

REVIEW

Atopic dermatitis: understanding the disease and its management

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ABSTRACT

Objective: Atopic dermatitis (AD) is a common, chronic, inflammatory skin disease that can significantly reduce the quality of life of not only patients but also entire families. This review will focus on the currently available non-pharmacologic and pharmacologic treatments for the control and management of AD.

Research design and methods: A review of English-language articles from January 1953 to May 2006 was performed within the MEDLINE database. Search terms included, but were not limited to, atopic dermatitis, topical corticosteroids, and topical calcineurin inhibitors. Studies evaluating the diagnosis, physical and psychological burden, and underlying pathophysiology of AD were included. Particular focus was placed on literature presenting key safety and efficacy data from clinical trials involving AD treatment.

Results: Although good skin care and trigger avoidance are fundamental to AD management, most patients also require pharmacologic intervention. Topical therapies comprise the foundation of AD treatment. In particular, topical corticosteroids have been a mainstay in AD treatment for several decades and the

newer topical calcineurin inhibitors have become a valuable addition to the therapeutic armamentarium. TCIs are a safe and effective AD treatment; they limit the number of disease flares, extend the time between flares, and provide a steroid-sparing option that may be of particular benefit in the pediatric population. The use of more potent therapies, such as systemic (oral/injected) agents or phototherapy, is typically limited to the treatment of severe, refractory disease. Additionally, owing to the increased risk for bacterial, viral, and fungal infections in patients with AD, topical or systemic antimicrobials are an important component of treatment.

Limitations: Case reports and small-scale studies were typically not included in this analysis and owing to the limited number of trials evaluating TCSs, consensus statements and comprehensive review articles were used to obtain information pertaining to the use of this treatment in AD.

Conclusions: AD is a common, chronic disease requiring a long-term management strategy that incorporates preventive measures and a multipronged treatment approach.

Introduction

Atopic dermatitis (AD) is a chronic, highly pruritic, inflammatory skin disease characterized by disease exacerbations (flares), and periods of remission¹⁻³.

Pruritus is one of the signature symptoms of AD and often leads to an itch-scratch cycle, which can increase the risk for an AD flare and infection and also can lead to exacerbation of an existing flare. One of the most common disorders observed in children^{4,5}, AD has a

lifetime prevalence of approximately 10–20%^{4,5}. Among children affected by AD, 45% typically experience onset of the disease during the first 6 months of life, 60% by the age of 1 year, and 85% by the age of 5 years. Furthermore, several studies have linked the incidence and severity of AD during childhood with the subsequent development of asthma and/or allergic rhinitis^{6–11}, thus suggesting that AD may be an entry point for the 'atopic march', the progressive development of systemic allergic disease that begins with a food allergy and advances to allergic rhinitis and ultimately to asthma^{12,13}.

Quality of life and the economic burden of AD

AD can have a profound impact on the quality of life (QoL) of pediatric^{14–17} and adult patients^{16,18}, as well as the caregivers and families of those affected¹⁶. Children with AD are adversely affected in terms of disrupted sleep, school performance, social activities, and participation in sports^{14,15,19} and may suffer embarrassment, peer rejection, teasing, and bullying¹⁵. Adult patients report feelings of embarrassment and limitations related to their clothing, social relationships, and leisure activities¹⁸. Parents report loss of sleep, stress, and loss of leisure time¹⁶; family life can be disrupted as parents change their lifestyles to care for a child with AD²⁰. Specifically, families can become socially isolated by avoiding interactions with relatives and friends to minimize awkward situations¹⁷, and overprotection of a child with AD can provoke feelings of jealousy in spouses and siblings²¹. The assistance of a mental health professional, particularly in cases of severe disease, may help both patients and family members cope with the psychological aspects of this chronic illness.

In the United States, the annual cost of medical care and prescription drugs for the treatment of AD is approximately \$1–\$4 billion²². In addition to direct costs, including non-reimbursed medications and household items¹⁶, indirect costs for adult patients with AD include a considerable amount of missed work; one study found that lost productivity accounted for almost half the economic burden of AD¹⁶.

Pathophysiology of AD

The causes of AD are not completely understood, but dysfunction of the skin barrier, likely the result of both genetic and environmental factors^{23,24}, and dysregulation of the immune system are important aspects of its pathophysiology²³. Genetic mapping studies have identified the epidermal differentiation complex (EDC), which has been linked to both AD

and psoriasis²⁵. In addition, the presence of two loss-of-function mutations in the filaggrin gene, a key protein that facilitates terminal differentiation of the epidermis and formation of the skin barrier, results in the development of ichthyosis vulgaris and is thought to predispose patients with AD to the development of asthma^{26,27}. In contrast to the skin of healthy persons, normal-appearing (uninvolved) skin of patients with AD exhibits xerosis²³. Both the lesional and non-lesional skin of affected patients are deficient in ceramides, the major component of lipids in the stratum corneum²⁸. Because ceramides are the principal water-retaining molecules in the extracellular space of the cornified envelope²⁹, reduced concentrations can lead to transepidermal water loss³⁰. The resulting dry skin often has microfissures and cracks that permit the entry of pathogens, antigens, and irritants, all of which may contribute to inflammation and infection³⁰.

