Evidence report for systemic treatment of patients with moderate to severe atopic eczema

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Evidence report for systemic treatment of patients with moderate to severe atopic eczema

Scoping

EBSCO Information Services

April 9, 2020

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Abbreviations

General abbreviations that may appear in this report

CI – confidence interval
CrI – credible interval
HR – hazard ratio
IQR – interquartile range
MA – meta-analysis
MD – mean difference
NA, N/A – not applicable
NMA – network meta-analysis
NR – not reported
OR – odds ratio
RCT – randomized, controlled trial
RR – risk ratio, relative risk
RtR – rate ratio
SD – standard deviation
SE – standard error
SMD – standardized mean difference
SR – systematic review
SRMA – systematic review and meta-analysis

Abbreviations specific to this report that may appear in this report

AD, AE - atopic dermatitis, atopic eczema (this condition is often referred to in the literature as atopic dermatitis and abbreviated as AD, but we will use the term "eczema" in evidence synthesis statements as relevant given its familiarity to patients)
ADAM – Atopic Dermatitis Assessment Measure
ADCT – Atopic Dermatitis Control Test
AZA – azathioprine
BAS – affected Body Surface Area
CsA – cyclosporine (A)
DLQI – Dermatology Life Quality Index
EASI – Eczema Area and Severity Index
IGA – Investigators' Global Assessment
ISS – itch severity scale
LIS – Leuven Itch Scale
MMF - mycophenolate mofetil
MTX – methotrexate
NRS – numeric rating scale
POEM – Patient-Oriented Eczema Measure
PO-SCORAD – Patient-Oriented SCORAD (see SCORAD for expansion)
QoL – quality of life
QoLIAD – Quality of Life Index for Atopic Dermatitis
RECAP – Recap of Atopic Eczema
SA-EASI – Self-Administered Eczema Area and Severity Index
SASSAD – Six-Area, Six-Sign Atopic Dermatitis
SCORAD – severity SCORing of Atopic Dermatitis
VAS – visual analogue scale

Methods

Using an established, structured template that delineates key elements for scoping (i.e., the population, interventions, and key outcomes to consider), we collaboratively agreed with UKSH on the scope of the present evidence report. Scoping was completed on April 9, 2020.

Where outcomes will be answered with systematic searches, critical appraisal, and evidence synthesis, we will state the intended approach after we state the outcome(s) of interest for that FAQ. For example, we might say: "The outcome of interest is all-cause mortality. We will obtain effect estimates from systematic reviews and meta-analyses of randomized, controlled trials or from individual trials if systematic reviews do not exist or meta-analysis is not the most appropriate method of synthesis." Otherwise, where we say: "We will include a description of", "We will include descriptive responses", or something similar, we will answer the FAQ with descriptive responses, which do not involve systematic evidence searches, critical appraisal, or evidence synthesis.

Results – Criteria Selection for Critical Appraisal

Population:

Inclusion criteria

Adult patients with moderate to severe atopic eczema

There is no established definition of moderate-to-severe AD, so studies will be eligible if the population is limited to ''patients with moderate-to-severe AD,'' ''patients with non-adequately controlled AD despite the use of topical anti-inflammatory therapy,'' or patients with moderate-to-severe AD according to severity criteria, such as Rajka and Langeland score > 4.52, SCORAD score > 20%, total body surface area > 10%, Pruritus numerical rating scale score ≥ 4, Physician's global assessment score ≥ 3, or Dermatology Life Quality Index score ≥ 10 (Roekevisch 2014, Lynde 2018).

Trials that also recruit children or adolescents will be included if majority of included participants are adults.

Exclusion criteria

Adolescents or children as the primary participants

Studies including mixed population of different dermatologic conditions without a separate analysis limited to adults with moderate to severe atopic eczema.

Intervention and Comparator/Options:

Cyclosporine
The intervention is cyclosporine.

Azathioprine
The intervention is azathioprine.

Mycophenolate Mofetil (MMF)
The intervention is MMF.

Methotrexate
The intervention is methotrexate.

