


# Practical algorithm to inform clinical decision-making in the topical treatment of atopic dermatitis

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## Abstract

Atopic dermatitis is a chronic relapsing, inflammatory skin disorder associated with skin barrier dysfunction, the prevalence of which has increased dramatically in developing countries. In this article, we propose a treatment algorithm for patients with mild-to-moderate and severe atopic dermatitis flares in daily clinical practice. An international panel of 15 dermatology and allergy experts from eight countries was formed to develop a practical algorithm for the treatment of patients with atopic dermatitis, with a particular focus on topical therapies. In cases of mild-to-moderate atopic dermatitis involving sensitive skin areas, the topical calcineurin inhibitor pimecrolimus should be applied twice daily at the first signs of atopic dermatitis. For other body locations, patients should apply a topical calcineurin inhibitor, either pimecrolimus or tacrolimus, twice daily at the first signs of atopic dermatitis, such as pruritus, or twice weekly in previously affected skin areas. Emollients should be used regularly. Patients experiencing acute atopic dermatitis

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flares in sensitive skin areas should apply a topical corticosteroid twice daily or alternate once-daily topical corticosteroid/topical calcineurin inhibitor until symptoms improve. Following improvement, topical corticosteroid therapy should be discontinued and patients switched to a topical calcineurin inhibitor. Maintenance therapy should include the use of pimecrolimus once daily for sensitive areas and tacrolimus for other body locations. This treatment algorithm can help guide clinical decision-making in the treatment of atopic dermatitis.

#### KEYWORDS

algorithm, atopic dermatitis, pimecrolimus, tacrolimus, therapeutics

## 1 | INTRODUCTION

Atopic dermatitis (AD) is a common chronic disease characterized by general skin dryness, eczematous lesions, and pruritus.<sup>1</sup> The worldwide prevalence of AD is estimated at 15–20% in children (aged 6–14 years) and 1–3% in adults;<sup>2</sup> however, there is substantial variation between countries,<sup>3</sup> and increases in the prevalence of AD have been observed over the past decade in developing countries.<sup>4</sup>

In China, the prevalence of AD in children has increased from 3% in 2004<sup>5</sup> to 13% in 2016,<sup>6</sup> although variations between urban and rural areas have been observed.<sup>5</sup> In Turkey, the prevalence of AD in children was 5% in 1994, 10% in 2004, and 7% in 2014,<sup>7</sup> and data published from Ukraine in 2018 reported that the prevalence of AD in children aged between 8 and 9 years in the Poltava region was 5%.<sup>8</sup> In 2010, a 10% prevalence of AD was observed in children from rural and urban areas of Belarus.<sup>9</sup> In Russia, data published between 2006 and 2016 reported that the incidence of AD was 6.2–15.5%, and was region dependent.<sup>10,11</sup> In 2016, 72% of all patients with AD were children (0–17 years old); 41% of these cases were among children aged 0–4 years.<sup>11</sup> The prevalence of AD among children aged 15–17 years was 1.16%.<sup>10,11</sup> In a study of allergic diseases conducted in Russian adolescents, the prevalence of AD was shown to be up to 5-times greater than that reported in official statistics.<sup>12</sup>

Alongside regional differences in the prevalence of AD, the progress and symptoms of AD can differ between races. Recent studies involving Asian, European American, and African American children and adults with AD have shown that AD is a complex disease characterized by different phenotypes related to age, chronicity of the disease, race, epidermal barrier, immunological status, and molecular endotypes.<sup>13,14</sup>

