Effective Health Care

Topical and Systemic Treatment of Atopic Dermatitis

Results of Topic Selection Process & Next Steps

The nominator American Academy of Dermatology, is interested in a new evidence review on Topical and Systematic Treatment of Atopic Dermatitis to inform a clinical practice guideline.

We identified several review(s) covering part of the scope of the nomination, therefore, a new review would be partially duplicative of an existing product. For the questions not covered by existing reviews, there is limited original research. No further activity on this nomination will be undertaken by the Effective Health Care (EHC) Program.

Topic Brief

Topic Numbers and Name: #0804, 0805, 0806 Topical and Systemic Treatment of Atopic Dermatitis

Nomination Date: 7/09/2018

Topic Brief Date: 10/11/2018

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Conflict of Interest: None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Background

Atopic dermatitis is a common chronic skin condition that causes itchy scaly red patches. The 1-year US prevalence of AD was estimated at 12.98% in children in 2007-2008 and 7.2%-10.2% in adults in 2010-2012[1]. There is no biomarker, objective diagnostic test, or even standard nomenclature for describing atopic dermatitis and related conditions such as other forms of eczema. NIH has funded an initiative to harmonize outcome measures in atopic dermatitis.[2]

Patients with atopic dermatitis typically try to control their symptoms through supportive care including bathing and moisturizing ointments, wearing soft breathable fabrics and avoiding contact with allergens.

The current American Academy of Dermatology guidelines do not recommend non-sedating antihistamines for atopic dermatitis, but recognize that sedating antihistamines may have value in controlling insomnia secondary to itching. Despite this, antihistamines are prescribed in 16-44% of doctor visits for atopic dermatitis, with prescriptions for non-sedating antihistamines by family practitioners and internists 55-100% of the time[3]. Adherence to guideline recommendations may be impacted by different recommendations in different guidelines, for example, the atopic dermatitis guidelines published by the American Academy of Allergy, Immunology and Asthma.[4]

There are two new classes of new drugs with one of each currently FDA approved: the PDE4 inhibitors (eucrisa/crisaborole) and antibody treatment (dupixent/dupilumab). There are other drugs already approved that may be used off label in these classes and new drugs in these classes and other novel mechanisms under development with some published information, but none yet approved by the FDA. According to GoodRx, the antibody treatment costs $3000 for two syringes (one month supply). The PDE4 cost is $620 for one 60g tube. Some insurers have instituted policies such as step therapy requirements to mitigate the cost.

Nominator and Stakeholder Engagement

The American Academy of Dermatology requested this review to inform new guidelines. We discussed suggested key questions and timing with the nominator. They could use our report to inform our guideline if we finished it by the end of 2019/early 2020.

Key Questions and PICOs

The key questions for this nomination are:

1. Contextual questions: what is the diagnostic criteria for atopic dermatitis? What is considered usual care? What outcomes are most important to patients?
2. What are the benefits and risks of PDE4 inhibitors in the treatment of atopic dermatitis?
    a. What are the patient characteristics in these studies? Particularly, how does the inclusion criteria compare to the diagnostic criteria for atopic dermatitis? What comorbidities are present in the patient population?
    b. What comparators were used in the studies and how does that compare to usual care?
    c. Which outcomes were measured in the studies? What is the MCID for these outcomes? What is the validity and reliability of the disease severity and QoL instruments that were used in the studies?

    d. How do the risks and benefits vary by patient population (age, comorbidities, disease severity, etc.)?
    e. What is the length of follow up in the studies?
    f. What prior and concurrent treatments were given in the studies?
3. What are the benefits and risks of systematic biologics in the treatment of atopic dermatitis?
    a. What are the patient characteristics in these studies? Particularly, how does the inclusion criteria compare to the diagnostic criteria for atopic dermatitis? What comorbidities are present in the patient population?
    b. What comparators were used in the studies and how does that compare to usual care?
    c. Which outcomes were measured in the studies? What is the MCID for these outcomes? What is the validity and reliability of the disease severity and QoL instruments that were used in the studies?
    d. How do the risks and benefits vary by patient population (age, comorbidities, disease severity, etc.)?
    e. What is the length of follow up in the studies?
    f. What prior and concurrent treatments were given in the studies?
4. What are the benefits and risks of antihistamines in the treatment of atopic dermatitis?
    a. What are the patient characteristics in these studies? Particularly, how does the inclusion criteria compare to the diagnostic criteria for atopic dermatitis? What comorbidities are present in the patient population?
    b. What comparators were used in the studies and how does that compare to usual care?
    c. Which outcomes were measured in the studies? What is the MCID for these outcomes? What is the validity and reliability of the disease severity and QoL instruments that were used in the studies?
    d. How do the risks and benefits vary by patient population (age, comorbidities, disease severity, etc.) and characteristic of treatment (sedating vs. non-sedating)?
    e. What is the length of follow up in the studies?
    f. What prior and concurrent treatments were given in the studies?