Dupilumab
The intervention is dupilumab.

Systemic corticosteroid
As noted by the 2018 European guidelines (Wollenberg 2018), evidence is very limited for this option, with only 1 small trial (n = 38) having evaluated a systemic corticosteroid in adults with severe atopic dermatitis (Schmitt 2010). This RCT compared prednisolone versus cyclosporine and found that cyclosporine was significantly more effective than prednisolone for inducing stable remission. Long-term use of systemic corticosteroids is well-known to have substantial risks. The 2018 European guidelines also emphasize corticosteroids have a limited evidence base and a "largely unfavourable risk/benefit ratio for treatment of AE". They recommend short-term (up to 1 week) treatment may be an option to treat an acute flare in exceptional cases of adult patients with severe atopic dermatitis but that long-term use is not recommended because of its side effects.

Because of this, we will adopt descriptive responses only for this option, highlighting the uncertainty in the evidence and utilizing the two above-noted guidelines for descriptive content.

Outcomes:

FAQ 1: What does the treatment involve?

We will include a description of the stepwise scheme as well as all corresponding therapies and note that our focus is systemic therapies (this corresponds to 'Step 4' of German guidelines [Werfel 2016] and may include concurrent use of topical therapy or UV-based therapy as "background" therapies as well as lifestyle modifications such as avoidance of triggers or general irritants). We will include a description of the scoped treatment options, which will include frequency of dosing, limitations on duration as relevant (such as cyclosporine), and frequency of monitoring as relevant. We will also include any relevant pre-examinations, including comorbidities that might contraindicate use (e.g., methotrexate in someone with pre-existing chronic hepatitis).

Descriptive responses are acceptable, and this does not involve systematic evidence searches, critical appraisal, or evidence synthesis.

Note: Our efficacy outcomes (FAQ2 and FAQ3) are guided by the global Harmonising Outcome Measures for Eczema (HOME) initiative; the core outcomes they discuss are clinical signs, symptoms, quality of life, and long-term control (Schmitt 2014; http://www.homeforeczema.org/research/index.aspx).

We have defined these efficacy outcomes as short-term (≤16 weeks' duration) and long-term / maintenance (>16 weeks); a 16-week cut off was selected based on its use in a recent randomized trial (Blauvelt 2017) and systematic review (Roekevisch 2014). If the study period is ≤16 weeks and reports multiple times of outcome measurement, we will use the data at the end of study and classify them as short-term outcomes. In Evidence Synthesis, we may report these outcomes as occurring "within 4 months" (or similar phrasing) unless the timeframes reported would call for a different approach (e.g., if no short-term data exist beyond 3 months, we will adjust phrasing accordingly). For studies >16 weeks, if the studies report multiple times of outcome measurement, we may use the data from either the most common timeframe reported across the eligible studies or from the end of the studies' follow-up if the timeframes are deemed sufficiently similar in the context of long-term therapy (e.g., outcomes at 1 and 2 years might be synthesized as a range and reported as "within 1 to 2 years" or similar phrasing).

FAQ 2: Will my skin and symptoms improve?

To maximize the clinical utility of this evidence report, we will preferentially seek patient-reported outcome measures (PROMs) over clinician-assessed outcome measures (CAOMs). We will consider validated CAOMs if PROMs are not available.

Patient-reported outcome measures

Validated instruments used in clinical research include the Patient-Oriented Eczema Measure (POEM) scale, the Self-Administered Eczema Area and Severity Index (SA-EASI) rating scale, and Itch Severity Scale (ISS), as well as less validated instruments such as the Atopic Dermatitis Assessment Measure (ADAM), Patient-Oriented SCORAD (PO-SCORAD), and the Leuven Itch Scale (LIS) (Sawangjit 2018). The HOME initiative highlights the POEM scale and the 11-point numeric rating scale (NRS) for intensity of itch as preferred core outcome instruments for PROMs, but we will consider any of the validated instruments and conclude on the preponderance of evidence to avoid selection bias that might result from a restricted focus on POEM and 11-point NRS. For long-term assessment, we will focus first on PROMs, such as repeated measurements from the aforementioned scales or from measurements on

scales specifically intended for assessment of long-term control, such as the Atopic Dermatitis Control Test (ADCT) or Recap of Atopic Eczema (RECAP) scales. If data are inadequate for the aforementioned measures, then we may consider long-term control of flares specifically (Barbarot 2016).

