JAMA Insights

Treatment of Atopic Dermatitis

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Atopic dermatitis, commonly called eczema, is the most common chronic inflammatory skin condition, with a global prevalence of 2%.[1] Prevalence varies by age; among patients receiving care in the UK, atopic dermatitis occurs in 12% of children, 5% of adults aged 18 to 74 years, and 9% of adults aged 75 to 99 years.[2]

Atopic dermatitis is a clinical diagnosis characterized by itch; xerosis; and red, inflamed rashes with or without scale that can occur anywhere on the body, but with a predilection for flexural areas, such as the antecubital and popliteal fossae. Early age of onset and a personal or family history of other atopic conditions, such as asthma, are common but not always present. The pathogenesis of atopic dermatitis includes epidermal barrier disruption and inflammation. Over the last 10 years, the US Food and Drug Administration (FDA) and other regulators have approved multiple new therapies, providing more options for patients and clinicians.

Topical Treatment

Recent guidelines from US dermatology and allergy groups recommend that people with atopic dermatitis of all severities use over-the-counter moisturizers.[3-5] However, based on current evidence, guidelines do not recommend specific moisturizers or ingredients, and do not make recommendations regarding the frequency or timing of application.[3] A 4-group randomized clinical trial of 550 children aged 6 months to 12 years with atopic dermatitis randomized to receive a lotion, cream, gel, or ointment emollient twice daily as required for 16 weeks reported no clinically meaningful differences in eczema symptoms, measured by Patient Oriented Eczema Measure scores, among the 4 groups (P = .77).[6]

Topical corticosteroids, available in a range of potencies, are inexpensive and effective treatments for atopic dermatitis. In a network meta-analysis, potent topical corticosteroids, such as fluocinolone acetonide, were among the most effective treatments for improving clinical signs compared with vehicle control (658 vs 191 improved per 1000 participants; odds ratio [OR], 8.15 [95% CI, 4.99-13.57]).[7] Prescribing topical corticosteroids once rather than twice daily may not compromise efficacy; in a meta-analysis, once-daily application of predominantly potent or very potent topical corticosteroids was as effective as twice-daily or more application (635 vs 628 per 1000 participants achieving treatment success; OR, 0.97 [95% CI, 0.68-1.38]).

Nonsteroidal topical treatments can be used similarly to topical corticosteroids and are particularly useful for people whose atopic dermatitis does not improve with use of topical corticosteroids or who have lesions affecting sensitive sites, such as the face and groin. Topical calcineurin inhibitors (TCIs; tacrolimus 0.03% and 0.1% ointment and pimecrolimus 1% cream) are typically prescribed twice daily. Although not FDA approved for children younger than 2 years, they are often prescribed off label for children in this age group. TCIs have an FDA black box warning due to concerns about potential increased risk of cancer (eg, lymphoma and skin cancers), but long-term safety monitoring has been reassuring.[4]

Since 2016, 3 new classes of topical medications have been FDA approved for atopic dermatitis: phosphodiesterase-4 inhibitors (crisaborole 2% ointment and roflumilast 0.15% cream), a Janus kinase (JAK) inhibitor (ruxolitinib 1.5% cream), and an aryl hydrocarbon receptor agonist (tapinarof 1% cream). These medications have been approved predominantly based on vehicle-controlled trials, making comparisons among them difficult. A network meta-analysis reported ruxolitinib cream to be among the most effective treatments based on dichotomous improvement on various investigator-assessed scales (eg, groups defined as improved or not improved on scales such as the Eczema Area and Severity Index [EASI; 645 improved per 1000 treated], similar to potent topical corticosteroids [658 improved per 1000 treated]).[7] Conversely, crisaborole was among the least effective (413 improved per 1000 treated). Large phase 3 trials for roflumilast and tapinarof were not published prior to publication of that network meta-analysis, so their relative efficacy is less certain.

Systemic Therapy

Prior to the approval of dupilumab in 2017, only UV phototherapy and off-label medications, such as methotrexate and cyclosporine, were available (**Table**).[8,9] These older treatments are conditionally recommended by recent American Academy of Dermatology guidelines, and use of systemic corticosteroids is conditionally recommended against.[10] Dupilumab, a monoclonal antibody approved for patients as young as 6 months, was followed by tralokinumab and lebrikizumab, all of which are subcutaneously administered biologics that target the interleukin (IL)-4 and -13 pathway. Nemolizumab, the most recently approved subcutaneously administered biologic, targets IL-31, an important cytokine in itch pathogenesis.