Another important aspect of AD pathophysiology is immune system dysregulation, particularly of the two major subsets of CD4+ T cells, Th1 and Th2 cells²³. Analyses of biopsies of atopic skin have shown an increased Th2 immune response compared with biopsies of normal skin³¹. Patients with AD have increased levels of circulating eosinophils, and AD flares are accompanied by eosinophil extravasation through selectins and recruitment of eosinophils to the skin²⁹. Between 70% and 80% of patients exhibit elevated serum immunoglobulin E levels and sensitization to environmental allergens. This type of AD has been referred to as extrinsic or allergic AD. In contrast, 20–30% of patients do not exhibit elevated serum immunoglobulin E levels nor any observable sensitization to environmental allergens and are described as having intrinsic or non-allergic AD²⁹. Although extrinsic and intrinsic AD historically have been categorized as two distinct subtypes, more recent theories postulate that the intrinsic form may constitute an early form of extrinsic AD³². Ongoing research will further elucidate the relationship between these two forms of AD.

Goals of AD management

Because the pattern of disease flares and periods of remission varies among patients with AD, treatment should be tailored to the individual and the current disease state. The major goal of disease management is to reduce the frequency and severity of flares. Comprehensive, long-term management should address both skin-barrier dysfunction and immune dysregulation, and requires an integrated approach that includes patient and caregiver education, flare prevention through trigger avoidance and hydration, and treatment of flares through pharmacologic and non-pharmacologic

measures. This review will focus on the currently available non-pharmacologic and pharmacologic treatments for the control and management of AD.

Methods

A review of English-language articles from January 1953 to May 2006 within the MEDLINE database was performed. Search terms included atopic dermatitis alone and in combination with the following terms: treatment, management, topical corticosteroids, topical calcineurin inhibitors, diagnosis, burden, cost, impact, family, society, and causes. Studies evaluating the diagnosis, physical and psychological burden, and underlying pathophysiology of AD were included. Particular focus was placed on literature presenting key safety and efficacy data from clinical trials involving AD treatment. Studies including adults (≥ 18 years), children (2–16 years), and infants (< 2 years) were included.

Prevention and non-pharmacologic management of AD

Daily preventive care for AD is central to any effective long-term treatment plan. Proper hydration can minimize exacerbations of AD by offsetting xerosis, which can precipitate the itch-scratch cycle wherein the patient scratches excessively and exacerbates the disease process^{33,34}. Applying wet dressings to severely affected areas or chronic lesions can improve hydration³⁰. There is no clear consensus regarding whether hydration through bathing is beneficial or harmful to patients with AD²⁴. Bathing may be helpful by hydrating the skin, increasing the penetration of topical treatments, and debriding infected eczema²⁴, but evaporation can also dry and disrupt the epidermal barrier and worsen AD. Therefore, short baths in warm rather than hot water, along with the use of mild, hypoallergenic cleansers, are recommended^{35,36}. Hydrophilic ointments^{33,35} and ceramide-rich barrier repair mixtures also help to maintain moisture³⁷. To maximize moisture retention, moisturizers or emollients should be applied liberally *at least* twice daily and within 3 min after bathing or swimming, even when the skin is clear^{2,24}. Recently approved medical devices known as hydrogels may also be used to provide a mechanical barrier to irritants and retain moisture, which may help promote healing of the skin barrier³⁸. Similar to other medical devices regulated by the US Food and Drug Administration (FDA), hydrogels do not work through a chemical action within or on the body and do not depend on metabolism to achieve their effects³⁹. Mimyx Cream (Stiefel Laboratories, Inc., Coral

Gables, FL, USA)³⁸, Epiceram Skin Barrier Emulsion (Ceragenix Pharmaceuticals, Inc., Denver, CO, USA)⁴⁰, and Atopiclair Non-steroidal Cream (Graceway Pharmaceuticals, LLC, Malvern, PA, USA)⁴¹ are three hydrogels that have recently received FDA approval in the United States to improve dry skin conditions and relieve and manage the burning and itching associated with various dermatoses, including AD. Although they hold promise for the relief of pruritus, rigorous clinical trials and the publication of additional data are needed to confirm their efficacy and safety.

Identification and avoidance of AD triggers are also important components of a first-line strategy². Triggers vary among patients³³, but common immunologic triggers include foods, such as eggs, milk, wheat, soy, and peanuts; aeroallergens (e.g., house dust mites, weeds, animal dander, mold); and infectious agents, such as *Staphylococcus aureus* and *Dermatophagoides pteronyssinus*. Other triggers more directly exacerbate xerosis and include irritants such as soaps or detergents; contact with chemicals, alcohol, and astringents found in toiletries or topical preparations being used to manage the patient's AD; abrasive clothing; and cold or dry weather³⁰. Psychologic stress can also be an aggravating factor^{30,42,43}.