Events that happen during the first 1000 days of life, including those that occur during gestation, may increase an individual's predisposition to developing AD.<sup>15</sup> The microbiome of the intestine and skin have been found to play an important role in AD; dysbiosis of both the gut and skin microbiome have recently been linked to alterations in immune responses, and can result in skin diseases, such as AD.<sup>16,17</sup> Frequent use of antimicrobials, as well as early use of antibiotics, has been associated with changes in

the gut microbiome, which has also been associated with AD.<sup>18–22</sup> Infants with *Staphylococcus epidermidis* or *Staphylococcus hominis* colonization experience milder AD than those colonized by *Staphylococcus aureus*.<sup>17,23</sup> Furthermore, studies investigating *S. aureus* colonization have shown that certain strains of *S. hominis* can prevent *S. aureus* colonization on the skin of patients with AD.<sup>17</sup> The increasing prevalence of AD in some developing countries may be attributed to lifestyle changes, including a Western diet.<sup>24</sup> Furthermore, food allergy is an increasingly common precursor to AD,<sup>25,26</sup> and is predisposed by food avoidance during infancy and childhood.<sup>27,28</sup>

Atopic dermatitis negatively impacts quality of life of patients and caregivers<sup>29,30</sup> and can predispose to mental health disorders,<sup>31–34</sup> highlighting that the prevention of AD progression must be considered through early and effective treatment. Proactive maintenance treatment, where therapies are applied in the absence of visible lesions, may also be required. Early diagnosis of AD is necessary for timely implementation of treatment and to prevent comorbid diseases by reducing contact with pro-inflammatory agents;<sup>35,36</sup> late diagnosis and subsequent undertreatment can lead to significant complications and further increases the burden of AD.<sup>37</sup> The general strategies adopted for treating AD should be adapted based on the patient's location, as geographical and genetic differences can lead to varying prevalence, presentation of symptoms, and availability of health care.<sup>38</sup>

In this article we propose a treatment algorithm for the management of patients with mild-to-moderate AD and severe flares in daily clinical practice, with a particular focus on topical treatments.

## 2 | METHODS

An international panel of 15 dermatology and allergy experts from eight countries (Belarus, China, Germany, Jordan, Russia, Turkey, Ukraine, and the United Arab Emirates) met to develop a practical algorithm for the treatment of patients with AD. The algorithm was developed based on a review of published treatment guidelines on AD, the experts' clinical experience, and an evaluation of relevant literature published up to May 2018.<sup>39–46</sup> The treatment algorithm has

been adapted for use in the Middle East<sup>47</sup> and in Asia<sup>48</sup> by separate groups of experts from these regions.

### 3 | TREATMENT ALGORITHM

The proposed algorithm for the treatment of AD is detailed in Figure 1.

#### 3.1 | Identification and early management of AD

The severity of AD should be established based on clinical signs, the extent of the disease, and patient-reported symptoms to determine the appropriate treatment options. The SCORing Atopic Dermatitis (SCORAD) clinical tool allows an assessment of AD severity based on clinical signs, including erythema, edema/papulation, and oozing/crusts, as well as subjective symptoms (pruritus and sleep loss).<sup>49</sup> Early disease control, such as the use of emollients and avoidance of environmental triggers (e.g., food allergies), may prevent AD persisting into later life and possibly, the atopic march to allergic rhinitis and asthma.<sup>50,51</sup> Furthermore, the effective treatment of mild-to-moderate AD lesions can prevent patients developing a more severe form of the disease.<sup>50,51</sup>

Education programs for health-care professionals in multiple specialties can ensure timely identification and diagnosis of AD, for instance, training for general practitioners to refer patients with a history of AD to a physician experienced in management of AD. In addition, workshop-style sessions could be established in health-care settings to educate patients and their families about AD and lifelong management.