To define the inclusion criteria for the key questions, we specify the population, interventions, comparators, and outcomes (PICO) of interest (Table 1).

Table 1. PICOs

Population	Patients with atopic dermatitis
Interventions	KQ2: PDE4 inhibitors KQ3: systemic biologics KQ4: antihistamines
Comparators	Supportive care (over the counter ointments, baths etc.), topical and systemic corticosteroids, other treatments
Outcomes	Disease severity, quality of life, long term control, adverse events of treatment

Abbreviations: PDE4: phosphodiesterase 4

Methods

We assessed nomination Topical and Systematic Treatment of Atopic Dermatitis for priority for a systematic review or other AHRQ EHC report with a hierarchical process using established selection criteria. Assessment of each criteria determined the need to evaluate the next one. See Appendix A for detailed description of the criteria.

1. Determine the *appropriateness* of the nominated topic for inclusion in the EHC program.
2. Establish the overall *importance* of a potential topic as representing a health or healthcare issue in the United States.
3. Determine the *desirability of new evidence review* by examining whether a new systematic review or other AHRQ product would be duplicative.
4. Assess the *potential impact* a new systematic review or other AHRQ product.
5. Assess whether the *current state of the evidence* allows for a systematic review or other AHRQ product (feasibility).
6. Determine the *potential value* of a new systematic review or other AHRQ product.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

Desirability of New Review/Duplication

We searched for high-quality, completed or in-process evidence reviews published in the last three years on the key questions of the nomination. See Appendix B for sources searched.

Impact of a New Evidence Review

The impact of a new evidence review was qualitatively assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for this review to influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

Feasibility of New Evidence Review

We searched for high-quality, completed or in-process evidence reviews published in the last three years on the key questions of the nomination using the key words “atopic dermatitis” and “antihistamine” or “PDE4” or “antibody” and the pubmed filter “systematic review” See Appendix B for sources searched.

We searched PubMed for studies published in the last five years using the same key words with the pubmed filter “clinical trials”. We reviewed all identified titles and abstracts for inclusion and classified identified studies by key question and study design to assess the size and scope of a potential evidence review. See Appendix C for the PubMed search strategy and links to the ClinicalTrials.gov search.

We searched clinicaltrials.gov for studies with a start date after 1/1/2013 using structured search terms condition: atopic dermatitis intervention: phosphodiesterase type 4 and crisaborole, monoclonal antibody or antihistamine for KQ2-4 respectively.

Value

We assessed the nomination for value. We considered whether or not the clinical, consumer, or policymaking context had the potential to respond with evidence-based change; and if a partner organization would use this evidence review to influence practice.

Results

See Appendix A for detailed assessments of all EPC selection criteria.

Appropriateness and Importance

This is an appropriate and important topic.

Desirability of New Review/Duplication

A new evidence review would be partially duplicative of an existing evidence review.
KQ1 (Contextual Question): several systematic reviews are underway investigating differences in symptoms by region and age, concordance of guideline recommendations and clinical practice with evidence, and characterization of the disease characteristics and outcome measures in trials.[5-7]

Key Question 2: ICER published a review of the FDA approved PDE4 and antibody drugs in 2017.[8]This report did not review study data available on the other PDE4 drugs in development.

Key Question 3: The ICER review did not include study data available on the other antibody drugs which may be used off label or are in development. In addition to the ICER report cited in question 2 above, there were four systematic reviews published on antibody therapies[9-12]. One review was published in April 2018 and is the most comprehensive, but one of the authors declared industry conflicts of interest, one review only includes consideration of one off-label drug, and two reviews focus on dupilumab (but one of these includes only a review of adverse events. There is also a protocol for a systematic review underway on immunomodulatory treatments that has an interesting multistakeholder group of authors (including a patient representative), but some of the authors have industry conflicts of interest.[13]

Key Question 4: We identified a Cochrane protocol for a review of oral antihistamines as add-on therapy published in 2016 but a full report was not yet published at the time we considered this nomination The full report has now been published[14].. We identified no other in-process or completed systematic reviews.

