



Immunomodulators, Atopic Dermatitis Therapeutic Class Review (TCR)

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MANAGEMENTSM

FDA-APPROVED INDICATIONS

Drug	Manufacturer	FDA-Approved Indications
crisaborole (Eucrisa®) ¹	Pfizer	Topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older
dupilumab (Dupixent®) ^{2*}	Regeneron/Sanofi	Treatment of patients 12 years and older with moderate to severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable; may be used with or without topical corticosteroids
pimecrolimus (Elidel®) ³	generic , Valeant/Bausch	Second-line therapy for the short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised adults and children 2 years of age and older, who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable
tacrolimus (Protopic®) ⁴	generic, Leo	Second-line therapy for the short-term and non-continuous chronic treatment of moderate to severe atopic dermatitis in non-immunocompromised adults and children who have failed to respond adequately to other topical prescription treatments for atopic dermatitis, or when those treatments are not advisable <ul style="list-style-type: none"> ▪ 0.03% ointment approved for patients 2 years to 15 years old ▪ 0.03% ointment and 0.1% ointment approved for adults

* Dupilumab (Dupixent) is also indicated as add-on maintenance treatment in patients with moderate to severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma. This indication will not be addressed in this therapeutic class review.

OVERVIEW^{5,6,7,8,9,10,11,12,13}

Atopic dermatitis (AD) is a chronic, non-contagious, inflammatory disease of the skin resulting from a combination of genetic and environmental factors. Approximately 70% of patients diagnosed with AD have a positive family history of atopic diseases.¹⁴ The odds of developing AD are 2 to 3 times higher in children with one atopic parent and increase to 3 to 5 times higher if both parents are atopic.

Often referred to as “eczema,” AD affects up to 25% of children and about 2% to 3% of adults.¹⁵ The majority of patients have a “mild” form of the disease, meaning the AD affects less than 20% of the body surface area (BSA). Still, left untreated, even the mild form can result in itching and rashes that becomes a significant and visible reminder of the disease. For people whose AD affects more than 20% of their bodies, the disease can be a physically painful condition.

Although symptoms of AD can develop at any age, it has been estimated that 60% of patients develop symptoms in the first year of life, while 90% develop symptoms before the age of 5 years.¹⁶ The majority of affected patients have resolution of the disease by adulthood, 10% to 30% do not, and a smaller percentage first develops symptoms as adults. Onset after age 30 years is less common and is often caused by exposure of the skin to harsh or wet conditions. AD commonly occurs in patients affected by asthma and other allergic conditions and is associated with elevated serum IgE levels. People who reside in cities and in dry climates appear to be more likely to develop this condition.

AD is characterized by extremely dry, itchy skin on the insides of the elbows, behind the knees, and on the face, hands, and feet.¹⁷ In response to the intense itching, patients may scratch or rub the affected area, which leads to further irritation and inflammation. As the skin loses moisture from the epidermal

layer, it becomes increasingly dry and may begin to crack, weep, crust, and scale. This damage to the integrity of the skin renders it less protective and more prone to infection. Despite the chronic nature of this dermatologic condition, there may be periods of the disease when the skin improves and periods when the skin worsens. Irritants, such as detergents, fumes, tobacco smoke, and alcohol-containing skin products, and allergens like dust mites, pollen, and animal dander can exacerbate AD or cause “flare ups”.

The American Academy of Dermatology (AAD) guidelines from 2014 state that emollients, topical corticosteroids, and topical calcineurin inhibitors are the standard of care for the treatment of AD.¹⁸ For patients whose eczema is not controlled by topical corticosteroids, or when there is a serious risk of adverse events from topical corticosteroids, topical calcineurin inhibitors should be used. Phototherapy is recommended as a treatment option after failure of emollients, topical steroids, and topical calcineurin inhibitors. Systemic immunomodulating agents are indicated for patients whose AD is not adequately controlled by topical regimens and/or phototherapy. Patients with this disease are prone to *Staphylococcus aureus* infections, and treatment with oral or topical antibiotics may be useful.

Like the AAD guidelines, the American Academy of Allergy, Asthma, and Immunology (AAAAI) 2012 guidelines state that pimecrolimus and tacrolimus are reasonable treatment options for patients as second-line treatment choices. First-line options include hydration (emollients), moisturizers, and topical corticosteroids.¹⁹ Crisaborole (Eucrisa) and dupilumab (Dupixent) were not available at the time of the development of these guidelines but may be considered as second-line treatment options for patients with mild to moderate atopic dermatitis.

Although topical corticosteroids are the standard of care in the treatment of AD, dermatologic effects, such as striae, atrophy, and tachyphylaxis, as well as potential non-dermatologic effects on linear growth rate, bone density, and hypothalamic-pituitary-adrenal (HPA) axis suppression, limit the long-term use of these agents.

Recent approvals of crisaborole (Eucrisa) and dupilumab (Dupixent) have expanded this class and provided additional alternative treatment options with different mechanisms of action for AD.