#### 3.2 | First-line treatment according to proposed algorithm: mild-to-moderate AD

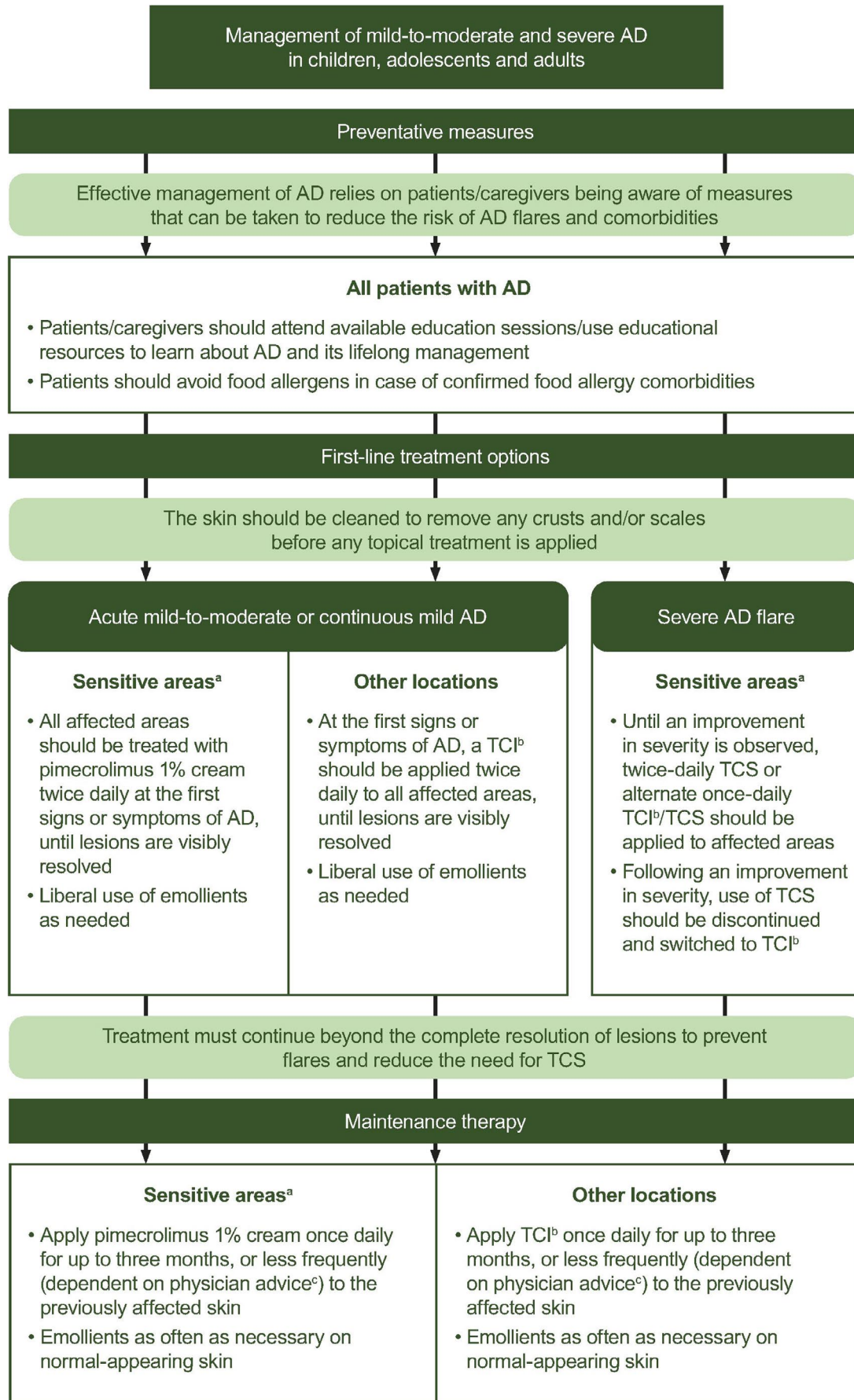
The topical calcineurin inhibitors (TCI) pimecrolimus and tacrolimus are licensed for the treatment of AD.<sup>44,52-54</sup> Tacrolimus 0.03% ointment is approved for the treatment of moderate-to-severe AD in patients aged 2–15 years, and tacrolimus 0.1% ointment for the treatment of patients aged 16 years or more. Pimecrolimus 1% cream is generally approved for mild-to-moderate AD in adults and children aged 2 years or more, but is also approved for use in infants aged 3 months or more in Australia, Brazil, Canada, India, Indonesia, Israel, New Zealand, the Philippines, Russia, and Thailand.<sup>55-65</sup> However, pimecrolimus is not available in some countries, including Japan. In the European atopic eczema (AD) guidelines, pimecrolimus is the preferred TCI for the treatment of facial lesions and children (according to overall recommendations), with tacrolimus recommended for long-term maintenance treatment.<sup>44</sup>

