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# Update on Treatment Options for Moderate to Severe Atopic Dermatitis

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Atopic dermatitis (AD) is chronic skin disorder characterized by pruritus and recurrent eczematous lesions accompanied by inflammation.[1] Other clinical features may include xerosis, erythema, erosions, oozing, and lichenification of the skin. The cause is unknown, but may be due immunologic dysfunction.[2] Atopic dermatitis affects 15-20% of children in developed countries and approximately 11% of children in the United States (U.S.).[3,4] The estimated prevalence of AD in U.S. adults is 3%.[3] Itching, sleep deprivation, and social embarrassment due to visible lesions can have substantial effects on the quality of life for people with AD.[5] The purpose of this newsletter is to review recently approved treatments for mild to moderate AD (crisaborole) and moderate to severe AD (dupilumab) and to evaluate their place in therapy for AD.

## Policy

In the Oregon Health Plan, the Health Evidence Review Commission (HERC) recently modified conditions funded on line 424 (moderate/severe inflammatory skin disease) to include psoriasis, AD, lichen planus, Darier disease, pityriasis rubra pilaris and discoid lupus.[6] Prior to this update, AD treatment was not funded. Guideline Note 21 defines severe inflammatory skin disease as having functional impairment (e.g. inability to use hands or feet for activities of daily living, or significant facial involvement preventing normal social interaction) and one or more of the following: 1) at least 10% of body surface area involved; and/or 2) hand, foot or mucous membrane involvement.[6] Due to these recent changes to the HERC prioritized list, moderate to severe AD became a funded condition effective January 1, 2018. Mild AD is classified on line 530 and will therefore remain unfunded.[6]

## Initial Treatment

The mainstays of therapy for AD are skin care with frequent application of an emollient to maintain the skin's epidermal barrier and avoidance of triggers. For patients with mild AD, initial treatment with a mild potency topical corticosteroid (TCS) applied 1-2 times a day for 2 to 4 weeks is recommended.[7] For moderate AD, short-term use of a medium to high potency TCS is recommended. Topical calcineurin inhibitor (TCIs) are nonsteroidal immunomodulating agents that are considered a second-line option in both adults and children with AD who have not responded to TCS or when those treatments are not advisable.[8,9] Tacrolimus 0.03% ointment and pimecrolimus cream are indicated for use in individuals age 2 years and older, whereas tacrolimus 0.1% ointment is only approved in those older than 15 years.[8,9]

The use of TCS and TCI therapies in AD is supported by the American College of Dermatology's 2014 guideline[7] and 2004 guidance from the National Institute for Health and Care Excellence (NICE).[10] Topical corticosteroids are recommended for AD-affected individuals who have failed to respond to good skin care and regular use of emollients alone. However, prolonged use of TCS can result in telangiectasia, increased hair, skin tears, and atrophic skin changes, which can be permanent.[11] The main rationale for use of TCIs is that they do not cause skin atrophy and are therefore of particular value in delicate skin areas such as the face, neck, and skin folds.[7]

A systematic review and meta-analysis was compiled by the Drug Effectiveness Review Project (DERP) to evaluate the effectiveness of TCIs.[12] Four fair quality head-to-head trials of tacrolimus ointment (0.03% or 0.1%) versus pimecrolimus 1% cream in patients with moderate to severe AD have been published.[13-16] All 4 trials reported response to treatment, with 3 trials using an Investigator Global Assessment (IGA) score of 0 or 1 to indicate disease clearing, while the 4th open label trial did not describe the method of determining treatment success. Improvements in the percent of body surface area affected by AD varied widely across the studies, from a 64.6% reduction with tacrolimus in one study down to a 7% improvement with tacrolimus in another study.[12] Common adverse reactions for TCIs are burning or stinging, itching, and erythema or irritation, with a similar incidence for pimecrolimus and tacrolimus.

The U.S. Food and Drug Administration (FDA) labeling for tacrolimus and pimecrolimus include boxed warnings regarding a theoretical risk for skin cancers and lymphoma associated with long-term TCI administration.[8,9] Therefore, continuous long-term use of TCIs in any age group should be avoided and application limited to areas of AD involvement.[8,9]

**Pimecrolimus and tacrolimus are recommend after trial of first line therapies for moderate to severe AD and are preferred agents on the Oregon Health Plan preferred drug list (PDL)**

## New Treatments for Atopic Dermatitis

Two additional agents with novel mechanisms of action have recently been added to AD treatment algorithms. Crisaborole is a topical phosphodiesterase 4 (PDE4) inhibitor approved for mild-to-moderate AD in adults and children. PDE4 is a regulator of inflammation, and intracellular inflammatory cell PDE4 activity is increased in AD.[17] Crisaborole is available as an ointment that is applied twice daily.