PHARMACOLOGY^{20,21,22,23,24,25}

Crisaborole (Eucrisa) is a phosphodiesterase 4 (PDE-4) inhibitor. Its PDE-4 inhibition leads to increased intracellular cyclic adenosine monophosphate (cAMP) levels; however, the specific therapeutic action of crisaborole for the treatment of atopic dermatitis is not well defined.

Dupilumab (Dupixent), a human monoclonal IgG4 antibody, inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling via binding to the IL-4 receptor alpha subunit found on both complexes, resulting in inhibition of cytokine-induced responses (e.g., proinflammatory cytokines, chemokines, IgE).

Pimecrolimus (Elidel) is a derivative of the macrolactam ascomycin. It binds to the intracellular protein macrophilin-12 (FKBP-12) and inhibits the calcium-dependent phosphatase calcineurin. As a consequence, it inhibits T-cell activation by blocking the transcription of cytokines. Cytokines of both the Th1-type (IL-2 and interferon-gamma) and Th2-type (IL-4 and IL-10) are inhibited in T-cells. In addition, pimecrolimus prevents the release of inflammatory cytokines and mediators from mast cells after stimulation by antigen/IgE. Pimecrolimus has no effect on the growth of fibroblasts or keratinocytes.

Tacrolimus (Protopic) is a topical macrolactam agent. It exerts its pharmacologic activity by binding to FKBP-12. A complex is then formed which includes calcineurin. This complex prevents the phosphatase activity of calcineurin and thus prevents gene transcription for the formation of various lymphokines (IL-2, interferon-gamma). Formation of other lymphokines may be inhibited, including IL-3, IL-4, IL-5, granulocyte macrophage colony stimulating factor, and tumor necrosis factor-alpha.

PHARMACOKINETICS^{26,27,28,29,30}

Systemic absorption occurs with crisaborole (Eucrisa). Once absorbed, it is highly protein bound (97%) and is metabolized to 2 inactive metabolites, which are primarily eliminated via renal excretion.

Dupilumab (Dupixent) reaches mean peak concentrations approximately 1 week post subcutaneous (SC) administration ($C_{max} = 70.1$ mcg/mL; SD of ± 24.1); however, trough concentrations were lower in patients with higher body weight in pharmacokinetic studies. Development of antibodies to dupilumab was associated with lower serum dupilumab concentrations. Steady-state is achieved by 16 weeks, bioavailability is estimated to be 64%, and the estimated volume of distribution is 4.8 ± 1.3 L. The metabolic pathway of dupilumab has not been characterized.

Minimal systemic absorption occurs from topical use of pimecrolimus (Elidel) or tacrolimus (Protopic).

CONTRAINDICATIONS/WARNINGS^{31,32,33,34,35,36}

All products in this class are contraindicated in those with known hypersensitivity to an active or inactive ingredient.

Hypersensitivity reactions, including contact urticaria, have been reported in patients using crisaborole (Eucrisa).

Hypersensitivity reactions, including generalized urticaria and serum sickness, have been reported in patients using dupilumab (Dupixent). In addition, conjunctivitis and keratitis were reported more frequently in clinical trials with dupilumab compared to placebo. Any new onset or worsening symptoms related to conjunctivitis or keratitis should be reported to a healthcare provider. Safety and efficacy of dupilumab have not been established in patients with asthma and patients with parasitic (helminth) infections were excluded from clinical trials; thus, the effect of dupilumab in these populations is unknown.

The Food and Drug Administration (FDA) in 2006 issued a public health advisory to inform healthcare professionals and patients about the potential cancer risk associated with use of pimecrolimus (Elidel) and tacrolimus (Protopic).³⁷ Animal studies, case reports in a small number of patients, and knowledge of the mechanism of action of these drugs form the basis for concern. With the true risk unknown, the FDA advises that these agents be used as second-line treatment options only as labeled for the short-term and intermittent treatment of AD after other prescription treatments have failed or cannot be tolerated. Both pimecrolimus (Elidel) and tacrolimus (Protopic) have a boxed warning regarding the long-term safety of topical calcineurin inhibitors, which has not been established. Rare cases of malignancy have occurred. Avoid continuous long-term use of calcineurin inhibitors and limit application to areas affected by AD. The safety of these drugs has not been established beyond 1 year of non-continuous use. If signs and symptoms of AD do not resolve within 6 weeks of pimecrolimus or tacrolimus use, patients should have their physician re-examine and confirm the diagnosis.

Bacterial and viral infections of treatment sites must be resolved prior to AD treatment with pimecrolimus and tacrolimus. AD patients should avoid use on malignant or pre-malignant skin conditions. In addition, some malignant skin conditions, such as cutaneous T-cell lymphoma (CTCL), may mimic atopic dermatitis. Patients with Netherton's syndrome or other skin diseases that may allow for increased systemic absorption should not use these products. Increased risk of varicella zoster virus infection, herpes simplex virus infection, and eczema herpeticum is associated with use of pimecrolimus and tacrolimus.