Clinician-assessed outcome measures
Validated or objective instruments used in clinical research include the SCORAD (severity SCORing of Atopic Dermatitis), the EASI (Eczema Area and Severity Index) score, the Six-Area Six-Sign Atopic Dermatitis severity score (SASSAD), Investigators' Global, Assessment (IGA), and the affected Body Surface Area (BSA) (Sawangjit 2018). The SCORAD and EASI have both been extensively validated, but the SCORAD has been more commonly used in existing trials (Roekevisch 2014). The HOME initiative highlights the EASI as the preferred core outcome instrument for CAOMs, but we will consider any of the validated instruments and conclude on the preponderance of evidence to avoid selection bias that might result from a singular focus on EASI.

We will obtain effect estimates from systematic reviews and meta-analyses of randomized, controlled trials or from individual trials if systematic reviews do not exist. The comparator of key interest is placebo.

FAQ 3: Will my quality of life improve?
The outcome of interest is health-related quality of life measured by a validated instrument, such as the Dermatology Life Quality Index (DLQI), Quality of Life Index for Atopic Dermatitis (QoLIAD), and Skindex (Sawangjit 2018).

We will obtain effect estimates from systematic reviews and meta-analyses of randomized, controlled trials or from individual trials if systematic reviews do not exist. The comparator of key interest is placebo.

FAQ 4: What are the risks or side effects?
We will report on serious adverse events and adverse events leading to discontinuation based on data from randomized, controlled trials (or systematic reviews thereof) identified as part of efforts for efficacy FAQs. For specific risks and side effects considered typical or frequent for a given therapy, we will adopt descriptive responses.

FAQ 5: What if I am pregnant or want to get pregnant?
We will provide descriptive summaries of the recommendations provided by the 2019 European guidelines (Vestergaard 2019) on the use of systemic therapies for atopic dermatitis in women and men wishing to conceive, women who are pregnant, and women who are breastfeeding.

Drucker AM, Ellis A, Jabbar-Lopez Z, Yiu ZZN, Arents BWM, Burton T, Spuls PI, Küster D, Schmitt J, Flohr C. Systemic immunomodulatory treatments for atopic dermatitis: protocol for a systematic review with network meta-analysis. BMJ Open. 2018 Aug 29;8(8):e023061. doi: 10.1136/bmjopen-2018-023061. PubMed

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Sawangjit R, Dilokthornsakul P, Lloyd-Lavery A, Chua S, Lai NM, Dellavalle R, Chaiyakunapruk N. Systemic treatments for eczema: a network meta-analysis (protocol). Cochrane Database Syst Rev. 2018 Nov 28;2018(11):CD013206. doi: 10.1002/14651858.CD013206. PubMed

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Wollenberg A, Barbarot S, Bieber T, Christen-Zaech S, Deleuran M, Fink-Wagner A, Gieler U, Girolomoni G, Lau S, Muraro A, Czarnecka-Operacz M, Schäfer T, Schmid-Grendelmeier P, Simon D, Szalai Z, Szepietowski JC, Taïeb A, Torrelo A, Werfel T, Ring J; European Dermatology Forum (EDF), the European Academy of Dermatology and Venereology (EADV), the European Academy of Allergy and Clinical Immunology (EAACI), the European Task Force on Atopic Dermatitis (ETFAD), European Federation of Allergy and Airways Diseases Patients' Associations (EFA), the European Society for Dermatology and Psychiatry (ESDaP), the European Society of Pediatric Dermatology (ESPD), Global Allergy and Asthma European Network (GA2LEN) and the European Union of Medical Specialists (UEMS). Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children.
Part I. J Eur Acad Dermatol Venereol. 2018 May;32(5):657-682. doi: 10.1111/jdv.14891. Erratum in: J Eur Acad Dermatol Venereol. 2019 Jul;33(7):1436. PubMed
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Evidence report for systemic treatment of patients with moderate to severe atopic eczema

Evidence Synthesis

EBSCO Information Services

May 12, 2020

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Methods

Where evidence is very limited, or the FAQ is scoped as a descriptive response, such that no evidence synthesis or processing is applied, the descriptive summary/-ies will be given.