Pharmacologic management of AD

Disease exacerbations or flares associated with AD are varied in their intensity, ranging from mild to severe and require treatment with topical therapies, which inhibit AD-associated inflammatory response (Figure 1). Treatment regimens should be tailored to the severity and location of the flare, as well as patient age²⁴.

Topical corticosteroids

Topical corticosteroids (TCSs), which have been used since the early 1950s, are effective in reducing the signs and symptoms of AD flares and have become a mainstay of AD treatment⁴⁴. TCSs have immunosuppressive, anti-inflammatory, and vasoconstrictive actions^{45,46} and are involved in the transactivation and transrepression of a number of genes⁴⁶. Furthermore, TCSs act directly upon monocytes, macrophages, Langerhans cells, and dendritic cells and their precursors, as well as block the synthesis of inflammatory cytokines^{47–49}. Because TCSs also affect classes of cells not involved in the anti-inflammatory response, they may have unwanted side effects⁵⁰.

TCSs range in potency from low (class 7) to ultra-high (class 1) and are available in a variety of vehicles, including ointments, creams, lotions, gels, foams, aerosol sprays, and shampoos^{45,51}. Despite their extensive use in the clinical setting, however, there are

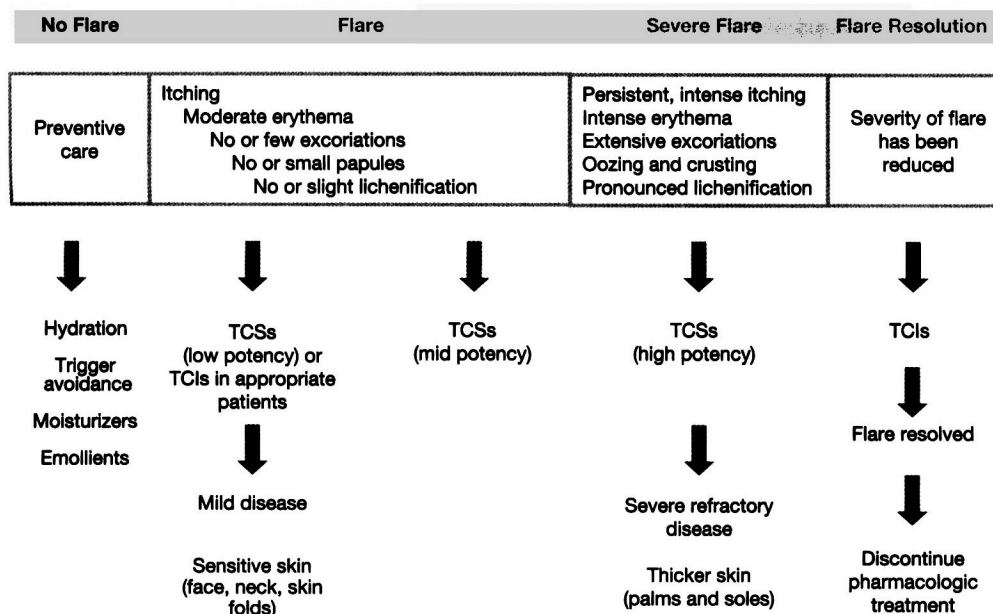


Figure 1. Long-term management of atopic dermatitis encompasses both daily disease management and treatment of flares. TCIs = topical calcineurin inhibitors; TCSs = topical corticosteroids

few clinical trials and limited data assessing optimal TCS concentration, duration of treatment, and frequency and quantity of application^{2,52}. Generally, treatment is initiated with higher-potency TCSs to bring the disease under immediate control when pruritus is intense or lesions are highly inflammatory or lichenified^{12,52,53}. Higher-potency TCSs also are often necessary for older children and adults who have more lichenified skin from chronic disease or patients with involvement of the hands and feet, which tend to be difficult areas to treat⁵¹. Vehicles such as foams or shampoos may be particularly useful on the face or scalp where cosmetic concerns are a factor. In contrast, ointments, which are more moisturizing, may be more appropriate for the soles of feet and other dry body areas⁵¹. Because of the risk of side effects, discussed in further detail below, it is recommended that TCS therapy be limited to a maximum of 3 weeks to control exacerbations^{34,54}. Once flare symptoms have been brought under control, application frequency can be decreased from twice daily to several times weekly and a less-potent TCS or a non-steroidal therapy can be used. Such gradual tapering of therapy will help minimize the risk of flare rebound upon discontinuation of TCS treatment.

With proper use, TCSs can provide safe, effective short-term management of AD, but their pleiotropic mechanism of action can result in unwanted side effects^{2,52}. Pharmacokinetic studies have shown a potential for systemic absorption, even with low-potency TCSs^{55,56}. Local side effects may include telangiectasia, striae, skin atrophy, hypopigmentation, rosacea, perioral dermatitis, acne, and increased hair

growth^{2,51,52}. Kao *et al.* have demonstrated that even short-term (3 days) use of a potent TCS resulted in altered epidermal structure and function, specifically impacting skin-barrier homeostasis and the integrity and cohesion of the stratum corneum, the outermost layer of the epidermis⁵⁷; such weakening of the skin barrier may make it more susceptible to inflammation and infection³⁰. Potential systemic side effects include reduced bone mineral density⁵⁸, hypothalamic-pituitary-adrenal (HPA) axis suppression, growth retardation in children, cataracts, and increased intraocular pressure^{51,52,59,60}.