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During treatment with pimecrolimus or tacrolimus, patients with AD should minimize or avoid natural and artificial sunlight, even if pimecrolimus or tacrolimus is not present on the skin. It is not known if either agent interferes with skin response to ultraviolet damage. Safety of these products under occlusive dressings, which may promote systemic exposure, has not been studied and therefore should not be used by patients.

Patients who develop lymphadenopathy should have the etiology examined to determine its cause. In clinical studies, less than 1% of cases of lymphadenopathy were reported while using pimecrolimus and tacrolimus, and were noted to resolve upon appropriate antibiotic therapy. The majority of these cases had either a clear etiology or resolved. In the absence of a clear etiology for the lymphadenopathy, or in the presence of acute infectious mononucleosis, pimecrolimus or tacrolimus should be discontinued.

DRUG INTERACTIONS^{38,39,40,41,42}

Potential interactions between these agents and other drugs, including immunizations, have not been evaluated. The use of live vaccines should be avoided in patients using dupilumab (Dupixent). Responses to select non-live vaccines were similar in both dupilumab- and placebo-treated patients in clinical trials; however, the full impact of use of non-live vaccines has not been fully evaluated.

One metabolite of crisaborole (Eucrisa) can weakly inhibit CYP1A2 and CYP2B6, and moderately inhibit CYP21C8 and CYP2C9. The other metabolite and parent drug are not expected to have an effect on cytochrome p450 (CYP450) metabolism. However, no clinically significant drug interactions have been noted to date with crisaborole.

Due to low blood levels of pimecrolimus (Elidel) and tacrolimus (Protopic) detected after topical application, systemic drug interactions are not expected. However, concomitant administration of known CYP 3A4 inhibitors (e.g., erythromycin, itraconazole, ketoconazole, fluconazole, calcium channel blockers, and cimetidine) with pimecrolimus or tacrolimus in patients with widespread and/or erythrodermic disease should be done with caution.

ADVERSE EFFECTS^{43,44,45,46,47}

Drug	Skin Burning (%)	Pruritus (%)	Skin Erythema (%)	Rash (%)
crisaborole (Eucrisa) n = 1,012 adults and children	4	-	-	reported
vehicle n = 499 adults and children	1			nd
pimecrolimus (Elidel) n = 328 adults	25.9	5.5	2.1	0
pimecrolimus (Elidel) n = 272 children	8.5	1.8	2.2	4 (viral rash in infants)
vehicle n = 75 children	6.7	0	0	0
tacrolimus 0.1% (Protopic) n = 209 adults	58	46	28	2
tacrolimus 0.03% (Protopic) n = 210 adults	46	46	25	5
vehicle n = 212 adults	26	37	20	1
tacrolimus 0.03% (Protopic) n = 118 children	43	41	12	2
vehicle n = 116 children	29	27	13	4

Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. nd = no data.

As a subcutaneous (SC) agent, dupilumab (Dupixent) is associated with differing adverse effects than those listed above. The most common adverse reactions (incidence $\geq 1\%$) reported in clinical trials were injection site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infection, and dry eye. As with all therapeutic proteins, dupilumab has the potential for immunogenicity. Approximately 7% of patients treated with dupilumab in clinical trials developed antibodies for dupilumab. When used in combination with topical corticosteroids, 14% of these were classified as neutralizing. When used as monotherapy, 30% of these were classified as neutralizing.

SPECIAL POPULATIONS^{48,49,50,51,52}

Pediatrics

Crisaborole (Eucrisa), pimecrolimus (Elidel), and tacrolimus 0.03% (Protopic) are approved for use in patients ≥ 2 years of age.

Dupilumab (Dupixent) is indicated for patients ≥ 12 years of age.

The safety and effectiveness of tacrolimus ointment 0.1% have not been established in pediatric patients.

Pregnancy

Pimecrolimus (Elidel) is Pregnancy Category C; tacrolimus (Protopic) was previously Category C, but labeling has been updated to comply with the Pregnancy and Lactation Labeling Rule (PLLR). There are no available adequate well-controlled studies in women for the use of pimecrolimus or tacrolimus in pregnant women.

There are no available data regarding use of crisaborole (Eucrisa) in pregnant women to inform of drug-associated risk of miscarriage or fetal harm.

Available data for use of dupilumab (Dupixent) in pregnant women have not identified a drug-associated fetal or maternal risks. However, as IgG antibodies are known to cross the placenta, dupilumab may be transferred to the developing fetus.

Renal and Hepatic Impairment

Pharmacokinetic studies with agents in this class are insufficient to provide information regarding use in renal or hepatic impairment.

Immunocompromised

Neither pimecrolimus nor tacrolimus should be used in adult and pediatric patients who are immunocompromised.