For each FAQ for which evidence synthesis or processing is considered, we will summarize the key concepts (results and factors affecting certainty of the results) from the included studies that are most relevant to evidence synthesis; we will prefer using a tabular format for this summary in most cases, but depending on the circumstances, we may adopt a non-tabular form instead. For each outcome, we will then articulate the method selected for evidence synthesis and justification of that method; again, we will prefer a tabular approach in most cases, but we may articulate the justification in a non-tabular form depending on the circumstances. We will do this for the effect estimate (i.e., answering the question "Is there a difference between the intervention and comparator?") and results will be presented with GRADE-based certainty of evidence ratings related to the certainty of effect estimates. For FAQs which require noncomparative/option-specific responses (i.e., the FAQ is "What will happen with this option?" rather than "How do things change with this option?") the evidence synthesis process will be extended to include the method to produce noncomparative responses.

For summary statements representing a plain language summary of evidence appraisal and synthesis

We will include the following 2 items immediately after the summary statement as a parenthetical, regardless of whether they occur in the Summary of Findings section or the individual FAQs in the body of the Evidence Synthesis document:

- our certainty in the summary statement (categorized as High, Moderate, Low, or Very low), and
- the number and type of studies informing the statement, as well as a label for the studies in "[Author] [Year]" format.

If the study informing the summary statement is a systematic review and meta-analysis, then unless there are compelling reasons to proceed in a different manner, we will cite the systematic review and meta-analysis as the source. We will do this even if the result on which our summary statement is based comes from a subset of studies in that systematic review and meta-analysis (e.g., a meta-analysis of 5 out of 10 studies, because only 5 of the 10 reported on the outcome of interest). If EBSCO Information Services conducts its own meta-analysis of studies to inform a summary statement, we will list the individual studies.

For summary statements representing a plain language summary of a descriptive response/summary

Certainty rating and provision of details about contributing studies do not apply. Accordingly, we will not include a parenthetical at the end of the summary statement. However, when descriptive summaries appear in the Summary of Findings section, we will include a general parenthetical citation of applicable references. We will place this at the end of the relevant FAQ in the Summary of Findings section. For summary statements occurring in the body of the Evidence Synthesis document, placement will depend on the context.

Results – Summary of Findings

FAQ 1: What does the treatment involve?

Cyclosporine

You can take cyclosporine by mouth. You will take it every day, and you may take it twice a day. You may see it start to work within 2 weeks. In most cases, cyclosporine is not used as a long-term medicine. It may be used for about 3 to 6 months to get your eczema under control, or it may be used for up to 1 or 2 years. After that, people often change to a different medicine. You should not use ultraviolet ("UV") light therapy (often also called "phototherapy") while taking cyclosporine. You should also protect your skin from UV light while taking cyclosporine, which means avoiding things like sun tanning or tanning beds and wearing sunscreen if you will have long periods where your skin is exposed to sunlight.

You will need blood tests and blood pressure checks before you start cyclosporine and while you are on cyclosporine. For people with certain conditions, cyclosporine may not be the best choice. You can discuss this more with your clinician.

Azathioprine

You can take azathioprine by mouth. You will take it every day. You may have to take it for 8 to 12 weeks before you start to see it work. Azathioprine can be used as a long-term medicine. You should not use ultraviolet ("UV") light therapy (often also called "phototherapy") while taking azathioprine. You should also protect your skin from UV light while taking azathioprine, which means avoiding things like sun tanning or tanning beds and wearing sunscreen if you will have long periods where your skin is exposed to sunlight.