The risk of side effects depends on the potency of the steroid, the amount used, the vehicle, the size of the area treated, whether the steroid was used under occlusion, the integrity of the skin, and the location and duration of use³⁶. Children, especially infants, are at greater risk for TCS side effects than adults³⁶. Furthermore, the use of TCSs on sensitive areas of thin skin, such as the face, neck, or groin, increases the risk of systemic absorption and local adverse events, such as skin atrophy⁵². It is worth noting that fluticasone propionate (0.05%), used for the treatment of moderate to severe AD in the infant and pediatric populations (3 months–16 years of age), is distinct from other members of the corticosteroid class in that it has not been found to cause skin thinning or HPA axis suppression, even when used over large areas^{61–63}. These findings confirm that adrenocortical suppression after treatment with fluticasone is uncommon⁶¹. Limiting the frequency of application and avoiding chronic use and overuse of TCSs can reduce the risk of side effects⁵¹; however, patients and caregivers fears about

the use of TCSs can lead to noncompliance, which can impede effective AD management^{24,64}.

Topical calcineurin inhibitors

Topical calcineurin inhibitors (TCIs) inhibit activation of T cells and mast cells by blocking calcineurin and suppressing inflammatory cytokines and other mediators of the allergic inflammatory reaction^{65,66}. Two TCIs are currently approved for the treatment of AD: tacrolimus 0.03% (in children aged 2–15 years and adults) and 0.1% (in adolescents over 15 and adults) ointment for moderate to severe AD (Protopic Ointment; Astellas Pharma US, Inc., Deerfield, IL, USA) and pimecrolimus 1% cream for mild to moderate AD in children 2 years and older and adults (Elidel Cream; Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA)^{67,68}. Both tacrolimus^{69–74} and pimecrolimus^{75–82} have demonstrated short-term (3 weeks) and long-term (24 months) safety and efficacy in the treatment of AD in adults and children. The results of several major trials are summarized in Table 1.

Tacrolimus ointment should be applied topically twice daily as a thin layer to affected areas of the skin, without occlusive dressings⁶⁷. In short- and long-term vehicle-controlled and open-label clinical trials in adults and children, tacrolimus reduced erythema, edema, other cutaneous symptoms of AD, and pruritus as measured by the original or modified versions of the Eczema Area and Severity Index (EASI), the Physician's Global Evaluation of clinical response, and other rating scales (Table 1)^{69–73}. Many patients experienced rapid clinical improvement, often within the first week of treatment^{69,71–73}. Tacrolimus therapy has also been shown to improve QoL in adults, children, and toddlers with AD⁸³.

As with tacrolimus, pimecrolimus should be applied topically twice daily as a thin layer to affected areas of the skin, without occlusive dressings⁶⁸. In short-term and long-term vehicle-controlled, clinical trials in adults and children, the use of pimecrolimus cream 1% intermittently (on an as-needed basis to prevent the progression to flares) reduced the number and severity of flares and prolonged the time to major flares, offering long-term control of AD (Table 2)^{75,77,78}. Pimecrolimus also reduced pruritus and cutaneous symptoms of AD as measured by the EASI, the Investigator's Global Assessment, and several other rating scales^{75–79}. Additionally, relative to a 'usual care' protocol (treatment with emollients and topical corticosteroids only), a treatment protocol that included pimecrolimus cream 1% improved the QoL of adult patients⁷⁸, pediatric patients⁸⁴, and the parents of infants and children with AD^{84–86}. Randomized, double-blind, vehicle-controlled clinical trials^{80,81,87} and open-

label extension studies^{82,87} suggest that pimecrolimus cream 1% is safe and effective in infants with AD (Table 2). A randomized, double-blind controlled study in healthy volunteers that evaluated the impact of topical application of vehicle, pimecrolimus 1.0%, betamethasone-17-valerate 0.1%, or triamcinolone acetonide 0.1%, found that, in contrast to the TCSs used, pimecrolimus did not induce skin atrophy⁸⁸. Clinical trial data also indicate that pimecrolimus is a safe and effective steroid-sparing option for the treatment of sensitive skin areas, such as the face and neck⁷⁶.

Overall, TCIs provide efficacy with a very favorable safety profile^{71,72,75,77,79}. Data indicate that the TCIs are associated with a low incidence of adverse events (AEs) and consistently low systemic drug exposure^{89,90}, even in the youngest patients with extensive disease^{90,91}. In clinical trials, the most common AE associated with TCIs was a transient application-site burning^{67,68}. Other frequently reported AEs were pruritus, flu-like symptoms, upper respiratory tract infection, nasopharyngitis, skin erythema, and headache^{67,68}. TCIs are also appropriate as an alternative therapeutic option when other topical prescription treatments (e.g., TCSs) have been unsuccessful, or when they are inadvisable. For example, TCSs may not be advisable for patients who have eczema on the face, neck, and/or other sensitive skin areas owing to the increased risk for adverse events in these regions; therefore, TCIs may be a good choice for such patients (i.e., patients with mild to moderate eczema, aged 2 years and older, with flares in these areas).

