Atopic dermatitis (AD) as an inflammatory skin condition that commonly follows a chronic course associated with periods of remission and relapse. Being the first step in the “atopic march”, it is often associated with other atopic manifestations, such as asthma, allergic rhinitis and food allergies (particularly in infants and children under the age of 2 years) [1–3]. The prevalence of AD is high, estimated to be 15–20% among children, and 1–3% in adults worldwide [1]. Representing a chronic, remitting-relapsing inflammatory dermatitis, AD is often diagnosed and managed by a multidisciplinary group of providers, including allergists, dermatologists, and primary care practitioners. Because the pathogenesis of AD is complex and multifactorial, there are numerous approaches to its therapeutic management. There is still a debate about whether atopy should be distinguished as an important but not required feature for the diagnosis of AD [7, 8]. Although both sides agree that the disease is diagnosed clinically based on the patient’s history, characteristic clinical findings mandate the exclusion of other common cutaneous disorders before diagnosis, particularly such as contact dermatitis and cutaneous lymphomas [7, 8], they also recommend against obtaining routine specific IgE serum levels, and point to the lack of specific biomarkers required not only for diagnosis or severity assessment, but also for assessment of therapeutic efficacy [9], results in divergent approaches to the management of AD [10–13].

For many years, topical corticosteroids (TCS) have been the most common treatment for AD, especially if non-pharmacologic interventions have failed [8, 11]; it has been hypothesized that TCS therapy can impede the mechanisms of antigen-processing, thereby inhibiting the release of proinflammatory cytokines [11]. The TCS are effective for both active inflammation and for prophylaxis; however, there are no data to support a specific agent among the TCS classes, and there is limited evidence to recommend an optimal dosing or frequency regimen [8, 11]. Although TCS have long been considered and offered as a first line therapy for treatment of AD, they are associated with serious adverse side effects [5–9].

Due to the chronic nature of AD, effective and safe treatment that can be used as long-term management is of utmost importance [2]. Introduction of the topical calcineurin inhibitors (TCIs), tacrolimus (T) and pimecrolimus (P) almost 15 years ago, was a major breakthrough for the topical anti-inflammatory treatment of AD [14]. TCIs, including T and P, were approved by the Food and Drug Administration (FDA) agency for the treatment of AD in 2000 and 2001, respectively. The TCIs are anti-inflammatory drugs with a lipophilic structure that act by inhibiting the calcineurin phosphatase which disrupts the activation of T cells and mast cells as well as the transcription and release of inflammatory cytokines [15, 16]. Topical T and topical P are the only TCIs in Europe. In 2002, topical T was approved for short or intermittent long-term treatment of moderate to severe AD in Europe. Two concentrations of topical T are available: 0.1% for patients over 16 years of age, and 0.03% for children over 2 years of age. The indication for topical T was extended in 2009 to maintenance treatment of AD. Topical P in a concentration of 1% was approved in 2002 for the treatment of mild-to-moderate AD in patients over 2 years of age. Both drugs are approved for second-line treatment, when other treatments have been ineffective or are contraindicated. [6]. The American Academy of Dermatology...
The age restriction was emphasized in a boxed warning added by the FDA agency in January 2006, which also highlights the lack of long-term safety data and the theoretical risk of skin malignancy and lymphoma [14, 22, 23]. Since then, P has been extensively investigated in short- and long-term studies including over 4000 infants (< 2 years old). These studies showed that P effectively treats AD in infants, with sustained improvement with long-term intermittent use [14, 16]. A decade’s worth of clinical experience, epidemiological data, post-marketing surveillance, and adverse event database monitoring failed to demonstrate a causal relationship between TCI use and malignancy [23]. This boxed warning was based on a theoretical increase in risk of malignancy including lymphoma [5]. Prior to its topical use in AD, oral and intravenous T had been used to suppress the systemic immune system in transplant patients. Malignancies have been associated with oral T when used systemically at high concentrations. An animal study with P using a 30 fold greater exposure than seen with topical use, also resulted with associated malignancy development [23]. These findings were used to support the addition of the black box warning. New malignancies have been reported in patients using topical P or T as well. These have been reported by the FDA agency and by the parent drug manufacturer. Independent experts reviewing these cases found no causal association between topical use of TCIs and malignancy. The rate of reported lymphoma in patients exposed to topical T was lower than the expected incidence in age-matched controls [24]. No increased risk of malignancy has been seen in recent meta-analyses or the 10-year Pediatric Eczema Efficacy Registry as of May 2014 [16, 25].

