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DERP Topic Brief:
Drugs to Treat Atopic Dermatitis

January 2019

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Objectives

The objectives of this topic brief are to (1) identify new drugs, formulations, indications, and serious harms (e.g., black boxed warnings); (2) identify randomized controlled trials (RCTs) that assess the efficacy, effectiveness, and harms of dupilumab, crisaborole, pimecrolimus, and tacrolimus for the management of atopic dermatitis; (3) indicate the number and nature of eligible upcoming RCTs for these drugs since the search date of the last Drug Effectiveness Review Project (DERP) report (September 2017). The research presented in this report is meant only to help DERP participants decide whether to commission a targeted updated evidence review on this topic. The topic brief is not an exhaustive review of the literature, and other important studies and information could be available. Comprehensive review, quality assessment, and synthesis of evidence from the systematic reviews, RCTs, and other information presented here will follow only if the participating organizations choose to update this topic.

Previous Reports

Final Report 1: December 2017, searches through September 2017[1]

Background and Context

Atopic dermatitis, or eczema, is an inflammatory skin condition that affects around 30% of the U.S. population, mostly children and adolescents.[2] It is a chronic, relapsing and remitting disease characterized by dry, itchy skin that can weep clear fluid when scratched.[2] People with eczema may be particularly susceptible to bacterial, viral, and fungal skin infections.[2] The majority of patients with atopic dermatitis can achieve clinical improvement and disease control with nonpharmacological interventions (e.g., emollient use), conventional topical therapies (e.g., corticosteroids and calcineurin inhibitors), and environmental and occupational modifications, when necessary.[3]

In 2017, the U.S. Food and Drug Administration (FDA) approved dupilumab for atopic dermatitis in adults. Dupilumab is the first approved biologic treatment for atopic dermatitis; other biologic therapies are in the research pipeline. Biologic therapies are anticipated as providing effective and safe long-term options for patients who have severe disease.[4] The role of individual topical corticosteroids and calcineurin inhibitors, relative to each other, is still evolving, as is the role of new systematic therapies. In this context, questions remain about the most effective therapies for maintenance, treatment of flares, and therapy in patients inadequately managed with topical treatments.[1] The safety of long-term treatment is also a concern, specifically the incidence of cancer.

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Populations

- Adults and children (all ages, including infants) with stable atopic dermatitis (eczema)

Interventions

Table 1. Included Interventions

Generic Name	Brand Name	Drug Class	Route of Administration	FDA Approved Use	Date of FDA Approval
Dupilumab	Dupixent	Interleukin-4 receptor alpha antagonist	Injection	Adults with moderate-to-severe atopic dermatitis	March 2017
Crisaborole	Eucrisa	Phosphodiesterase 4 inhibitor	Ointment	Adults and children, age 2 and older, with mild-to-moderate atopic dermatitis	December 2016
Pimecrolimus	Elidel	Calcineurin inhibitor immunosuppressant	Cream	Adults and children, age 2 and older, with mild-to-moderate atopic dermatitis	December 2001
Tacrolimus	Protopic	Calcineurin inhibitor immunosuppressant	Ointment	Adults and children, age 2 and older, with moderate-to-severe atopic dermatitis	December 2000

Abbreviation. FDA: U.S. Food and Drug Administration.

Comparators

- Another included intervention type (Table 1)
- Topical corticosteroids

Efficacy and Effectiveness Outcomes

- Response to treatment (e.g., Investigator's Global Assessment [IGA])
- Disease symptoms (e.g., Eczema Area and Severity Index [EASI] score, pruritus numerical-rating scale, percentage of body-surface area affected)
- Quality of life

Harm Outcomes

- Adverse events
- Withdrawal due to adverse events
- Serious adverse events

Key Questions

1. For adults and children with atopic dermatitis, do dupilumab, crisaborole, pimecrolimus, or tacrolimus differ in effectiveness compared to each other or to topical corticosteroids?
    a. Are there differences based on the location of application (e.g., face, hands, feet), body-surface area involved, or treatment duration?
2. For adults and children with atopic dermatitis, do dupilumab, crisaborole, pimecrolimus, or tacrolimus differ in harms compared to each other or to topical corticosteroids?
    a. Are there differences based on the location of application (e.g., face, hands, feet), body-surface area involved, or treatment duration?
3. Are there subgroups of patients based on demographics and comorbidities for which dupilumab, crisaborole, pimecrolimus, or tacrolimus are more effective or have fewer adverse events?

Methods

Literature Search

We searched Ovid MEDLINE and Ovid MEDLINE In-Process & Other Non-Indexed Citations from September 2017 to November 2018, using terms for included drugs and limits for English language and human participants. We searched the FDA website to identify newly approved drugs for atopic dermatitis, new indications, and new serious harms (e.g., boxed warnings) for the included interventions. To identify new drugs, we also searched CenterWatch, a privately owned database of clinical trials information. In addition, we conducted an internet search using Google and Google Scholar for dupilumab, crisaborole, pimecrolimus, and tacrolimus for the management of atopic dermatitis. We also searched ClinicalTrials.gov the ISRCTN registry, and the FDA website for relevant ongoing studies.