You will need blood tests before you start azathioprine and while you are on azathioprine. For people with certain conditions, azathioprine may not be the best choice. You can discuss this more with your clinician.

Mycophenolate mofetil

You can take mycophenolate by mouth. You will take it every day. You may have to take it for 8 to 12 weeks before you start to see it work. Mycophenolate can be used as a long-term medicine.

You will need blood tests before you start mycophenolate and while you are on mycophenolate. For people with certain conditions, mycophenolate may not be the best choice. You can discuss this more with your clinician.

Methotrexate

You can take methotrexate by mouth. You can take it once a week, but some people may want to take a lower dose that they take every day. You may have to take it for 8 to 12 weeks before you start to see it work. Methotrexate can be used as a long-term medicine.

You will need blood tests before you start methotrexate and while you are on methotrexate. For people with certain conditions, methotrexate may not be the best choice. You can discuss this more with your clinician.

Dupilumab

Dupilumab is given under your skin. The first time you take it, you will get two doses in different spots on your body. After that, you will need one dose every other week. You can give yourself the medicine under your skin once you learn how. You may have to take it for 4 to 6 weeks before you start to see it work. Dupilumab can be used as a long-term medicine.

People do not usually need any tests before taking dupilumab or while they are on dupilumab. Most people can take dupilumab even if they have other conditions. You can discuss this more with your clinician.

Systemic corticosteroids

You can take steroids by mouth, but they are sometimes given in your muscle or vein. Steroids are usually only used for a week or two to get eczema under control. For people with certain conditions, steroids may not be the best choice. Some people may need blood tests or blood pressure checks while they take steroids. You can discuss this more with your clinician.

(References consulted for the above descriptive responses include DynaMed 2018-2020, Gooderham 2017, Sidbury 2014, Vestergaard 2020, Wollenberg 2016, Wollenberg 2018)

FAQ 2: Will my skin and symptoms improve?

Cyclosporine

Cyclosporine may help how much of your body has eczema and how bad the eczema is (things like the amount of dryness, redness, scaling, cracking, and so on) within the first few months of use, but the research on this is not very good. (Very low certainty; based on 5 systematic reviews: Drucker 2020, Hoare 2000, Roekevisch 2014, Schmitt 2007A, and Schmitt 2007B) If you notice your skin get better, it may last over time, but we do not have enough research on long-term use of cyclosporine.

Azathioprine

Azathioprine may help how much of your body has eczema and how bad the eczema is (things like the amount of dryness, redness, scaling, cracking, and so on) within the first few months of use, but the research on this is not very good. (Very low certainty; based on 5 systematic reviews: Drucker 2020, Hoare 2000, Roekevisch 2014, Schmitt 2007A, and Schmitt 2007B) If you notice your skin get better, it may last over time, but we do not have enough research on long-term use of azathioprine.

Mycophenolate mofetil

Mycophenolate may help how much of your body has eczema and how bad the eczema is (things like the amount of dryness, redness, scaling, cracking, and so on) within the first few months of use, but the research on this is not very good. (Very low certainty; based on indirect reasoning from the evidence for cyclosporine vs. placebo and 1 randomized trial of mycophenolate vs. cyclosporine [Haeck 2011]). If you notice your skin get better, it may last over time, but we do not have enough research on long-term use of mycophenolate.

Methotrexate

Methotrexate may help how much of your body has eczema and how bad the eczema is (things like the amount of dryness, redness, scaling, cracking, and so on) within the first few months of use, but the research on this is not very good. (Very low certainty; based on indirect reasoning from the evidence for cyclosporine vs. placebo and methotrexate vs. cyclosporine [see corresponding sections], indirect reasoning from the evidence for azathioprine vs. placebo and methotrexate vs. azathioprine [see corresponding sections], and indirect estimates for methotrexate vs. placebo from 1 systematic review [Drucker 2020]). If you notice your skin get better, it may last over time, but we do not have enough research on long-term use of methotrexate.