DOSAGES^{53,54,55,56,57}

Drug	Adult	Children (2 to 15 years)	Availability
crisaborole 2% (Eucrisa)	Apply a thin layer to affected skin twice daily	Apply a thin layer to affected skin twice daily	Ointment: 60 gm tubes
dupilumab (Dupixent)	600 mg (2 x 300 mg at different injection sites) for 1 dose, followed by 300 mg every other week thereafter Administer in the thigh, abdomen (excluding area around the navel), or upper arm; rotate the injection site May be used with or without topical corticosteroids May be used with or without topical calcineurin inhibitors, but use of these should be reserved for problem areas only (e.g., face, neck, intertriginous and genital areas)	--	SC injection: 300 mg/2 mL single-dose, prefilled syringe
pimecrolimus 1% (Elidel)	Apply a thin layer to affected skin twice daily	Apply a thin layer to affected skin twice daily	Cream: 30, 60, and 100 gm tubes
tacrolimus 0.03% (Protopic)	Apply a thin layer to affected skin twice daily	Apply a thin layer to affected skin twice daily	Ointment: 30, 60, and 100 gm tubes
tacrolimus 0.1% (Protopic)	Apply a thin layer to affected skin twice daily	--	Ointment: 30, 60, and 100 gm tubes

Missed doses of dupilumab (Dupixent) should be administered within 7 days of the missed dose, followed by the original schedule thereafter. If this cannot be done, the patient should wait until their

next scheduled dose on the original schedule. Dupilumab may be self-administered with proper training. It is not for ophthalmic, oral, or intravaginal use.

Pimecrolimus (Elidel) cream and tacrolimus (Protopic) ointment are not associated with skin atrophy and therefore, can be used on sensitive areas such as the face, neck, and skin folds.^{58,59} Avoid contact with eyes or mouth.

CLINICAL TRIALS

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, comparative, controlled trials comparing agents within this class for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Comparative studies that are investigator-blinded have not been included.^{60,61,62}

crisaborole (Eucrisa) versus vehicle in adults and pediatrics

Two multicenter, randomized, double-blind, parallel-group, vehicle-controlled trials (AD-301 and AD-302) included a total of 1,522 patients with AD affecting a 5% to 95% treatable BSA.^{63,64} The subjects ranged from 2 to 79 years of age, 86.3% of which were from 2 to 17 years of age. On the Investigator's Static Global Assessment (ISGA) severity scale of 0 to 4, 38.5% of the subjects had a score of 2 (mild), and 61.5% had an ISGA score of 3 (moderate) in the overall assessment of AD (erythema, induration/papulation, and oozing/crusting) at baseline. In both trials, subjects were randomized 2:1 to receive crisaborole or vehicle applied twice daily for 28 days. The primary efficacy endpoint was the proportion of subjects at Day 29 who achieved an ISGA grade of clear (score of 0) or almost clear (score of 1) with a 2-grade or greater improvement from baseline. The primary efficacy endpoint was achieved in more crisaborole-treated subjects versus vehicle-treated subjects (AD-301: 32.8% versus 25.4%, $p=0.038$; AD-302: 31.4% versus 18%; $p<0.001$). More crisaborole-treated subjects achieved an ISGA score of clear (0) or almost clear (1) versus vehicle-treated subjects at Day 29 (AD-301: 51.7% versus 40.6%, $p=0.005$; AD-302: 48.5% versus 29.7%, $p<0.001$). At Day 29, pooled data showed crisaborole improved disease severity versus vehicle-treated patients as evidenced by a reduction in signs and symptoms of AD including pruritus ($p=0.002$), erythema ($p<0.001$), exudation ($p=0.001$), excoriation ($p<0.001$), induration/papulation ($p=0.002$), and lichenification ($p<0.001$). Crisaborole was well tolerated, with similar incidence of adverse effects as the vehicle.

dupilumab (Dupixent) versus placebo in adults

Two randomized, 16-week, double-blind, placebo-controlled, phase 3 trials established the safety and efficacy of dupilumab for the treatment of AD (SOLO 1, $n = 671$; and SOLO 2, $n = 708$).^{65,66} In both trials,

adults with moderate to severe AD for which topical treatment provided inadequate control or was medically inadvisable and with chronic AD for ≥ 3 years prior to screening were randomized 1:1:1 to subcutaneous (SC) dupilumab 300 mg or placebo weekly or dupilumab 300 mg every 2 weeks. Concomitant topical corticosteroids and calcineurin inhibitors, immunomodulating biologic agents, systemic glucocorticoids, and nonsteroidal systemic immunosuppressants were prohibited. Rescue treatment for AD was available in select circumstances. Disease severity was defined by an Investigator's Global Assessment (IGA) score ≥ 3 (range, 0 to 4) in the overall assessment of AD lesions, an Eczema Area and Severity Index (EASI) score ≥ 16 (range, 0 to 72), and a minimum BSA involvement of $\geq 10\%$. The primary outcome was the proportion of patients with a score of 0 or 1 (clear or almost clear) on the IGA and a reduction of ≥ 2 points from baseline at 16 weeks. In SOLO 1, this primary endpoint occurred in 38% of patients receiving every other week dupilumab, 37% of patients receiving weekly dupilumab, and 10% of patients receiving placebo ($p < 0.001$ for both dupilumab regimens versus placebo). In SOLO 2, this primary endpoint occurred in 36% of patients receiving every other week dupilumab, 36% of patients receiving weekly dupilumab, and 8% of patients receiving placebo ($p < 0.001$ for both dupilumab regimens versus placebo). In both trials, an improvement from baseline to 16 weeks of $\geq 75\%$ on the EASI was also higher in patients receiving dupilumab compared to placebo ($p < 0.001$). Injection-site reactions and conjunctivitis were reported more frequently with dupilumab compared to placebo. Notably, only the dupilumab every other week regimen is FDA-approved.