Owing to rare cases of lymphoma and skin malignancy reported in postmarketing surveillance of patients treated with TCIs, data from animal studies of carcinogenicity, and similarities in the mechanism of action between TCIs and oral calcineurin inhibitors, a boxed warning was added to the labels of tacrolimus ointment and pimecrolimus cream in January 2006^{67,68}. Although the warning states that 'long-term safety of topical calcineurin inhibitors has not been established', it also notes that 'a causal relationship has not been established' and that the risk of malignancy is theoretical^{67,68}. In response to the boxed warning, several organizations^{52,92,93} have published statements asserting that currently available data do not provide evidence of systemic immunosuppression, impact on delayed-type hypersensitivity, or increased risk of malignancy with TCIs. While it is beyond the scope of this article to address this topic in depth, we refer the reader to the following references for further information: Fonacier *et al.*⁹²; Hultsch *et al.*⁹⁰; Lebwohl and Gower⁹⁴; Ring *et al.*⁹³; Bieber *et al.*⁹⁵; Berger *et al.*⁹⁶; and Fonacier *et al.*⁹⁷. Furthermore, as outlined in the previous sections, data from clinical trials of up to 24 months in duration in adult and pediatric patients (Table 2), as well as

Table 1. Studies evaluating the safety and efficacy of tacrolimus in patients with AD

Active agent, dosage/strength	First author, publication date	Study description	N, age range, disease characteristics	Primary efficacy endpoint(s), results	Safety results
Tacrolimus 0.03%, 0.1%, 0.3% ointment	Ruzicka ⁶⁹ , 1997	RCT, DB, PG, VC, MC, 3-week treatment phase	N = 213, 13-60 years, moderate-severe AD	Primary endpoint: change in score based on erythema, edema, pruritus. Results: for trunk and extremities, median percentage score decreases were 66.7%, 83.3%, 75.0%, and 22.5% for patients receiving tacrolimus 0.03%, 0.1%, 0.3%, and vehicle, respectively; for face and neck, values were 71.4%, 83.3%, 83.3%, and 25.0%, respectively. Improvement noted within 3 days	Burning sensation at application site was only AE with significantly higher incidence in tacrolimus group than control group ($p < 0.001$)
Tacrolimus 0.03%, 0.1%, 0.3% ointment	Boguniewicz ⁷⁰ , 1998	RCT, DB, PG, VC, MC, 22-day treatment phase	N = 180, 7-16 years, moderate-severe AD, 5-30% BSA involvement	Primary endpoint: physician's global evaluation of clinical response. Results: marked to excellent AD improvement or clearing in 69%, 67%, 70%, and 38% of patients receiving tacrolimus 0.03%, 0.1%, 0.3%, and vehicle, respectively; clinical improvement generally noticed within first 1-2 weeks	No significant differences between treatment groups
Tacrolimus 0.1% ointment	Reitamo ⁷¹ , 2000	OL, NC, MC, 6- or 12-month	N = 316, ≥ 18 years, moderate-severe AD, 5-60% BSA involvement	Primary endpoint: change in mEASI* scores. Results: greatest decrease in symptoms during first week of treatment, with continued mEASI improvements until Month 3; maximal improvement continued throughout remainder of study	(NC study)
Tacrolimus 0.1% ointment	Kang ⁷² , 2001	OL, NC, MC, 12-month	N = 255, 2-15 years, moderate-severe AD	Primary endpoints: clinical signs of AD, % of BSA affected, and EASI* scores. Results: improvement in all efficacy variables noted after 1 week; most patients continued to improve during remainder of study	(NC study)
Tacrolimus 0.03% or 0.1% ointment	Paller ⁷³ , 2001	RCT, DB, PG, VC, MC, 12-week	N = 351, 2-15 years, moderate-severe AD, 10-100% BSA involvement	Primary endpoint: incidence of success based on physician's global evaluation of clinical response. Results: patients with clinical improvement $\geq 90\%$ included 35.9%, 40.7%, and 6.9% of those in tacrolimus 0.03%, 0.1%, and vehicle groups, respectively ($p < 0.001$, tacrolimus vs. vehicle); tacrolimus produced substantial clinical improvement during first week	AEs with significantly greater incidence in tacrolimus 0.03% group than vehicle group were 'skin burning' (42.7% vs. 29.0%, $p = 0.040$), pruritus (41.2% vs. 26.6%, $p = 0.030$), varicella (4.8% vs. 0%, $p = 0.042$), and vesiculobullous rash (3.8% vs. 0%, $p = 0.042$)

AD = atopic dermatitis; AE = adverse event; BSA = body surface area; DB = double-blind; EASI = Eczema Area and Severity Index; MC = multicenter; mEASI = modified Eczema Area and Severity Index; NC = non-comparative; NOS = not otherwise specified; NS = not statistically significant; OL = open-label; PG = parallel-group; RCT = randomized controlled trial; TCS = topical corticosteroid; VC = vehicle-controlled

