring therapeutic intervention (6).
*Pimecrolimus 1% cream is indicated for treatment of mild-to-moderate AD in infants aged ≥ 3 months (21). †Pimecrolimus 1% cream from age ≥ 3 months; tacrolimus 0.03% ointment from age 2 years to 15 years (21,22). ‡Pimecrolimus is recommended as a first-line treatment of mild-to-moderate AD in the 2022 European guidelines (7). AD, atopic dermatitis; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids.

topical treatment of mild-to-moderate AD in infants and children, including AD of sensitive skin areas, before resorting to TCS. Pimecrolimus cream twice daily and emollients (as required) should be used for the treatment of mild AD (including for acute flares; Figure 1) and for the treatment of infants and those with sensitive skin areas diagnosed with moderate AD (Figure 2). Meanwhile, pimecrolimus cream or tacrolimus ointment twice daily and emollients (as required) should be used for children (≥ 2 years old) with moderate AD (Figure 2). Using the TCS-sparing treatment management approach in combination with regular emollient use may also reduce the risk of recurrence of disease flares. Notably, we encourage the use of low-to-moderate TCS to control acute flares in infants and children with moderate AD before treatment with pimecrolimus cream (or tacrolimus ointment in children but not infants).

4. Conclusions

AD is a chronic condition, which is associated with significant comorbidities and requires early treatment and long-term treatment strategies. Currently, there is a need for alternative treatments to TCS due to the associated side effects and lack of long-term potency. In this article, we propose a TCS-sparing treatment algorithm for the management of mild-to-moderate AD in infants and children, including AD of sensitive skin areas. Further prospective real-world studies are needed to reconfirm the benefits of this approach, especially since the recommendations presented in this article are based on collective clinical experience (through structured discussions) and available evidence (from a review of the current literature) thus limitations such as potential selection bias and reliance on expert opinions may have been introduced. Collaboration between dermatologists, pediatricians, family care physicians, and other healthcare providers for infants and children will be important in achieving effective and tolerable long-term management of pediatric AD. Additionally, it may be necessary to adapt the treatment algorithm in different locations and regions, to account for local factors including differences in healthcare systems, genetic backgrounds, and AD prevalence.

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Ethics approval and patient consent statement

Ethical approval and patient consent were not required, as no interventional studies were conducted.

Author contributions

All authors were involved in the development of the manuscript from inception and have commented on previous versions. All authors read and approved the final manuscript.

Disclosure statement

MA served as a consultant, lecturer, researcher, and/or received research grants from companies producing atopic dermatitis drugs, including AbbVie, Almirall, Bayer, Beiersdorf, Eli Lilly, Galderma, Incyte, La Roche Posay, LEO Pharma, Menlo, MSD, Novartis, Pfizer, Regeneron, Sanofi-Genzyme, Trevi and Viatris. TL participated as a Principal Investigator in clinical trials, attended advisory boards and gave lectures sponsored by Almirall, Novartis, Pfizer, Sanofi, and Viatris; received consultancy/speaker honoraria from Almirall, Galderma, Janssen, La Roche Posay, Mylan, Novartis, Sanofi, and Viatris; acted as a scientific advisory board member for AbbVie, Celgene, CERIES, Galderma, Janssen, La Roche Posay, Pfizer, Symrise, and Viatris; and received research grants from Celgene, Janssen-Cilag, LEO Pharma, Pfizer, and Viatris. CP received honoraria from Viatris and is a consultant for PinCell s.r.l. AR worked as a consultant/speaker for AbbVie, Almirall, Alvotech, AstraZeneca, Bioderma, Celgene, Chema Elektromet, Eli Lilly, Galderma, Janssen,

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Data availability statement

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