LIBERTY AD CHRONOS: A third trial with similar methodology compared 52 weeks of dupilumab 300 mg once weekly, once every 2 weeks, or placebo in adults with moderate to severe AD not adequately controlled by topical medications; however, in both groups, patients also received background topical corticosteroids ($n = 740$).⁶⁷ Patients were also permitted to receive as needed topical calcineurin inhibitors for problem areas only (e.g., face, neck, intertriginous and genital areas). The primary outcome was the proportion of patients with a score of 0 or 1 (clear or almost clear) on the IGA and a reduction of ≥ 2 points from baseline at 16 weeks. The primary endpoint occurred in 39% of patients receiving dupilumab compared to 12% of patients receiving placebo ($p < 0.0001$). In addition, an improvement from baseline to 16 weeks of $\geq 75\%$ on the EASI was also higher in patients receiving dupilumab compared to placebo (64% or 69% versus 23%, respectively; $p < 0.0001$). Adverse events were reported more often in the dupilumab groups than placebo.

dupilumab (Dupixent) versus placebo in pediatrics

The efficacy and safety of dupilumab monotherapy was evaluated in a multicenter, randomized, double-blind, placebo-controlled trial (NCT03054428) in adolescent patients 12 to 17 years of age ($n=251$) with moderate-to-severe AD and a minimum BSA involvement of $\geq 10\%$ (mean 57%).⁶⁸ Patients had previous inadequate response to topical medication. Patients who weighed < 60 were started on dupilumab 400 mg at week 0, followed by 200 mg every 2 weeks for 16 weeks; those weighing ≥ 60 kg were started on dupilumab 600 mg at week 0, followed by 300 mg every 2 weeks for 16 weeks. At week 16, the proportion of patients with IGA 0 or 1 was 24% with dupilumab and 2% with placebo. EASI-75 and EASI-90 were reported in 42% and 23% of dupilumab-treated patients, respectively, compared to 8% and 2% of patients who received placebo, respectively. Peak Pruritus Numeric Rating Scale (NRS) with ≥ 4 -point improvement was reported as 37% with dupilumab and 5% with placebo. Patients who received rescue treatment were considered non-responders (59% with dupilumab and 21% with placebo).

pimecrolimus (Elidel) versus topical corticosteroids in adults

A randomized, double-blind, multicenter European study compared the long-term safety and tolerability of pimecrolimus 1% cream and TCS in 658 adults with moderate-severe AD.⁶⁹ Patients applied either pimecrolimus or TCS (e.g., triamcinolone acetonide 0.1% cream and/or hydrocortisone acetate 1% cream) twice daily to all affected areas until complete clearance or for up to 1 year. A majority of patients treated with either pimecrolimus or TCS used the drug on a continuous basis over 1 year. In patients who had greater than 30% BSA involvement, the incidence rate of all skin infections was significantly lower in the pimecrolimus group than in the TCS group (95% confidence interval [CI] of the treatment difference: -25.3% to -3.4%). The most frequent application site reaction was burning (25.9% pimecrolimus and 10.9% TCS). Three TCS-treated patients reported skin striae. Efficacy was better in patients on continuous TCS therapy, although patients completing the study were similarly well-controlled in both groups. About 42% of the pimecrolimus-treated patients were maintained for 1 year without TCS.

pimecrolimus (Elidel) versus vehicle in pediatrics

A double-blind, randomized study assessed the time of onset of pruritus improvement in 174 children and adolescents (aged 2 to 17 years) with mild to moderate AD with moderate to severe pruritus.⁷⁰ In the 8-day study, patients applied twice daily pimecrolimus 1% cream or vehicle control. Pruritus was assessed by subjects using a 4-point pruritus severity scale (0 to 3). The primary outcome parameter, the time to a 1-point or more improvement from baseline for the pruritus score, was 48 hours in the pimecrolimus group and 72 hours for the vehicle group ($p=0.038$). From day 3 onward, significantly more patients receiving pimecrolimus had complete pruritus resolution compared to those receiving vehicle ($p=0.023$). At the end of the seven-day treatment, significantly more patients in the pimecrolimus group had improved or completed resolution of pruritus compared to the group assigned to the vehicle control ($p=0.008$).