Study Selection

We included studies published since the search in the last report (September 2017),[1] comparing dupilumab, crisaborole, pimecrolimus, and tacrolimus with each other or with topical corticosteroids for atopic dermatitis.

Findings

FDA Actions

New Drugs or Formulations

No new drugs or formulations were identified since the search in the last report.

New Indications

No new indications were identified since the search in the last report.

New Serious Harms

No new serious harms were identified since the search in the last report.

Clinical Evidence

Systematic Reviews

We did not identify any systematic reviews comparing dupilumab, crisaborole, pimecrolimus, and tacrolimus with each other or with topical corticosteroids for atopic dermatitis.

Randomized Controlled Trials

We identified 1 eligible RCT[5] comparing pimecrolimus with topical corticosteroids and with a placebo (Table 2). We did not identify any RCTs comparing other eligible intervention types (i.e., dupilumab, crisaborole, or tacrolimus) with each other or with topical corticosteroids for atopic dermatitis.

Table 2. Identified RCTs of Eligible Interventions for Atopic Dermatitis

Author, Year Trial Registry Number	Population	Intervention	Comparator	Outcomes
Guttman-Yassky et al., 2017[5] NCT02376049	30 adults with mild to moderate atopic dermatitis	Pimecrolimus	Betamethasone dipropionate Clobetasol propionate Placebo	Disease symptoms Molecular skin markers

Secondary Analyses

We did not identify any secondary analyses comparing dupilumab, crisaborole, pimecrolimus, or tacrolimus with each other or with topical corticosteroids for atopic dermatitis.

Ongoing Studies

We identified 4 ongoing studies registered in ClinicalTrials.gov.[6-9] Of these, the 2 active controlled randomized trials are evaluating the effectiveness of crisaborole in adults and children with mild to moderate atopic dermatitis (Table 3).[7,8] The first trial is comparing crisaborole with pimecrolimus and topical corticosteroids in adults and children with mild to moderate atopic dermatitis.[7] The second trial is comparing crisaborole with tacrolimus in children with mild to moderate atopic dermatitis.[8]

We also identified 2 extension studies assessing the long-term safety of dupilumab (Table 3).[6,9] The extension studies are not eligible based on the current scope, but might provide information on serious harms. We did not identify any ongoing studies comparing pimecrolimus or tacrolimus with dupilumab or topical corticosteroids. Table 3 summarizes the interventions and comparators, along with a summary of the main outcomes of response to treatment, quality of life, and safety. The ongoing studies are expected to be completed in December 2018 to October 2023.

Table 3. Ongoing Studies of Dupilumab and Crisaborole for Atopic Dermatitis

NCT Number Study Description	Intervention and Comparator	Estimated Completion Date Enrollment	Outcomes
NCT03539601[7] An RCT of the safety and efficacy of crisaborole ointment 2% compared with a topical calcineurin inhibitor and a topical corticosteroid	Crisaborole Pimecrolimus Hydrocortisone Placebo (vehicle)	May 2020 600 adults and children (ages 2 years and older) with mild to moderate atopic dermatitis	• Response to treatment • Disease symptoms • Quality of life • Treatment-emergent AEs • Serious AEs
NCT03645057[8] An RCT to monitor the effects of crisaborole and tacrolimus 0.03% on patient-reported outcomes and caregiver burden	Crisaborole Tacrolimus	August 2020 160 children (ages 5 to 12 years) with mild to moderate atopic dermatitis	• Disease symptoms • Quality of life, including sleep • Anxiety and depression • Caregiver burden
NCT01949311[6] An open-label extension study of dupilumab in patients with atopic dermatitis	Dupilumab No comparator	December 2018 2,000 adults who participated in placebo-controlled dupilumab atopic dermatitis trials	• Treatment-emergent AEs • Serious AEs • AEs • Response to treatment • Disease symptoms • Quality of life
NCT02612454[9] An open-label extension study to assess the long-term safety and efficacy of dupilumab in patients with atopic dermatitis	Dupilumab No comparator	October 2023 765 children (ages ≥ 6 months to < 18 years) who participated in dupilumab atopic dermatitis trials	• Treatment-emergent AEs • Serious AEs • Response to treatment • Disease symptoms • Quality of life

Abbreviations. AE: adverse events; RCT: randomized controlled trial.

We found the following studies that appear to be recently completed (i.e., since 2016), but we did not find any results published:

- NCT02395133
- NCT02601703
- NCT02791308
- NCT02896101
- NCT03050151

- NCT03054428
- NCT03107611
- NCT03233529
- NCT03260595
- NCT03297502

Delays in publication of studies can occur for many reasons, such as delays in manuscript development, lengthy time from submission to publication, rejection of publication, or other factors. However, the lack of publications for these registered trials could also be an indication of publication bias.