To date, there are only 3 short-term trials of crisaborole, all compared to placebo in patients with mild to moderate AD.[18,19] A good quality systematic review compiled by the Institute for Clinical and Economic Review (ICER) evaluated the 3 studies.[17] Two 4-week studies similar in design enrolled children (n = 1522) with mild to moderate AD (39% mild), with 18% body surface area affected.[18] The other trial enrolled adults (n = 25) for 6 weeks and compared crisaborole with placebo.[19] Modest improvement was observed by investigators in more pediatric patients using crisaborole than placebo in erythema, exudation, excoriation, induration/papulation and lichenification.[18] In these trials there were no serious adverse events reported, and very few patients withdrew due to adverse events. Application site pain was the most common adverse event reported (crisaborole 4.6% vs. placebo 1.7%).[12] The other adverse events reported in the trials were not different between groups. No studies have evaluated crisaborole

with TCI or TCS formulations to assess comparative efficacy or harms.

The second new therapy approved by the FDA for systemic management of AD is dupilumab. Dupilumab is an injectable interleukin (IL)-4 receptor antagonist approved for use in adults with moderate to severe AD not controlled with topical therapy.[20] Binding the interleukin-4 receptor by dupilumab results in inhibition of IL-4 and IL-13 signaling which alters cell mediated immune responses and improves epidermal barrier abnormalities in AD.[21] Dupilumab therapy is initiated with a 600 mg subcutaneous (SC) injection loading dose followed by 300 mg SC every other week.[20]

In clinical trials, a 5-point Investigator Global Assessment (IGA) scale ranging from 0 (clear) to 4 (severe) was used to assess changes in the severity of skin lesions. In 2 placebo-controlled trials, the number of patients with clear or almost clear with at least a 2 point reduction in the Investigator Global Assessment (IGA) scale was higher with dupilumab every other week and weekly compared with placebo with an absolute risk reduction (ARR) of 27-28% and a number needed to treat (NNT) of 4.[22] A trial comparing dupilumab plus a TCA to placebo in adult patients with moderate to severe AD found the combination to be more effective than placebo (ARR 27%/NNT 4).[23] The most common adverse reactions were injection site reactions and conjunctivitis.[20] Limitations of the dupilumab trials include: 1) insufficient duration of the trials to assess long-term safety and 2) the trials only enrolled adults, although AD is more prevalent in children.

Safety and efficacy of dupilumab in pediatric patients has not been established, although trials are currently being conducted in this population. Clinical trials are currently underway with other biologics including ustekinumab, secukinumab, and apremilast to assess their efficacy in treating patients with moderate to severe AD.[1] **Table 1** summarizes the mechanism, dosage form and FDA approved populations for the 4 second-line drugs FDA-approved to treat AD after first line therapy with TCS has failed or is contraindicated.

**Table 1.** Drug Information for Second-Line Atopic Dermatitis Therapeutic Agents

| Generic Name | Trade Name | Mechanism | Dosage Form | FDA-Approved Population |
|---|---|---|---|---|
| Crisaborole | Eucrisa™ | PDE4 inhibitor | Ointment | Mild to moderate AD |
| Pimecrolimus | Elidel® | Calcineurin inhibitor | 1% Cream | Mild to moderate AD |
| Tacrolimus | Protopic® | Calcineurin inhibitor | 0.03% and 0.1% Ointment | Moderate to severe AD |
| Dupilumab | Dupixent® | Monoclonal antibody | Subcutaneous Injection | Moderate to severe AD |

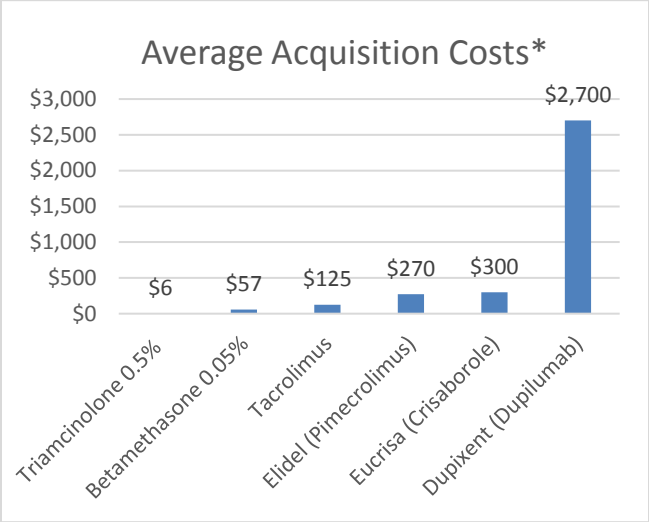
Abbreviations: AD = Atopic Dermatitis; FDA = Food and Drug Administration; PDE4 = Phosphodiesterase 4

## Conclusion

In conclusion, first line pharmacologic therapy for AD is topical steroids. If TCS therapy is not effective or contraindicated, TCI therapy should be initiated. Crisaborole is a possible alternative to TCS or TCI treatments for patients with mild to moderate AD. For patients with moderate to severe AD unresponsive to topical therapy or systemic therapy with immunomodulators (i.e. cyclosporine, methotrexate, or azathioprine), dupilumab has proven efficacy in managing AD symptoms, although long-term safety has not been adequately evaluated.