A randomized, double-blind, multicenter study compared twice daily pimecrolimus cream 1% to vehicle cream in 521 patients aged 2 to 17 years, with a history of mild or moderate AD.⁷¹ These patients were clear or almost clear of disease prior to randomization. Treatment was initiated at the first signs and/or symptoms of recurring AD. A moderately potent TCS was allowed in both groups if AD worsened (as confirmed by the investigator) despite the application of study medication for at least 3 days. The primary efficacy endpoint was the number of days on study without TCS use for a flare. The mean number of TCS-free days was significantly higher ($p<0.0001$) in the pimecrolimus group compared to the vehicle group (160.2 versus 137.7 days, respectively). Patients treated with pimecrolimus cream 1% experienced 50% fewer flares requiring topical corticosteroids than patients who received vehicle cream (mean number of flares 0.84 versus 1.68, respectively; $p<0.0001$).

A randomized, double-blind study of less than or equal to 6 weeks, followed by a 6-week, open-label phase compared pimecrolimus cream 1% to vehicle twice daily in 200 children aged 2 to 11 years with mild to moderate facial AD dependent on or intolerant of topical corticosteroids.⁷² Patients were treated with the pimecrolimus cream or vehicle twice daily until clearance of facial AD or for a maximum of 6 weeks. Significantly more patients on pimecrolimus compared to vehicle patients were cleared/almost cleared of facial AD (IGA 0/1) on day 22 (57.1% versus 36.0%; $p=0.004$) and day 43 (74.5% versus 51%; $p<0.001$). Median time to clearance was 22 days compared to 43 days for the pimecrolimus group versus the vehicle group, respectively. Statistically significant differences for pimecrolimus compared with

vehicle were also seen on head and neck EASI, overall EASI, and head and neck pruritus scores. There were no differences in adverse events between treatment groups.

pimecrolimus (Elidel) versus hydrocortisone in pediatrics

In the 1-year, controlled, double-blind study, 713 AD patients ages 2 to 17 years were randomized 2:1 to a pimecrolimus-based or conventional AD regimen consisting of vehicle and topical corticosteroids.⁷³ The proportion of patients who completed 6 or 12 months with no flares was approximately twice as high in the pimecrolimus group compared with control (61% versus 34.2% at 6 months; 50.8% versus 28.3% at 12 months). Fewer flares were observed in the pimecrolimus group regardless of baseline disease severity. There were no appreciable differences between treatment groups in the overall incidence of adverse events. The authors concluded that pimecrolimus ointment appears to be safe and effective in children with atopic dermatitis.

tacrolimus (Protopic) versus topical corticosteroids in adults

A randomized, double-blind study compared the efficacy and safety of twice daily tacrolimus ointment 0.1% to a corticosteroid ointment regimen in 972 adults with moderate to severe AD, for a maximum of 6 months.⁷⁴ Tacrolimus ointment was applied to all affected areas over the whole body. For the corticosteroid group, hydrocortisone butyrate ointment 0.1% was applied to affected areas on the trunk and extremities, and hydrocortisone acetate ointment 1% was applied to affected areas on the face and neck. The study primary endpoint was the response rate defined as the proportion of patients with at least 60% improvement in the modified Eczema Area and Severity Index (mEASI) between baseline and month 3. More patients in the tacrolimus group responded to treatment by the third month compared to the corticosteroid group, 72.6% versus 52.3%, respectively ($p < 0.001$). The tacrolimus patients also showed greater improvement in mEASI, EASI, affected BSA, and physician and patient assessments of global response. More patients in the tacrolimus group experienced skin burning compared to the corticosteroid group, 52.4% versus 13.8%, respectively ($p < 0.001$). Skin burning was mild to moderate in severity and decreased rapidly after the first week of treatment in the majority of patients. There was no increase in the incidence of infections or malignancies over time in either treatment group.

A 3-week randomized, double-blind, parallel-group, multicenter study compared twice daily tacrolimus 0.03% and 0.1% ointment with hydrocortisone 17-butyrate 0.1% ointment in the treatment of 570 adults with moderate to severe AD.⁷⁵ Patients applied ointment twice daily to all affected areas for 3 weeks. The primary outcome of median mEASI mean area under the curve as a percentage of baseline was 47%, 36.5%, and 36.1% for patients who received 0.03% tacrolimus, 0.1% tacrolimus, and 0.1% hydrocortisone butyrate, respectively. There was no statistically significant difference between 0.1% tacrolimus and 0.1% hydrocortisone butyrate. The lower improvement in mEASI for 0.03% tacrolimus was statistically significant when compared with 0.1% tacrolimus ($p < 0.001$) or hydrocortisone butyrate ($p = 0.002$). The tacrolimus groups had more skin burning and pruritus at the application site compared to the hydrocortisone butyrate group ($p < 0.05$).

tacrolimus (Protopic) versus vehicle in pediatrics

The safety and efficacy of tacrolimus 0.03% and 0.1% ointment for the treatment of AD were evaluated in a 12-week, randomized, double-blind, vehicle-controlled study of 351 children 2 to 15 years of age with moderate to severe AD.⁷⁶ The mean percentage of BSA affected was 47.7%. Significantly more patients ($p < 0.001$) achieved clinical improvement of 90% or better with tacrolimus 0.03% or 0.1% ointment compared with vehicle. Significant improvements in the signs and symptoms of AD, percent