Impact of a New Evidence Review
A new systematic review may have moderate impact. The AAD is interested in using this review to inform new clinical practice guidelines. However, there is some evidence that practitioners do not follow guidelines in this clinical area as described in the background section.

Feasibility of a New Evidence Review
A new evidence review is feasible, though the evidence base is likely small.

Key Question 2: Two publications summarizing three RCTs were included in the ICER systematic review. In addition, studies were published in the last five years include: one study on drugs already on the market (on-label or off-label)[15] and four studies of drugs in development and clinical trials for FDA approval[16-19].

Key Question 3: Six publications and one abstract on 11 RCTs were included in the ICER systematic review. Other clinical trials published in the last five years include:
Five studies on drugs on the market (on-label and off-label)[20-24] and one study of drugs in development and clinical trials for FDA approval[25]

Key Question 4: Feasibility is demonstrated by studies that were found but not reviewed in a 2013 Cochrane review of oral antihistamines as monotherapy in eczema[26]. In this review no study met the inclusion criteria for monotherapy, but there were 35 studies that investigated antihistamines together with other therapies such as steroids. In addition, one randomized controlled trial was found in the last five years which used a novel wristwatch acoustic scratching counting device.[27]

26 potentially relevant studies are registered in clinicaltrials.gov with a start date after 1/1/2013 (see Appendix C for distribution across key questions).

Value
The potential for value is high because atopic dermatitis is a common condition with currently rapid development of new treatments that have cost implications for the health care system.

Summary of Findings

- Appropriateness and importance: The topic is both appropriate and important.
- Duplication: For KQ4 a new review would not be duplicative. For KQ2 and KQ3, there is some duplication with existing systematic reviews, but there is no single recent review that includes all new and emerging drugs and comprehensively discusses contextual issues such as diagnostic criteria and validity of outcome measures.
- Impact: The AAD is interested in using this review to inform new clinical practice guidelines. However, there is some evidence that practitioners do not follow guidelines in this clinical area.
- Feasibility: A new review is feasible though the evidence base is likely small.
- Value: Atopic dermatitis is a common condition with currently rapid development of new treatments that have cost implications for the health care system.

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Appendix A. Selection Criteria Assessment

Selection Criteria	Assessment
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.?	Yes
1b. Is the nomination a request for a systematic review?	Yes
1c. Is the focus on effectiveness or comparative effectiveness?	Yes
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	The 1-year US prevalence of AD was estimated at 12.98% in children in 2007-2008 and 7.2%-10.2% in adults in 2010-2012
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes, costs of the new drugs are concerning to payers.
2c. Represents important uncertainty for decision makers	Yes, especially KQ4.
2d. Incorporates issues around both clinical benefits and potential clinical harms	Yes
2e. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes
3. Desirability of a New Evidence Review/Duplication	
3. Would not be redundant (i.e., the proposed topic is not already covered by available or soon-to-be available high-quality systematic review by AHRQ or others)	For KQ4 a new review would not be duplicative. While we found a 2016 systematic review protocol, it is unknown when it will be completed and available for use by the nominator. For KQ2 and KQ3, there is some duplication with existing systematic reviews, but there is no single recent review that includes all new and emerging drugs and comprehensively discusses contextual issues such as diagnostic criteria and validity of outcome measures.
4. Impact of a New Evidence Review	
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	The rapid pace of introduction of new drugs is leading to the need for new guidelines. In addition guidelines from American Academy of Dermatology and American Academy of Allergy, Immunology and Asthma are not consistent, and may lead to practice variation.
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	Yes, there is some evidence that practitioners do not follow guidelines in this clinical area.

Selection Criteria	Assessment
5. Primary Research	
5. Effectively utilizes existing research and knowledge by considering: - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies)	The evidence base is small based on the studies identified in the ICER review, a Cochrane SR relevant to KQ4, and the feasibility search. We identified 13 studies across KQ 2-4 published in the last five years. We identified a number of studies in clinicaltrials.gov, indicating that there is a rapidly advancing evidence base due to the introduction of new drugs.
6. Value	
6a. The proposed topic exists within a clinical, consumer, or policy-making context that is amenable to evidence-based change	Yes.
6b. Identified partner who will use the systematic review to influence practice (such as a guideline or recommendation)	Yes. AAD is planning on developing a clinical practice guideline on atopic dermatitis.