In non-sensitive body locations, either pimecrolimus or tacrolimus are recommended for use (Figure 1). Patients with

mild-to-moderate AD aged 2–15 years treated with tacrolimus 0.03% ointment showed a significantly greater percent improvement in Eczema Area and Severity Index (EASI) scores compared with vehicle ointment (54.8% vs. 20.8%), alongside improvements in the total body surface area affected by AD and a lower itch score in the tacrolimus group.<sup>66</sup> Pimecrolimus 1% cream has been shown to reduce the number of AD flares and increase the median time to first AD flare when compared with a vehicle cream control (144 vs. 26 days,  $p < 0.001$ ).<sup>67</sup>

While both TCI are preferred over topical corticosteroid (TCS) for the treatment of sensitive skin areas, pimecrolimus is preferred over tacrolimus for use in sensitive areas.<sup>68</sup> Sensitive areas include the head, face (eyelids and perioral region), neck, axilla region, inguinal folds, and genital area. In direct head-to-head comparisons of topical pimecrolimus with tacrolimus, pimecrolimus demonstrated greater efficacy in reducing the signs and symptoms of AD in sensitive skin areas, specifically in the head and neck region (54% reduction in AD with pimecrolimus treatment vs. 35% with tacrolimus treatment; treatment difference not significant).<sup>69</sup> Alongside these results, local erythema was less common and was experienced for a shorter duration of time in patients being treated with pimecrolimus than with tacrolimus.<sup>69</sup> TCI do not impair the skin barrier and may even be able to restore barrier function in damaged skin.<sup>70,71</sup> Systemic exposure is lower for pimecrolimus than tacrolimus, making it more suitable for patients with extensive lesions and in children, as systemic absorption is minimized.<sup>72,73</sup> This difference in systemic absorption is due to pimecrolimus being more lipophilic with a greater binding affinity for skin proteins and lower skin permeability.<sup>74,75</sup> The use of pimecrolimus 1% cream was well tolerated and demonstrated marked improvements in treating patients with Netherton syndrome, even when applied to 50% of the total body surface area.<sup>76</sup> In contrast to tacrolimus, pimecrolimus systemic absorption in children with Netherton syndrome is very low after 4 weeks of treatment resulting in a significant improvement of the skin lesions.<sup>76</sup> Pimecrolimus has a selective action on T lymphocytes, mast cells and basophils, and, unlike tacrolimus, has no action on Langerhans cells.<sup>77-79</sup>

Skin burning is a common adverse event following TCI application,<sup>80,81</sup> within the clinic, this usually occurs in the first 3 days of treatment. Based on clinical experience, cooling the product in the refrigerator for 15–20 min before application may help to reduce the sensation of burning at the application site or, in adults, administering oral acetylsalicylic acid 1 h prior to treatment for the first 3 days may help avoid or alleviate burning.<sup>82,83</sup> A shorter duration of warmth, stinging, and burning reactions was reported in patients treated with pimecrolimus compared with those treated with tacrolimus. Although the incidence of these specific application site reactions was similar between groups in this particular study,<sup>69</sup> the incidence of burning sensations experienced by patients treated with pimecrolimus in clinical trials has been found to be generally low (~7–10%),<sup>84,85</sup> whereas tacrolimus-treated patients may experience a high incidence (36–50%) of application-site burning.<sup>81,84,86</sup>