The Fee-For-Service (FFS) PA criteria for TCIs and crisaborole requires: 1) documentation of functional impairment due to moderate or severe AD and 2) documented contraindication, intolerance or failed trial of at least 2 first line agents indicated for treatment of moderate to severe AD (topical steroids). The FFS PA criteria for dupilumab requires: 1) documentation of moderate to severe AD, 2) patient age ≥ 18 years, and 3) trial of at least 2 first line therapies for moderate to severe AD including moderate to high potency TCS, phototherapy, TCIs, or oral immunomodulators.

**Table 2:** Comparative Monthly Costs of Atopic Dermatitis Treatments




*Based on commonly prescribed maintenance doses as of July 2018

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References:

1. Nomura T, Kabashima K. Advances in atopic dermatitis in 2015. *Journal of Allergy and Clinical Immunology.* 2016;138(6):1548-1555.
2. Weidinger S, Novak N. Atopic dermatitis. *Lancet.* 2016;387(10023):1109-1122.
3. Silverberg JI, Hanifin JM. Adult eczema prevalence and associations with asthma and other health and demographic factors: a US population-based study. *J Allergy Clin Immunol.* 2013;132(5):1132-1138.
4. Shaw TE, Currie GP, Koudelka CW, Simpson EL. Eczema prevalence in the United States: data from the 2003 National Survey of Children's Health. *The Journal of investigative dermatology.* 2011;131(1):67-73.
5. Beattie* PE, Lewis-Jones MS. A comparative study of impairment of quality of life in children with skin disease and children with

other chronic childhood diseases. *Br J Dermatol.* 2006;155(1):145-151.
6. Health Evidence Review Commission. Value-Based Benefits Subcommittee. Minutes from November 9, 2017 meeting. http://www.oregon.gov/oha/HPA/CSI-HERC/MeetingDocuments/VbBS-Handout-11-9-2017.pdf. Accessed December 20, 2017.
7. Eichenfield LF, Tom WL, Berger TG, et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol.* 2014;71(1):116-132.
8. Protopic® (tacrolimus) Product Information. Northbrook, IL: Astellas Pharma US Inc. May 2012.
9. Elidel® (pimecrolimus) Product Information. Bridgewater, NJ: Valeant Pharmaceuticals. June 2017.
10. Tacrolimus and pimecrolimus for atopic eczema. National Institute for Health and Care Excellence (NICE). August 25, 2004. https://www.nice.org.uk/guidance/ta82/resources/tacrolimus-and-pimecrolimus-for-atopic-eczema-pdf-2294815625413. Accessed December 28, 2017.
11. Furue M, Terao H, Rikihisa W, et al. Clinical dose and adverse effects of topical steroids in daily management of atopic dermatitis. *Br J Dermatol.* 2003;148(1):128-133.
12. McDonagh M, Crabtree E, Blazina I, Liebow S. Drugs to Treat Atopic Dermatitis. Final Report prepared by the Pacific Northwest Evidence-Based Practice Center for the Drug Effectiveness Review Project. Oregon Health and Science University, Portland, Oregon. December 2017.
13. Paller AS, Lebwohl M, Fleischer AB, Jr., et al. Tacrolimus ointment is more effective than pimecrolimus cream with a similar safety profile in the treatment of atopic dermatitis: results from 3 randomized, comparative studies. *J Am Acad Dermatol.* 2005;52(5):810-822.
14. Kempers S, Boguniewicz M, Carter E, et al. A randomized investigator-blinded study comparing pimecrolimus cream 1% with tacrolimus ointment 0.03% in the treatment of pediatric patients with moderate atopic dermatitis. *J Am Acad Dermatol.* 2004;51(4):515-525.
15. Abramovits W, Fleischer AB, Jr., Jaracz E, Breneman D. Adult patients with moderate atopic dermatitis: tacrolimus ointment versus pimecrolimus cream. *J Drugs Dermatol.* 2008;7(12):1153-1158.
16. Onumah N, Kircik L. Pimecrolimus cream and Tacrolimus ointment in the treatment of atopic dermatitis: a pilot study on patient preference. *J Drugs Dermatol.* 2013;12(10):1145-1148.
17. Institute for Clinical and Economic Review. Dupilumab and Crisaborole for Atopic Dermatitis: Effectiveness and Value. Final Evidence Report. June 8, 2017. https://icer-review.org/material/atopic-dermatitis-final-report/. Accessed December 13, 2017.
18. Paller AS, Tom WL, Lebwohl MG, et al. Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. *J Am Acad Dermatol.* 2016;75(3):494-503.e496.
19. Murrell DF, Gebauer K, Spelman L, Zane LT. Crisaborole Topical Ointment, 2% in Adults With Atopic Dermatitis: A Phase 2a, Vehicle-Controlled, Proof-of-Concept Study. *J Drugs Dermatol.* 2015;14(10):1108-1112.
20. Dupixent® (dupilumab) Product Information. Bridgewater, NJ: Regeneron Pharmaceuticals, Inc. March 2017.
21. Beck LA, Thaci D, Hamilton JD, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. *N Engl J Med.* 2014;371(2):130-139.
22. Simpson EL, Akinlade B, Ardeleanu M. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. *N Engl J Med.* 2017;376(11):1090-1091.
23. Blauvelt A, de Bruin-Weller M, Gooderham M, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet.* 2017;389(10086):2287-2303.