BSA affected, and the patient's/caregiver's assessment of pruritus were also observed early in treatment and were maintained throughout the study. Adverse events with a statistically significantly greater incidence in the tacrolimus 0.03% ointment treatment group compared with vehicle were limited to the sensation of skin burning, pruritus, varicella, and vesiculobullous rash ("blisters"). No adverse event occurred at a statistically higher incidence in the tacrolimus 0.1% ointment-treated group compared with vehicle. Both tacrolimus ointment concentrations were safe and significantly more effective than vehicle for the treatment of AD in children.

In the randomized, double-blind, vehicle-controlled multicenter trial, children ages 7 to 16 years were treated with tacrolimus 0.03%, 0.1%, or 0.3% ointment twice daily or vehicle for up to 22 days with a 2-week follow-up period.⁷⁷ The Physician's Global Evaluation of clinical response showed that 69% of patients in the 0.03% tacrolimus group, 67% in the 0.1% tacrolimus group, and 70% in the 0.3% tacrolimus group, compared with 38% in the vehicle group, had a marked to excellent (>75%) improvement or clearing of their AD ($p=0.005$, $p=0.007$, and $p=0.004$, respectively, for the 3 tacrolimus groups compared with the vehicle group). The mean percent improvement for the modified EASI at end of treatment for each of the tacrolimus groups (0.03%, 72%; 0.1%, 77%; and 0.3%, 81%) was significantly greater than that of the vehicle group (26%, $p<0.001$). The median percentage reduction in pruritus was significantly greater for tacrolimus-treated patients (74% to 89%) than for vehicle-treated patients (51%, $p=0.027$).

tacrolimus (Protopic) versus hydrocortisone in pediatrics

The efficacy and safety of tacrolimus 0.03% ointment applied once or twice daily over a 3-week period were compared with the twice daily application of hydrocortisone acetate 1% ointment in children with moderate to severe AD.⁷⁸ The primary study endpoint was the percentage change in the modified EASI between baseline and treatment end. Patients ages 2 years to 15 years were randomized in the double-blinded study to tacrolimus 0.03% ointment once daily ($n = 207$) or twice daily ($n = 210$) or hydrocortisone acetate 1% twice daily ($n = 207$). By the end of treatment, application of tacrolimus 0.03% ointment both once or twice daily resulted in significantly greater median percentage decreases in modified EASI (66.7% and 76.7%, respectively) compared with hydrocortisone acetate 1% (47.6%; $p<0.001$). Furthermore, the median percentage decrease in modified EASI was significantly greater for patients applying 0.03% tacrolimus twice daily compared with once daily ($p=0.007$). Patients with severe AD benefited especially from twice daily application of 0.03% tacrolimus ointment compared with once daily application ($p=0.001$). Transient mild to moderate skin burning occurred significantly more often in the tacrolimus groups but resolved in most cases within 3 to 4 days ($p=0.028$).

tacrolimus (Protopic) versus fluticasone in pediatrics

A randomized, double-blind, non-inferiority trial compared tacrolimus 0.03% ointment to fluticasone 0.005% ointment in 479 children ages 2 to 15 years old with moderate to severe AD who had not responded sufficiently to conventional therapies.⁷⁹ Ointments were applied twice daily until clearance or for a maximum of 3 weeks and, if lesions remained, once daily for up to 3 weeks further. Primary endpoint was week 3 response rate (improvement of $\geq 60\%$ in mEASI and not withdrawn for lack of efficacy). Response rates were 86.3% and 91.5% with tacrolimus and fluticasone, respectively. Lower limit of the 95% CI was -11.8%, which exceeded the non-inferiority limit of -15% and met the primary endpoint. Moderate or better improvement on secondary endpoints of the physicians' global assessment occurred in 93.6% and 92.4% of patients in the tacrolimus and fluticasone groups, respectively, while median pruritus scores improved by 84% and 91.5%, respectively. Sleep quality

improved by approximately 92% in both treatment groups. After day 21, new flare-up occurred in 5.5% and 11.3% of patients receiving tacrolimus and fluticasone, respectively. Mean times to new flares were 6.5 ± 5 days and 8.6 ± 5.2 days. Adverse events were similar between the 2 arms, but burning at application-site was higher in the tacrolimus arm.