### 3.3 | First-line treatment according to proposed algorithm: severe AD flares

For severe AD flares in sensitive skin areas, TCS can be used as initial treatment until an improvement in severity has been observed (Figure 1). Alternatively, once-daily TCS/TCI can be used in alternate until an improvement in severity is observed (Figure 1). Following an improvement in severity, TCS use should be discontinued and switched to TCI. Although TCS are effective for the short-term treatment of AD,<sup>85,87,88</sup> long-term use is not recommended. Application to sensitive areas should be minimized due to potential side-effects,<sup>89</sup> particularly as the increased skin permeation of TCS, relative to pimecrolimus, increases the risks of side-effects.<sup>74</sup> Side-effects associated with TCS include local cutaneous events (e.g., impairment of epidermal barrier function,<sup>70,90</sup> skin atrophy, and acne) and systemic effects (e.g., hypothalamic–pituitary–adrenal axis suppression).<sup>88,89</sup> Awareness and fear of these side-effects, or corticophobia, is common in several European and Asian countries<sup>91–96</sup> and is associated with non-adherence to treatment.<sup>95,97,98</sup>

### 3.4 | Management of AD in infants

Early treatment of AD during infancy and early childhood may reduce the progression of AD and prevent atopic march.<sup>50</sup> Emollients are an important part of treatment, and long-term use of emollients has demonstrated preventative effects in infants who are at risk of developing AD.<sup>50,51</sup>

Topical calcineurin inhibitors are an effective treatment option in infants with mild-to-moderate AD,<sup>55,99</sup> although only pimecrolimus is currently approved for use in children under 2 years of age in certain countries, for example, Russia.<sup>55</sup> Comprehensive evidence of the clinical efficacy and safety of pimecrolimus in infants and children comes from nine studies that were conducted in more than 6700 patients (including 4799 infants and 1312 children).<sup>85,100–107</sup> For example, results from the Petite study support the safe and efficacious long-term use of pimecrolimus in infants with mild-to-moderate AD with short-term use of TCS as rescue therapy during AD flares;<sup>105</sup> this study enrolled 2418 infants with up to 5 years of follow-up.<sup>105</sup> Similarly, over a period of 2 years in an open-label phase 2 study of 50 infants, treatment with tacrolimus 0.03% ointment resulted in substantial clinical improvement of AD, with similar tolerability as reported in older children.<sup>108</sup>

### 3.5 | Maintenance treatment for AD

Maintenance treatments are important to prevent flares and reduce TCS use. Pimecrolimus is the recommended TCI for maintenance

treatment for sensitive skin in the algorithm proposed, and either tacrolimus or pimecrolimus may be used as maintenance therapy for other areas of the body (Figure 1). Both pimecrolimus and tacrolimus have demonstrated clinical benefits as maintenance treatments for AD. Proactive treatment with tacrolimus 0.1% ointment significantly reduced the number of disease exacerbations (DE) requiring substantial therapeutic intervention (median difference, 2;  $p < 0.001$ ) and the proportion of DE treatment days (median difference, 15.2%;  $p < 0.001$ ), as well as increasing the time to first DE (142 vs. 15 days;  $p < 0.001$ ) when compared with vehicle ointment in a 12-month study.<sup>109</sup> Following 16 weeks of maintenance treatment with pimecrolimus, the disease relapse rate was reduced in patients receiving once- and twice-daily applications (14.7% and 9.9%, respectively).<sup>110</sup> Furthermore, a 12-month efficacy study of pimecrolimus treatment at the early signs of AD, showed a significant reduction in the incidence of flares (67.6% vs. 30.4%,  $p < 0.001$ ) and an improvement in the overall control of AD when treated with pimecrolimus compared with vehicle.<sup>106</sup> Long-term safety data for TCI, together with guideline recommendations, support the use of pimecrolimus as the preferred treatment option for sensitive skin areas.<sup>44,111</sup> Currently, there is no evidence that proactive treatment is superior to treatment started at the first signs and symptoms, usually itch, of a new AD flare. Proactive treatment with TCS may also be considered for patients with frequent flares, as there is evidence to indicate that using TCS plus emollients as maintenance therapy is more effective for preventing relapses compared with emollients alone.<sup>41,112</sup> Regular use of emollients in AD is recommended as epidermal barrier dysfunction can negatively affect skin hydration and increase transepidermal water loss.<sup>113,114</sup>