*The EASI is a composite, validated score objectively assessing the severity of erythema, infiltration/papulation, excoriations, and lichenification in the head/neck, trunk, upper and lower limbs and the surface area involvement. Combining the results from each region, age-adjusted for the percentage of each body area involved, gives a total score in the range of 0-72. Lower scores indicate less severe disease

Table 2. Studies evaluating the safety and efficacy of pimecrolimus in patients with AD

Active agent, dosage/strength	First author, publication date	Study description	N, age range, disease characteristics	Primary efficacy endpoint(s), results	Safety results
Pimecrolimus cream 1%	Meurer ⁷⁵ , 2002	RCT, DB, PG, VC, MC, 24-week	N = 192, 18–69 years, IGA† score 3–4, ≥ 5% BSA involvement	Primary endpoint: % days on which patients received TCS treatment. Results: mean % days of TCS use was 14.2% in pimecrolimus group and 37.2% in control group ($p < 0.001$)	Incidence of drug-related AEs was 24.0% in the pimecrolimus group and 20.8% in the control group
Pimecrolimus cream 1%	Eichenfield ⁷⁶ , 2002	Pooled analysis of two studies with identical designs: RCT, DB, PG, VC, MC, 6-week	N = 403, 1–17 years, IGA† score 2–3, ≥ 5% BSA involvement	Primary endpoint: IGA† score. Results: at Day 43, 34.8% of pimecrolimus group vs. 18.4% of controls rated as clear or almost clear of disease ($p \leq 0.05$)	Incidence of common AEs was 44.0% in the pimecrolimus group and 42.6% in the control group
Pimecrolimus cream 1%	Wahn ⁷⁷ , 2002	RCT, DB, PG, VC, MC, 1-year	N = 713, 2–17 years, IGA† score ≥ 2, ≥ 5% BSA involvement	Primary endpoint: AD flares at 6 months. Results: patients in the pimecrolimus group had fewer flares than those in the control group ($p < 0.001$)	Higher overall incidence of viral skin infections in the pimecrolimus than the control group (12.4% vs. 6.3%, $p = 0.038$)
Pimecrolimus cream 1%	Meurer ⁷⁸ , 2004	RCT, DB, PG, VC, MC, 6-month	N = 192, adults, IGA† score = 3, ≥ 5% BSA involvement	Primary endpoint: % days on which TCSs were used. Results: patients in the pimecrolimus group used TCSs for mean of 9.7% study days vs. 37.8% of days in the control group ($p < 0.001$)	Incidence of any AE 74.2% in the pimecrolimus group and 75.0% in the control group; incidence of drug-related AEs 22.6% in the pimecrolimus group and 23.1% in the control group
Pimecrolimus cream 1% or 0.1% triamcinolone acetonide cream ± 1% hydrocortisone acetate cream	Luger ⁷⁹ , 2004	RCT, DB, PG, active-controlled, MC, 1-year	N = 658, 18–79 years, moderate–severe AD, ≥ 5% BSA involvement	Primary endpoint: EASI* scores. Results: among study completers in the pimecrolimus group, marked overall improvement in AD (median overall EASI score of 3.2) compared with baseline (score of 11.8); median EASI scores were lower in the TCS group than the pimecrolimus group at all time points	Significantly higher incidence of skin papilloma in the TCS group than the pimecrolimus group (2.1% vs. 0%); treatment difference, –2.1% (95% confidence interval, –3.7% to –0.6%)
Pimecrolimus cream 1%	Ho ⁸⁷ , 2003	RCT, DB, PG, VC, MC, 6-week (DB), 20-week (OL extension with pimecrolimus only)	N = 186, 3–23 months, IGA† score 2–3, ≥ 5% BSA involvement	Primary endpoint: IGA† score at end of DB period. Results: after 6 weeks, 54.5% in the pimecrolimus group and 23.8% in the vehicle group were rated as clear or almost clear	Incidence of ≥ 1 treatment-emergent AE 74.8% in the pimecrolimus group and 65.1% in the control group during DB phase; incidence of AEs approximately 80% during OL extension
Pimecrolimus cream 1%	Breuer ⁸⁰ , 2004	RCT, DB, PG, VC, MC, 4-week (DB), 12-week (OL extension with pimecrolimus only)	N = 196, 3–23 months, IGA† score 2–5, ≥ 5% BSA involvement	Primary endpoint: EASI* score. Results: mean EASI score decreased by 71.5% in the pimecrolimus group and increased by 19.4% in the control group between baseline and Day 29 ($p < 0.001$); response to pimecrolimus evident by Day 4	Pimecrolimus treatment was consistently well tolerated

Table 2. (Continued)