Summary and Report Options

A summary for this Topic Brief is in Table 4, including evidence and information identified in searches since September 2017. If DERP participants would like to move forward with a targeted updated report, this would comprise the following:

- A synthesis of head-to-head RCTs comparing dupilumab, crisaborole, pimecrolimus, and tacrolimus with each other or with topical corticosteroids (Appendix A), including 1 new RCT in 30 patients comparing pimecrolimus with topical corticosteroids that was published since the last report.

This report could be completed in 2 months for $10,000.

Using the *Is There a There There Scale* (ITS), we rated this topic as *No* (see Appendix B for ratings and definitions).

Table 4. Summary and ITS Rating

FDA Actions	Yes Description	No
New Drug or Formulation		☒
New Indication		☒
New Serious Harm		☒
Clinical Evidence	**Yes How Many?**	**No**
New Systematic Review		☒
New Comparative Trial	☑ 1	

New Meaningful[a] Study		☒
Meaningful[a] Upcoming Study Likely to be Published in the Next Year		☒
ITS Rating: No		

Abbreviation. ITS: Is There a There There Scale. Note. [a] Large studies (> 400 participants), studies that have long-term follow-up (> 6 months), studies that compare one drug with another that is considered the standard of care or has not been reported and is clinically important, and studies that include an intervention or outcome that is not previously reported in the literature or is clinically important (e.g., mortality) and adds to the body of literature.

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Appendix A. Comparative Trials to Date

Table A1. Identified Comparative RCTs of Eligible Interventions for Atopic Dermatitis

Status	Author, Year	Population	Intervention	Comparator	Outcomes
Compared With Topical Corticosteroids					
New in this report	Guttman-Yassky et al., 2017[5]	30 adults with mild to moderate atopic dermatitis	Pimecrolimus	Betamethasone dipropionate Clobetasol propionate Placebo	• Disease symptoms • Molecular skin markers
Included in Final Report 1	Bieber et al., 2007[10]	265 children with severe to very severe flare of atopic dermatitis	Tacrolimus	Methylprednisolone	• Response to treatment • Disease symptoms • Quality of life • Costs • Safety
Included in Final Report 1	Jensen et al., 2013[11]	15 adults with mild to moderate atopic dermatitis	Pimecrolimus	Triamcinolone acetonide	• Response to treatment • Disease symptoms • Safety
Included in Final Report 1	Kahn et al., 2014[12]	60 adults and children with atopic dermatitis	Tacrolimus	Mometasone furoate	• Response to treatment • Disease symptoms
Included in Final Report 1	Rahman et al., 2015[13]	60 children with atopic dermatitis	Tacrolimus	Hydrocortisone acetate	• Response to treatment • Disease symptoms • Safety
Included in Final Report 1	Reitamo et al., 2004[14]	624 children with moderate to severe atopic dermatitis	Tacrolimus	Hydrocortisone acetate	• Response to treatment • Disease symptoms • Safety

Status	Author, Year	Population	Intervention	Comparator	Outcomes
Compared With Other Eligible Interventions					
Included in Final Report 1	Abramovits et al., 2008[15]	188 adults with moderate atopic dermatitis	Pimecrolimus	Tacrolimus	• Response to treatment • Safety
Included in Final Report 1	Kempers et al., 2004[16]	141 children with moderate atopic dermatitis	Pimecrolimus	Tacrolimus	• Response to treatment • Disease symptoms • Safety
Included in Final Report 1	Onumah and Kircik, 2013[17]	20 adults and children with moderate atopic dermatitis	Pimecrolimus	Tacrolimus	• Response to treatment • Disease symptoms • Quality of life
Included in Final Report 1	Paller et al., 2005[18]	426 children with mild atopic dermatitis	Pimecrolimus	Tacrolimus	• Response to treatment • Disease symptoms • Safety
Included in Final Report 1	Paller et al., 2005[18]	226 children with moderate to severe atopic dermatitis	Pimecrolimus	Tacrolimus	• Response to treatment • Disease symptoms • Safety
Included in Final Report 1	Paller et al., 2005[18]	413 adults with moderate to severe atopic dermatitis	Pimecrolimus	Tacrolimus	• Response to treatment • Disease symptoms • Safety

Abbreviation. RCT: randomized controlled trial.

Appendix B. ITS Ratings and Definitions

The Is There a There There Scale (ITS) consists of 3 ratings: *no*, *maybe,* and *yes*. The definitions of these ratings and methods for selection are described below.

No

- Center researchers did not find evidence or information that would indicate a need to update the report or develop a derivative research product.
- A rating of *No* is typically given when there are few new studies or no new meaningful studies and no new serious harms.

Maybe

- Center researchers found some evidence or information that might suggest a need to update the report or develop a derivative research product.
- A rating of *Maybe* is typically given when there are multiple new comparative trials or at least 1 new meaningful study or serious harm.

Yes

- Center researchers found evidence or information that suggests a need to update the report or develop a derivative research product.
- A rating of *Yes* is typically given when there are multiple new comparative trials, meaningful studies, serious harms, or new drugs, formulations, or indications.