Dupilumab

Dupilumab may help how much of your body has eczema and how bad the eczema is (things like the amount of dryness, redness, scaling, cracking, and so on) within the first few months of use, and this may last for a year or more. (Moderate certainty; based on 1 systematic review with pairwise meta-analysis [Wang 2018] and 1 systematic review with network meta-analysis [Drucker 2020])

Systemic corticosteroids

There is not much research on using steroids in eczema, but they can be used for a short time to get eczema under control quickly. Because of side effects with long-term use, they should not be used for long-term control.

FAQ 3: Will my quality of life improve?

Cyclosporine

Cyclosporine may help improve your quality of life (things like how much your eczema gets in the way of daily activities, how much you worry about what others think about your eczema, how much you find treatment to be a problem, and so on), but the effect may be small, and the evidence is uncertain. (Very low certainty; based on 1 randomized trial [Salek 1993] and indirect reasoning from the evidence for FAQ 2 [Will my skin and symptoms improve?]). How your quality of life might change while taking cyclosporine probably depends a lot on how well cyclosporine works for you and if you have side effects from cyclosporine.

Azathioprine

Azathioprine may help improve your quality of life (things like how much your eczema gets in the way of daily activities, how much you worry about what others think about your eczema, how much you find treatment to be a problem, and so on), but the effect may be small, and the evidence is uncertain. (Very low certainty; based on 1 randomized trial [Meggitt 2006]). How your quality of life might change while taking azathioprine probably depends a lot on how well azathioprine works for you and if you have side effects from azathioprine.

Mycophenolate mofetil

Mycophenolate may help improve your quality of life (things like how much your eczema gets in the way of daily activities, how much you worry about what others think about your eczema, how much you find treatment to be a problem, and so on), but the effect may be small, and the evidence is uncertain. (Very low certainty; based on indirect reasoning from the evidence for cyclosporine vs. placebo and 1 randomized trial of mycophenolate vs. cyclosporine [Haeck 2011]). How your quality of life might change while taking mycophenolate probably depends a lot on how well mycophenolate works for you and if you have side effects from mycophenolate.

Methotrexate

Methotrexate may help improve your quality of life (things like how much your eczema gets in the way of daily activities, how much you worry about what others think about your eczema, how much you find treatment to be a problem, and so on), but the effect may be small, and the evidence is uncertain. (Very low certainty; based on indirect reasoning from the evidence for cyclosporine vs. placebo and methotrexate vs. cyclosporine [see corresponding sections], indirect reasoning from the evidence for azathioprine vs. placebo and methotrexate vs. azathioprine [see corresponding sections], and indirect estimates for methotrexate vs. placebo from 1 systematic review [Drucker 2020]). How your quality of life might change while taking methotrexate probably depends a lot on how well methotrexate works for you and if you have side effects from methotrexate.

Dupilumab

Dupilumab may help improve the quality of your life (things like how much your eczema gets in the way of daily activities, how much you worry about what others think about your eczema, how much you find treatment to be a problem, and so on). (Moderate certainty; based on 1 systematic review with pairwise meta-analysis [Wang 2018] and 1 systematic review with network meta-analysis [Drucker 2020]) How your quality of life might change while taking dupilumab probably depends a lot on how well dupilumab works for you and if you have side effects from dupilumab.

Systemic corticosteroids

Steroids might improve your quality of life by helping improve your eczema more quickly. But some people have side effects from steroids. How your quality of life might change while taking steroids probably depends a lot on how well the steroids work for you and if you have side effects from steroids.

FAQ 4: What are the risks or side effects?

Cyclosporine

Side effects may include:

- Headache
- Shaking ("tremor")
- Feeling like certain body parts are numb, tingly, or have a "pins and needles" feeling
- Growing hair or more hair in places where you usually do not have hair or a lot of hair
- Your gums getting bigger and more sensitive (they may bleed more easily)
- Nausea, vomiting, diarrhea
- Flu-like symptoms
- Increased blood pressure
- Increased triglycerides

Risks may include:

- Damage to the kidneys
- Problems with things like sodium and potassium in your blood
- Infection, including serious infection
- Skin cancer or blood cancer

The risks can be kept as low as possible by the tests you will have while taking this medication (see "What does the treatment involve?").