### 3.6 | Novel topical therapies for AD

Crisaborole ointment is a topical phosphodiesterase-4 inhibitor used for the treatment of mild-to-moderate AD,<sup>115</sup> which is currently approved in a limited number of countries. A pooled analysis of clinical data showed that crisaborole 2% ointment significantly reduced the severity of pruritus compared with treatment with vehicle.<sup>115</sup> Safety analyses showed crisaborole 2% ointment to be well tolerated, with the most commonly reported treatment-related adverse events being application site pain, pruritus, and dermatitis.<sup>115</sup> Microbiome-targeting treatments are being developed due to the promising results of a phase 1/2 trial investigating treatment with topical *Roseomonas mucosa*. In this study, significant decreases in AD severity, TCS requirements, and *S. aureus* burden were observed following treatment with *R. mucosa* in patients with AD.<sup>116</sup> Janus kinase (JAK), a family of tyrosine kinases, has been implicated in AD, with inhibition of JAK resulting in sustained anti-pruritic effects.<sup>117</sup>

**FIGURE 1** Algorithm for the topical treatment of atopic dermatitis in children, adolescents, and adults. <sup>a</sup>These areas include the head, face (eyelids and perioral region), neck, axilla region, inguinal folds, and genital area. In these areas, a cream is preferred to an ointment. <sup>b</sup>Pimecrolimus 1% cream for all ages; tacrolimus 0.1% ointment for adults; tacrolimus 0.03% ointment for children. Pimecrolimus is indicated for mild-to-moderate AD and tacrolimus is indicated for moderate-to-severe AD.<sup>55,124c</sup> Not included in the Summary of Product Characteristics for pimecrolimus. Abbreviations: AD, atopic dermatitis; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid

In a recent phase 2 trial in patients with AD, treatment with ruxolitinib cream, a potent JAK1/JAK2 inhibitor, significantly improved EASI score versus vehicle cream at week 4 (71.6% improvement vs. 15.5%,  $p < 0.001$ ).<sup>118</sup> Treatment with topical ruxolitinib also significantly improved the Investigators Global Assessment (IGA) score and pruritus compared with vehicle at week 4.<sup>118</sup> Another JAK inhibitor, delgocitinib, has been approved in Japan for topical use in patients with AD.<sup>119</sup> In both phase 2 and phase 3 trials in Japanese patients with AD, delgocitinib demonstrated significantly reduced modified EASI scores versus vehicle ointment after 4 weeks.<sup>120,121</sup> Tapinarof is a topical aryl hydrocarbon receptor agonist that has been investigated in patients with AD.<sup>122</sup> In a recent study, the rate of treatment success (minimum 2-grade IGA score improvement) with tapinarof cream at week 12 was shown to range from 34% to 53% (dose dependent) and was significantly higher than that with vehicle treatment (24%).<sup>122</sup> It should be noted that some of these novel treatments are costly, which may limit their use. The treatments recommended in the proposed algorithm (Figure 1) are economical<sup>123</sup> and effective for the management of AD.

## 4 | CONCLUSIONS

The proposed treatment algorithm should help guide physicians in clinical practice when treating patients with mild-to-moderate AD and those with severe flares. According to the algorithm, pimecrolimus is the preferred TCI for application on sensitive skin areas due to its efficacy, tolerability, and selectivity profile compared with tacrolimus. However, both pimecrolimus and tacrolimus are recommended for other areas of the body. TCS are recommended for short-term use only in cases of severe flares due to their side-effects, such as thinning of the epidermal barrier. This treatment algorithm can help guide clinical decision-making in the treatment of AD, potentially reducing the burden of AD for patients, their families, and health-care systems.