Active agent, dosage/strength	First author, publication date	Study description	N, age range, disease characteristics	Primary efficacy endpoint(s), results	Safety results
Pimecrolimus cream 1%	Kapp ⁸¹ , 2002	RCT, DB, PG, VC, 1-year	N = 251, 3–23 months, IGA† score ≥ 2, ≥ 5% BSA involvement	Primary endpoint: incidence of flares at 6 months. Results: pimecrolimus associated with lower incidence of flares than conventional treatment ($p < 0.001$); 67.6% in the pimecrolimus group completed 6 months on study without flare compared with 30.4% in the control group	No significant differences between treatment groups
Pimecrolimus cream 1%	Papp ⁸² , 2005	OL, NC, 1-year extension to 1-year study of Kapp <i>et al.</i> ⁸¹	N = 91, 3–23 months at inclusion, mild–severe AD	Primary endpoint: proportion of patients with no flares. Results: among all patients, 76.9% had no flares during second year; among those who received pimecrolimus for 2 years, proportion with no flares increased from 77.6% during first year to 85.5% during second year	(NC study)

AD = atopic dermatitis; AE = adverse event; BSA = body surface area; DB = double-blind; EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; MC = multicenter; NC = non-comparative; NOS = not otherwise specified; NS = not statistically significant; OL = open-label; PG = parallel-group; RCT = randomized controlled trial; TCS = topical corticosteroid; VC = vehicle-controlled

*The EASI is a composite, validated score objectively assessing the severity of erythema, infiltration/papulation, excoriations, and lichenification in the head/neck, trunk, upper and lower limbs and the surface area involvement. Combining the results from each region, age-adjusted for the percentage of each body area involved, gives a total score in the range of 0–72. Lower scores indicate less severe disease

†The IGA is a static, 6-point measure of disease severity, based on an overall assessment of skin lesions. A score of 0 indicates no inflammatory signs of AD; a score of 5 indicates severe erythema and severe papulation/infiltration with oozing/crusting

postmarketing experience, indicate that TCIs are safe and effective when used appropriately, and can play an important role in a comprehensive treatment strategy for AD^{52,92,93}.

Adjunct therapies for severe AD

Patients with severe AD may benefit from adjunct therapies, including antihistamines and topical and systemic anti-infectives. Antihistamines are sometimes prescribed to relieve the pruritus associated with AD^{33,52}, but evidence from methodologically sound clinical trials does not indicate that antihistamines have a direct therapeutic effect^{98,99}. Sedating antihistamines, however, may alleviate the sleep disturbances associated with AD^{98,99}.

Patients with AD are at increased risk for bacterial, viral, and fungal skin infections, and these infections can have a negative impact on the course of the disease². In many patients, the affected and unaffected skin is colonized with *S. aureus*¹⁰⁰. Both topical and systemic antibiotics are effective against skin infections caused by *S. aureus* and other types of bacteria, but duration of therapy should be limited to minimize the risk of antibiotic resistance⁵². Patients with cutaneous fungal infections may benefit from topical or systemic treatment with ketoconazole or other azole antifungal agents³⁰. Antiviral therapy (e.g., acyclovir) should be initiated in patients with viral infections (a frequent and recurring complication of AD), especially in the case of life-threatening dissemination of cutaneous herpes simplex virus (eczema herpeticum), which may occur in those with extensive AD³³.

Treatment of refractory AD

In most patients, AD can be controlled with topical therapies, but systemic therapy may be warranted in those with severe disease². Systemic agents used for the treatment of refractory AD include oral steroids, cyclosporine, mycophenolate mofetil, azathioprine, methotrexate, and interferon. Patients with refractory disease can also have a clinical response to phototherapy.

Some patients experiencing acute exacerbations of AD may benefit from short courses of oral corticosteroids, but rebound flare upon discontinuation is a concern^{30,33,52}. Well-designed clinical trials have not established appropriate dosing regimens or elucidated the safety of oral corticosteroids in this population^{33,52}. Because of the risk of side effects, the use of systemic corticosteroids is limited to very severe, refractory cases¹⁰¹.

The use of cyclosporine is recommended by the American Academy of Dermatology for AD based on the results of randomized controlled trials, but it is not currently approved by the FDA for this indication⁵².

In a randomized, open-label, 12-month study in patients with severe AD, treatment with cyclosporine at a starting dose of 3 mg/kg/day was efficacious, well tolerated, and associated with low rates of increases in serum creatinine and diastolic blood pressure¹⁰². Other work has shown that patients often have a clinical response within 10–20 days after beginning treatment, but relapse may occur upon cessation of therapy^{103,104}. Short-term therapy is usually advisable³³, and in most patients treatment can be tapered slowly after 8 weeks¹⁰⁵. However, in a randomized comparison in 40 children, Harper and colleagues¹⁰⁶ found that relative to multiple courses with short-term (12 weeks) therapy, continuous therapy for 1 year resulted in more consistent control of AD¹⁰⁶. Of note, at the 12-month time point, only patients in the continuous arm exhibited significant ($p = 0.01$) improvements from baseline with respect to quality of life and the impact of AD on the family.