The American Academy of Allergy, Asthma & Immunology, American College of Allergy, Asthma & Immunology/ the Joint Council of Allergy, Asthma & Immunology, and the AAD Guidelines, advocate for proactive therapy regimen regarding the boxed warning on TCI, although a causal relationship has not been established [10]. For reactive therapy, a twice-daily application of TCS is commonly recommended in the treatment of acute AD. For “proactive” maintenance therapy, the AAD suggests once- to twice-weekly application of TCS in commonly flaring areas to prevent relapses [8, 11]. The Joint Task Force and the AAD Guidelines review large prospective studies that suggest a correlation between increased risks of lymphoma with AD disease severity, without an association with TCI use [10]. Most importantly, the studies of P in infants provided no evidence for systemic immunosuppression, and a comprehensive body of evidence from clinical studies, post-marketing surveillance and epidemiological investigations does not support potential safety concerns [14]. Pimecrolimus 1% is approved for second-line therapy in children (≥ 2 years old) and adults with mild-to-moderate AD [26]. Despite these FDA agency approved indications, clinical trials have shown drug safety in patients as young as 3 months and in long-term use in patients

**Abbreviations**

AD – atopic dermatitis  
TCS – topical corticosteroids  
TCI – topical calcineurin inhibitor  
T – tacrolimus  
P – pimecrolimus  
FDA – Food and Drug Administration  
AAD – American Academy of Dermatology  

(AAD) Guidelines recommend that TCS can be initially used to control a flare, whereas TCI can be applied as maintenance therapy to prevent relapse, although the evidence for this concurrent regimen has been inconsistent. The TCIs are usually offered as a second-line therapy for acute and chronic treatment of AD in patients who have not responded adequately to other topical treatments or when those treatments are not recommended [2]. The guidelines agree that use of TCI, particularly P, at sites of sensitive or thin skin, offers an advantage over use of TCS [8, 11, 14]. A practical algorithm for topical treatment of AD in the Middle East emphasizes the importance of sensitive skin areas [17]. Twice-daily application of either T ointment or P cream is efficacious in treating inflamed AD lesions and resolving pruritus. Unlike TCS, long-term TCI use does not carry the risks of skin atrophy, impaired epidermal barrier function or enhanced percutaneous absorption, and so it is suitable for AD treatment especially in sensitive skin areas [14]. Tacrolimus has been shown to impact Langerhans cells while P does not [12]; in addition to their anti-inflammatory effects, both TCIs have been shown to have additional positive effects on epidermal integrity [18–20]. Murrell et al. reported that patients treated with P saw a reversal of skin thinning of the neck and head, including the eyelids [21]. These treatments provide a safe alternative to TCS, particularly in the treatment of sensitive skin sites such as the head and neck [2, 21]. The most common side effects of TCI are localized site reactions, including burning, stinging, and pruritus, which commonly occur during the first week of treatment; it is important to counsel patients on these potential side effects to prevent premature discontinuation of treatment [10].

There was a temporary decrease in the use of topical T and persistent reduction in topical P in Europe since 2004. Safety warnings issued by regulatory agencies about a potential risk of cancer may have contributed to the reduction in users especially in children, in all countries [6]. In 2006, the FDA agency issued a label change; in the European Union as well as in the United States the labeling of topical T and topical P was updated by adding a warning about cautious use, in order to reduce the potential risk of skin cancer and lymphoma. In 2006, the FDA agency instituted a boxed warning for both TCIs based on a theoretical risk of malignancy (including lymphomas). Currently, P 1% cream is indicated in patients with mild-to-moderate AD aged > 2 years [10]. The age restriction was
of all ages [16, 27, 28]. Clinical trials have demonstrated that P is safe for long-term management, as well as effective in achieving clearance of AD lesions and associated symptoms: pruritus was shown to be significantly reduced in as early as 48 hours after initiation of treatment. With photoprotection, TCIs have a favorable safety profile without evidence for increased risk for lymphoma [29].

Although many studies have shown that long-term use of T and P is effective with a favorable safety profile and low systemic absorption, the black box warning has remained in place. A recent systematic review of clinical trials and meta-analyses has shown no significant increased risk of malignancy with TCI use [25]. Systematic analysis has shown efficacy and safety of TCI therapy (at least 6 weeks long), in comparison with low or mid-potency TCS (hydrocortisone 1% or hydrocortisone butyrate 0.1% cream/oointment), in children with AD aged < 12 years. This comprehensive literature review supports the safety of the long-term TCI and intermittent low- to mid-potency TCS therapy in children with AD, with no evidence of cutaneous atrophy or cumulative systemic exposure and no reports of lymphoma [25].

**Conclusion**

Long-term management of mild-to-moderate atopic dermatitis in infants ≥ 3 to < 12 months old with pimecrolimus or topical corticosteroids has shown that both pimecrolimus and topical corticosteroids had a rapid onset of action with 50% of patients achieving treatment success by week 3; after 5 years, 85% and 95% of patients in each group achieved overall and facial treatment success, respectively. The profile and frequency of adverse events was similar in the 2 groups; there was no evidence for impairment of humoral or cellular immunity in either of groups. The data suggest and support the use of pimecrolimus as a first-line treatment of mild-to-moderate atopic dermatitis in infants and children [16]. No firm conclusions can be made on the theoretically increased risk for malignancies associated with a long-term use of pimecrolimus in infants [30].

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