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; KQ=Key Question;

Appendix B. Search for Evidence Reviews (Duplication)

Listed below are the sources searched, hierarchically.

Primary Search
AHRQ: Evidence reports and technology assessments https://effectivehealthcare.ahrq.gov/; https://www.ahrq.gov/research/findings/ta/index.html; https://www.ahrq.gov/research/findings/evidence-based-reports/search.html
Cochrane Systematic Reviews http://www.cochranelibrary.com/
HTA (CRD database): Health Technology Assessments http://www.crd.york.ac.uk/crdweb/
ICER (https://icer-review.org/)
Secondary Search
Cochrane Protocols http://www.cochranelibrary.com/
Tertiary Search
PubMed https://www.ncbi.nlm.nih.gov/pubmed/

In addition, we searched for high-quality, completed or in-process evidence reviews published in the last three years on the key questions of the nomination using the key words “atopic dermatitis” and “antihistamine” or “PDE4” or “antibody” and the pubmed filter “systematic review”

Appendix C. Search Strategy & Results (Feasibility)

We searched PubMed for studies published in the last five years using the same key words with the pubmed filter “clinical trials”.

Clinicaltrials.gov results

KQ 2:

	Title	Status	Study Results	Conditions	Interventions
1	A Study of Crisaborole Ointment 2% in Children Aged 3-24 Months With Mild to Moderate Atopic Dermatitis	Recruiting	No Results Available	Atopic Dermatitis	• Drug: Crisaborole ointment 2%
2	A Study of Crisaborole Ointment 2% in Adult Japanese Healthy Subjects and Adult Japanese Subjects With Mild To Moderate Atopic Dermatitis	Completed	No Results Available	Healthy Atopic Dermatitis	• Drug: Crisaborole ointment 2% • Drug: Vehicle
3	A Study of Crisaborole Ointment 2%; Crisaborole Vehicle; TCS and TCI in Subjects Aged # 2 Years, With Mild-moderate AD	Recruiting	No Results Available	Atopic Dermatitis	• Drug: Crisaborole ointment, 2% • Drug: Hydrocortisone butyrate cream, 0.1% • Drug: Pimecrolimus cream, 1% • Drug: Crisaborole Vehicle
4	ASPIRE: PROs & Caregiver Burden in Children With Atopic Dermatitis	Not yet recruiting	No Results Available	Atopic Dermatitis	• Drug: Crisaborole • Drug: Tacrolimus 0.03% Ointment
5	Crisaborole Ointment 2% Skin Biomarker Biopsy Study in Atopic Dermatitis	Completed	No Results Available	Dermatitis, Atopic	• Drug: Crisaborole ointment 2% BID • Drug: Placebo ointment (vehicle)
6	Safety and Efficacy of AN2728 Topical Ointment, 2% in Children, Adolescents, and Adults (Aged 2 Years and Older) With Atopic Dermatitis	Completed	Has Results	Dermatitis, Atopic	• Drug: AN2728 Topical Ointment, 2% • Drug: Matching vehicle control
7	Safety and Efficacy of AN2728 Topical Ointment, 2% in Children, Adolescents, and Adults (Ages 2 Years and Older) With Atopic Dermatitis	Completed	Has Results	Dermatitis, Atopic	• Drug: AN2728 Topical Ointment, 2% • Drug: Matching vehicle control

	Title	Status	Study Results	Conditions	Interventions
8	Eucrisa for Atopic Dermatitis	Recruiting	No Results Available	Mild to Moderate Atopic Dermatitis	• Behavioral: Online Treatment response • Drug: EUCRISA
9	Topical Roflumilast in Adults With Atopic Dermatitis	Completed	Has Results	Atopic Dermatitis	• Drug: 0.5% Roflumilast Cream • Drug: Vehicle Cream

KQ 3:

	Title	Status	Study Results	Conditions	Interventions
1	Study of an Anti-OX40 Monoclonal Antibody (KHK4083) in Subjects With Moderate to Severe Atopic Dermatitis	Recruiting	No Results Available	Atopic Dermatitis	• Drug: KHK4083 • Drug: Placebo
2	A Phase II Study of Bermekimab (MABp1) in Patients With Moderate to Severe Atopic Dermatitis	Recruiting	No Results Available	Atopic Dermatitis	• Drug: Bermekimab Monoclonal Antibody 200 mg • Drug: Bermekimab Monoclonal Antibody 400 mg
3	Long-term Extension Trial in Subjects With Atopic Dermatitis Who Participated in Previous Tralokinumab Trials - ECZTEND	Not yet recruiting	No Results Available	Atopic Dermatitis	• Drug: Tralokinumab
4	Dupilumab Phase 4 Study	Enrolling by invitation	No Results Available	Atopic Dermatitis	• Biological: Dupilumab
5	Pilot Study of Ustekinumab for Subjects With Chronic Atopic Dermatitis	Completed	Has Results	Atopic Dermatitis	• Drug: Ustekinumab • Other: Placebo
6	A Study Investigating the Efficacy, Safety, and PK Profile of ANB020 Administered to Adult Subjects With Moderate-to-Severe AD	Recruiting	No Results Available	Atopic Dermatitis	• Biological: ANB020 • Drug: Placebo
7	Tralokinumab Monotherapy for Adolescent Subjects With Moderate to Severe Atopic Dermatitis - ECZTRA 6 (ECZema TRAlokinumab Trial no. 6).	Recruiting	No Results Available	Atopic Dermatitis	• Drug: Tralokinumab • Drug: Placebos
8	A Study to Assess Efficacy, Safety, Tolerability and Pharmacokinetics (PK)/Pharmacodynamics (PD) of MOR106 in Subjects With Moderate to Severe Atopic Dermatitis	Recruiting	No Results Available	Atopic Dermatitis	• Drug: MOR 106 • Drug: Placebo

	Title	Status	Study Results	Conditions	Interventions
9	Tralokinumab Monotherapy for Moderate to Severe Atopic Dermatitis - ECZTRA 2 (ECZema TRAlokinumab Trial no. 2)	Active, not recruiting	No Results Available	Atopic Dermatitis	• Drug: Tralokinumab • Drug: Placebo
10	Tralokinumab Monotherapy for Moderate to Severe Atopic Dermatitis - ECZTRA 1 (ECZema TRAlokinumab Trial no. 1)	Active, not recruiting	No Results Available	Atopic Dermatitis	• Drug: Tralokinumab • Drug: Placebo
11	Tralokinumab in Combination With Topical Corticosteroids for Moderate to Severe Atopic Dermatitis - ECZTRA 3 (ECZema TRAlokinumab Trial no. 3)	Recruiting	No Results Available	Atopic Dermatitis	• Drug: Tralokinumab • Drug: Placebo
12	Study to Determine the Safety and Effectiveness of Dupilumab (REGN668/SAR231893) for Treatment of Atopic Dermatitis (AD)	Completed	No Results Available	Atopic Dermatitis (AD)	• Drug: dupilumab • Drug: placebo
13	A Study to Test Safety, Tolerability, and the Way the Body Absorbs, Distributes, and Gets Rid of a Study Drug Called MOR106, in Healthy Subjects and in Patients With Moderate to Severe Atopic Dermatitis	Recruiting	No Results Available	Healthy Atopic Dermatitis	• Drug: MOR106 • Drug: Placebo
14	Vaccine Responses in Tralokinumab-Treated Atopic Dermatitis - ECZTRA 5 (ECZema TRAlokinumab Trial No. 5)	Recruiting	No Results Available	Atopic Dermatitis	• Drug: Tralokinumab • Drug: Placebo • Biological: Tdap vaccine • Biological: Meningococcal vaccine
15	Drug-drug Interaction Trial With Tralokinumab in Moderate to Severe Atopic Dermatitis - ECZTRA 4 (ECZema TRAlokinumab Trial no. 4)	Not yet recruiting	No Results Available	Atopic Dermatitis	• Drug: Tralokinumab • Drug: Caffeine • Drug: Warfarin • Drug: Omeprazole • Drug: Metoprolol • Drug: Midazolam Hydrochloride

KQ 4:

	Title	Status	Study Results	Conditions	Interventions
1	Efficacy and Safety Study of Desloratadine (MK-4117) in Japanese Participants With Eczema/ Dermatitis and Dermal Pruritus (MK-4117-202)	Completed	Has Results	Eczema Dermatitis Dermal Pruritus	• Drug: Desloratadine 5 mg
2	A Confirmatory Study of TAU-284 in Pediatric Patients With Atopic Dermatitis	Completed	Has Results	Dermatitis Atopic	• Drug: Bepotastine besilate • Drug: ketotifen fumarate