JAK inhibitors baricitinib (approved for atopic dermatitis in Europe but not in the US), upadacitinib, and abrocitinib (approved in the US) are new oral medications taken once daily. Despite their established efficacy, including more rapid onset of action than biologics, there is concern, mainly based on data for JAK inhibitors used to treat conditions such as rheumatoid arthritis, that patients treated with these medications may experience serious adverse events, including severe infection, clots, cancer, and cardiovascular events. Therefore, the FDA does not consider JAK inhibitors first-line systemic therapy for atopic dermatitis.

In a living systematic review and network meta-analysis of systemic treatment for atopic dermatitis, including biologics and JAK inhibitors, high-dose upadacitinib (30 mg daily) was the most effective treatment overall after up to 16 weeks of treatment (mean difference [MD] in change in EASI score vs placebo, −13.5 [95% CrI, −15.2 to −11.9]) and dupilumab was the most effective biologic (MD, −10.5 [95% CrI, −11.9 to −9.2]) among adults.[8] A difference in EASI score of 3.3, which is half the minimal clinically important difference at the individual patient level, is considered clinically important at the trial group level, indicating that these medications are associated with clinically meaningful improvement relative to placebo. An update of this systematic review and network meta-analysis

Table. Systemic Treatments for Atopic Dermatitis[a]

Treatment	Mechanism	Route and dosing	Efficacy	Notes
Systemic treatments			MD in change in Eczema Area and Severity Index score (95% CrI) vs placebo[8,9]	
Methotrexate, cyclosporine, azathioprine, mycophenolate	Immunomodulatory medications	Oral; various dosing regimens Methotrexate also available SC and intramuscularly		Used off label for atopic dermatitis
Dupilumab	Anti-interleukin-4 receptor α biologic	600 mg, Then 300 mg SC every 2 weeks[b]	MD, −10.5 (95% CrI, −11.9 to −9.2)	First targeted systemic treatment approved for atopic dermatitis
Tralokinumab	Anti-interleukin-13 biologic	600 mg, Then 300 mg SC every 2 weeks	MD, −6.2 (95% CrI, −7.8 to −4.7)	Lower efficacy than dupilumab in a network meta-analysis[8]
Lebrikizumab	Anti-interleukin-13 biologic	500 mg, Then 250 mg SC every 2 weeks until week 16 then 250 mg every 4 weeks	MD, −8.5 (95% CrI, −10.4 to −6.5)	Similar efficacy to dupilumab in a network meta-analysis[8]
Nemolizumab	Anti-interleukin-31 biologic	60 mg, Then 30 mg SC every 4 weeks	MD, −4.4 (95% CrI, −6.5 to −2.4)	Lower efficacy than dupilumab in a network meta-analysis, other than for itch as the outcome[9]
Upadacitinib	Janus kinase inhibitor	15 mg or 30 mg orally daily	15 mg: MD, −11 (95% CrI, −12.6 to −9.4) 30 mg: MD, −13.5 (95% CrI, −15.2 to −11.9)	Usually start the 15-mg dose, then increase if needed; 30 mg daily was the most effective treatment in a network meta-analysis[8]
Abrocitinib	Janus kinase inhibitor	100 mg or 200 mg orally daily	100 mg: MD, −8.5 (95% CrI, −10.3 to −6.7) 200 mg: MD, −12.8 (95% CrI, −14.6 to −11.1)	Usually patients will start the 100-mg dose, then increase as needed

Abbreviations: MD, mean difference; SC, subcutaneous.

[a] Information on relative safety not provided, as serious adverse events are rare in clinical trials for atopic dermatitis, making results from network meta-analyses uncertain and difficult to interpret clinically.

[b] Adult dose given; different pediatric dosing regimens used based on age and weight.

provided information about nemolizumab, which was less effective than dupilumab at improving EASI scores (MD, 6.0 [95% CrI, 3.7-8.5]), but the medications were similar in their effect on itch (MD on peak itch numeric rating scale, 0.1 [95% CrI, −0.4 to 0.6]).[9]

Conclusions

Emollients and topical corticosteroids are recommended for patients with atopic dermatitis given their efficacy, safety, and cost. Nonsteroidal anti-inflammatory topical medications, including TCIs, phosphodiesterase-4, JAK inhibitors, and aryl hydrocarbon receptor agonists, are additional options, particularly for atopic dermatitis that does not improve with topical corticosteroids or that affects sensitive sites. Biologics can be used as first-line systemic treatment for severe and refractory atopic dermatitis, and oral JAK inhibitors are considered second-line treatment.

ARTICLE INFORMATION

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