META-ANALYSIS

A meta-analysis to evaluate the efficacy and safety of pimecrolimus cream 0.1% in the treatment of AD in the pediatric population was conducted up to July 2013.⁸⁰ The analysis included 7 studies with a total of 2,170 pediatric patients and concluded that pimecrolimus cream 0.1% was not significantly better than the vehicle for AD based on the Odds Ratios (ORs). The ORs for response for pimecrolimus versus vehicle at day 8, day 26, and 6 weeks were 4.95 (95% CI, 2.79 to 8.8), 9.69 (95% CI, 4.12 to 22.83), and 3.83 (95% CI, 1.94 to 7.56), respectively. Pimecrolimus also did not show beneficial effects when analyzed for mild or absent pruritus at day 4 (OR, 8.29; 95% CI, 3.88 to 17.72 favoring vehicle), day 43 (OR, 1.81; 95% CI, 1.13 to 2.89 favoring vehicle), and 1 week (OR, 2.29; 95% CI, 1.45 to 3.6 favoring vehicle) as compared with vehicle. There was no significant difference in achieving mild or absent pruritus in 1 study that compared pimecrolimus with tacrolimus (OR, 0.94; 95% CI, 0.44 to 1.99). The care givers of the pediatric patients assessed that more patients showed an improvement in overall disease in the vehicle group at day 8 (OR, 3.3; 95% CI, 2.03 to 5.35), day 29 (OR, 14.14; 95% CI, 6.87 to 29.13), and day 43 (OR, 4.11; 95% CI, 2.59 to 6.52), as compared with pimecrolimus 0.1% group. There was no significant difference seen between the adverse effects in both groups (pimecrolimus versus vehicle/tacrolimus; OR, 1.19; 95% CI, 0.85 to 1.65).

A meta-analysis conducted in 2005 concluded that success rates for tacrolimus (Protopic) and pimecrolimus (Elidel) were statistically similar.⁸¹ A 2007 Cochrane Database systematic review found pimecrolimus was less effective than tacrolimus and also less effective than moderate to potent corticosteroids.⁸² However, these results were based on mostly investigator-blinded trials.^{83,84} Pimecrolimus was associated with significantly more overall withdrawals and skin burning compared to corticosteroids. There were more withdrawals with pimecrolimus than tacrolimus but no significant difference in proportions of patients experiencing adverse events.

A 2009 systematic review and meta-analysis found pimecrolimus was less effective than topical corticosteroids, but it showed that use of pimecrolimus for 6 months resulted in reduction in flares and had a steroid-sparing effect when used early in treatment.⁸⁵ Both 0.1% and 0.03% tacrolimus ointments were as effective as moderate potency corticosteroids and more effective than mild corticosteroids. Large, double-blind, comparative trials of pimecrolimus and tacrolimus are needed.

A meta-analysis to evaluate the efficacy and safety of tacrolimus and pimecrolimus was performed up to December 2008 and included 6,288 infants and children with AD.⁸⁶ ORs for response for the tacrolimus arm versus response in control groups including vehicle, 1% hydrocortisone acetate and 1% pimecrolimus, were 4.56 (95% CI, 2.8 to 7.44), 3.92 (95% CI, 2.96 to 5.2) and 1.58 (95% CI, 1.18 to 2.12), respectively. The effect difference between 0.03% tacrolimus and 0.1% tacrolimus ointments was not statistically significant (OR, 0.9; 95% CI, 0.55 to 1.48). The incidence of adverse events of tacrolimus ointment or pimecrolimus cream was similar to the vehicle with burning and pruritus reported as major adverse events.

SUMMARY

Liberal use of emollients is recommended by the 2014 American Academy of Dermatology (AAD) and the American Academy of Allergy, Asthma, and Immunology (AAAAI) 2012 guidelines; as emollients or moisturizing agents may reduce disease severity and the need for pharmacologic intervention. In addition, both guidelines consider topical corticosteroids the standard of care to which other treatments are compared and are effective in a majority of patients with AD (atopic dermatitis). The calcineurin inhibitors, pimecrolimus (Elidel) and tacrolimus (Protopic), are second-line agents that can be used for the treatment of acute flares of AD. In cases with disease persistence and/or frequent recurrences, topical calcineurin inhibitors are options for maintenance therapy until remission is achieved, and patients can revert back to emollient use. Unlike corticosteroids, pimecrolimus and tacrolimus are not reported to cause skin atrophy. Two other agents have been approved for the treatment of atopic dermatitis: crisaborole (Eucrisa) and dupilumab (Dupixent). These agents differ in mechanism of action, potentially offering an alternative treatment option; however, they have only been evaluated in placebo-controlled trials. Like the calcineurin inhibitors, crisaborole is a topical product administered twice daily and may be used in pediatric patients ≥ 2 years of age. Dupilumab, indicated as second-line treatment, is a subcutaneous product administered every other week and is approved in patients ≥ 12 years of age. Its use has been studied in combination with topical corticosteroids as well as topical calcineurin inhibitors applied to select locations.

Rare cases of malignancies have been reported with the use of the calcineurin inhibitors, pimecrolimus and tacrolimus, although a causal relationship has not been established. Therefore, the Food and Drug Administration (FDA) has recommended that these agents be used for the short-term and intermittent treatment of AD. Hypersensitivity reactions may occur with all agents within this class. In addition, as a therapeutic protein, patients may develop antibodies to dupilumab.

No double-blind direct comparative clinical trials exist that demonstrate clear advantages of 1 product over another.

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