Mycophenolate mofetil is a purine biosynthesis inhibitor indicated for the prophylaxis of organ rejection¹⁰⁷. Data from several small studies suggest that it has a possible benefit in the treatment of severe AD^{107,108}. AEs reported in patients with AD include nausea, lactate dehydrogenase elevations, thrombocytopenia, and insomnia¹⁰⁷.

Azathioprine is a DNA and RNA biosynthesis inhibitor with immunosuppressant and cytotoxic action^{33,109}. Case reports, retrospective analyses, and a few small clinical trials support its use in refractory AD^{109–111}. Significant side effects (e.g., gastrointestinal disturbances, fever, rigors, myalgia, arthralgia, pancreatitis) limit the use of azathioprine, and dose-dependent hepatotoxicity and myelotoxicity are also of concern^{109–111}. Long-term use is not recommended because of the potential for developing malignancies, particularly squamous cell skin cancer and non-Hodgkin's lymphoma¹¹¹.

A number of small studies support the use of various types of ultraviolet (UV) light therapy, including combination broadband UVB and UVA, narrowband UVB, psoralen plus UVA (PUVA), and UVA1⁵². In one study, patients who received UVA1 irradiation five times per week for three consecutive weeks had a significant decrease in AD severity as determined by the SCORing Atopic Dermatitis (SCORAD) index, but efficacy was not sustained beyond 3 months after stopping treatment¹¹². Chronic narrowband UVB administration is associated with the potential risk of photocarcinogenesis¹¹¹, and phototherapy has been used with success in combination with TCSs⁵².

Data from case reports and uncontrolled studies suggest that recombinant interferon gamma, leukotriene inhibitors, oral pimecrolimus, methotrexate, intravenous immunoglobulin, and biologic agents (e.g., etanercept, infliximab) may be effective in patients

with severe refractory disease, but these agents are not approved by the FDA for this indication and data from controlled clinical trials are not available^{33,52}.

Comprehensive management of AD

Together, emollients, TCSs, TCIs, adjunctive therapy, and systemic treatments (for severe or refractory AD) play important roles in a comprehensive AD management plan tailored to the patient's age, disease severity, extent, and location, and the presence or absence of co-morbid conditions, such as infection. TCSs and TCIs may be used in a stepwise treatment approach^{2,33} that accelerates the time to flare reduction or clearance and minimizes corticosteroid use. As discussed previously, higher-potency TCSs can be used initially to reduce inflammation and pruritus and bring the flare under 'control'. At this point, a TCI can be applied until the flare resolves. Physicians should re-evaluate patients if symptoms worsen or persist beyond 6 weeks. Some physicians may prefer to re-evaluate their patients earlier and/or more frequently. Transition to TCI therapy may be particularly useful in patients with 'steroid phobia', who are unwilling to complete the prescribed course of TCS therapy owing to fears about side effects⁶⁴. This treatment approach also can help prevent flare rebound upon discontinuation of TCS therapy in predisposed patients^{2,33}. Additionally, clinical data have shown that use of pimecrolimus at the first sign or symptom of a flare can prevent progression to a severe flare^{75,77,78,81}. Irrespective of the specific treatment regimen, physicians should closely monitor patient progress and response to therapy. Furthermore, counseling patients and caregivers about the chronic nature of AD is necessary so as to create realistic expectations about the disease course and the effects of therapy.

It should be noted that this analysis has focused primarily upon relatively recent, key open-label and randomized trials evaluating the treatment of AD. Thus, case-reports and small-scale studies, which may provide additional data pertaining to treatment, were typically not included in this analysis. Additionally, as there are few trials evaluating the treatment of AD with corticosteroids, the majority of the information pertaining to this therapeutic option was obtained from consensus statements and comprehensive review articles. Despite some of these inherent limitations, the results presented and the conclusions drawn are applicable to the majority of physicians treating, and patients with, AD.

Conclusions

Individuals with AD have a poorer QoL and experience increased psychological and financial burdens compared

with the general population. Treatment of AD should be based on a careful initial assessment, the extent and severity of the disease, and the impact of the disease on the patient and the patient's family. Patient education and daily preventive care are crucial to overall disease control. Appropriate maintenance care of the skin barrier can reduce xerosis and, thereby, minimize disease exacerbations.

The proven efficacy of TCSs has made them a mainstay of AD therapy for several decades. However, physician and patient concerns about local and systemic side effects limit their long-term utility. Possessing a favorable safety profile and demonstrating clear efficacy in the treatment of AD by reducing the number and severity of flares, TCIs have become an important treatment option in recent years. Accordingly, despite the addition of a boxed warning to the prescribing information, based on a potential risk of malignancy, TCIs are a valuable addition to the existing therapeutic armamentarium, overcoming some of the drawbacks of existing therapies, and can assist in the long-term management of AD. Longitudinal data from ongoing safety studies may provide additional information on the long-term safety of TCIs.

Physicians and patients should have an open dialog regarding the risks and benefits associated with all treatment options so that together they may best determine the most appropriate treatment strategy. A treatment algorithm tailored to the individual that includes non-pharmacologic, pharmacologic, and educational strategies will provide the greatest opportunity for successful long-term disease management.

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