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## CONFLICT OF INTEREST

T.L. has participated as principal investigator in clinical trials and advisory boards, and has given lectures, sponsored by Viatrix, Novartis, Lilly, Pfizer, Janssen, and Sanofi. He has received consultancy/speaker honoraria from Novartis, Abbvie, Galderma, La Roche Posay, Viatrix, Janssen, and Sanofi, and has acted as a scientific advisory board member for Abbvie, Celgene, La Roche Posay, Janssen, Pfizer, Menlo, Viatrix, Galderma, Symrise, Sandoz, and Lilly. He has received research grants from Celgene, Janssen-Cilag, Leo, Viatrix, and Pfizer. U.A. has nothing to disclose. M.A.

has participated in an advisory board sponsored by Loreal. She has received consultancy/speaker honoraria from Meda Pharma S.p.A. (*a Viatrix company*), Loreal, Bayer, Delta Medical, and Bausch Health. X.D. has nothing to disclose. N.N.M. has participated as a principal investigator in clinical trials sponsored by Novartis, Lilly, and Janssen. He has received consultancy/speaker honoraria from Abbvie, Bayer, Galderma, Pierre Fabre, Pfizer, Leo Pharma, Meda Pharma S.p.A. (*a Viatrix company*), and Janssen Pharmaceutical, and has acted as a scientific advisory board member for Meda Pharma S.p.A. (*a Viatrix company*), Galderma, and Pierre Fabre. L.N.B. has received research grants and consultancy/speaker honoraria from pharmaceutical companies Pierre Fabre, Genzyme Europe B. V., AstraZeneca Pharmaceuticals LLC, Gilead/PRA Pharmaceutical Research Associates CIS, Bionorica, Teva Branded Pharmaceutical Products R&D Inc/PPD Development LLC (Smolensk), Stallergen C.A./Quintiles Geismbh (Austria), MSD, Pfizer, Abbvie, Galderma, Meda Pharma S.p.A. (*a Viatrix company*), Sanofi, Astellas, and Takeda (formerly Shire). O.N. has received consultancy/speaker honoraria from Meda Pharma S.p.A. (*a Viatrix company*), Nestle, and Delta Medical. A.R. has nothing to disclose. T.V.S. reports that she has received consultancy/speaker honoraria from Meda Pharma S.p.A. (*a Viatrix company*) and Dr. Reddy's Laboratories. Z.T. has received consultancy/speaker honoraria from Numil and Sandoz, and acted as scientific advisory board member for Numil and Meda Pharma S.p.A. (*a Viatrix company*). M.T. has nothing to disclose. E.A.V. has participated as a principal investigator in clinical trials sponsored by Sanofi. She has received research grants and consultancy/speaker honoraria from Abbvie, AstraZeneca, Meda Pharma S.p.A. (*a Viatrix company*), MSD, Novartis, Sandoz and Stallergenes Greer, and has acted as scientific advisory board member for Meda Pharma S.p.A. (*a Viatrix company*), MSD, Pfizer, Sanofi, Stallergenes Greer, and Takeda (formerly Shire). S.V. has nothing to disclose. H.W. has acted as scientific advisory board member for LEO, Meda Pharma S.p.A. (*a Viatrix company*) and Sanofi. Z.Z. has participated as a principal investigator in clinical trials sponsored by Novartis and Pfizer. He has received consultancy/speaker honoraria from Novartis, Pfizer, Astellas, Galderma, Janssen, GSK, BAYER, LEO, and Meda Pharma S.p.A. (*a Viatrix company*), and has acted as a scientific advisory board member for Pfizer, Novartis, Astellas, LEO, and Meda Pharma S.p.A. (*a Viatrix company*). He has received research grants from Astellas, Pfizer, Novartis, and ALK Pharma.

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