Azathioprine

Side effects may include:

- Nausea, vomiting, diarrhea

Risks may include:

- Your bone marrow not working like it should, which can lead to not having enough red blood cells, white blood cells, or platelets
- Hepatitis
- Pancreatitis
- Infection, including serious infection
- Skin cancer or blood cancer

Some people who take azathioprine also have an allergic reaction to it. This can be mild or serious. Mild cases have symptoms like join and muscle pain, fever, chills, nausea, and vomiting. More serious cases can have low blood pressure that is dangerous, pancreatitis, or inflammation in the blood vessels.

The risks can be kept as low as possible by the tests you will have while taking this medication (see "What does the treatment involve?").

Mycophenolate mofetil

Side effects may include:

- Nausea, vomiting, diarrhea, stomach cramps
- Pain when you urinate, feeling like you need to urinate often or suddenly
- Flu-like symptoms
- Difficulty sleeping
- Fluid buildup in your feet, ankles, or legs
- Increased blood pressure
- Increased cholesterol

Risks may include:

- Your bone marrow not working like it should, which can lead to not having enough red blood cells, white blood cells, or platelets
- Problems with things like sodium and potassium in your blood
- Pancreatitis
- Infection, including serious infection
- Skin cancer or blood cancer

The risks can be kept as low as possible by the tests you will have while taking this medication (see "What does the treatment involve?").

Methotrexate

Side effects may include:

- Nausea, vomiting, diarrhea, stomach cramps
- Painful ulcers in your mouth
- Flu-like symptoms
- Dizziness
- Your skin being sensitive to light
- Your skin feeling burned
- Hair loss
- Liver test numbers being too high or too low

Risks may include:

- Your bone marrow not working like it should, which can lead to not having enough red blood cells, white blood cells, or platelets
- Problems with the liver
- Inflammation and scarring in your lungs
- An ulcer in your stomach or intestines, which may bleed
- Infection, including serious infection
- Skin cancer or blood cancer

The risks can be kept as low as possible by the tests you will have while taking this medication (see "What does the treatment involve?").

Dupilumab

Side effects may include:

- Injection site reactions
- Different symptoms or problems with the eyes or eyelids, such as pain, itchiness, redness, dryness, tearing, feeling like something is in your eye, sensitivity to light, and decreased or blurry vision
- Pain in throat or mouth

Risks may include:

- Infection, mostly herpes simplex infections

Systemic corticosteroids

Side effects may include:

- increased blood sugar
- your body holding on to water
- your immune system not being as strong as it usually is
- feeling happier, sadder, angrier, more agitated, more energetic, or more anxious than usual
- difficulty sleeping

Risks with short-term use are usually low as long as people do not have other health issues that might put them at risk. However, some people may have problems with things like sodium and potassium in the blood. Some people may have a bad reaction to the steroids. These people may have problems thinking, make poor choices, see or hear things that are not there, or believe things that are not true.

(References consulted for the above descriptive responses include DynaMed 2018-2020, FDA 2019, Gooderham 2017, Ou 2018, Sidbury 2014, Vestergaard 2020, Wollenberg 2016, Wollenberg 2018; these references were consulted when it became clear the available randomized trial evidence would be insufficient to provide insight on this FAQ as described later in this report)

FAQ 5: What if I am pregnant or want to get pregnant?

Cyclosporine

Women and men can take cyclosporine before trying to conceive a child. Women who are pregnant or breastfeeding can use cyclosporine if creams, ointments, and similar treatments have not helped enough. Pregnant or breastfeeding women should let their clinicians know about all medicines they are taking or are thinking about taking.

Azathioprine

Women and men can take azathioprine before trying to conceive a child. For pregnant women, cyclosporine is preferred to azathioprine. Breastfeeding women can use azathioprine, but they should not use any breastmilk they make within 4 hours of taking azathioprine. Pregnant or breastfeeding women should let their clinicians know about all medicines they are taking or are thinking about taking.

Mycophenolate mofetil

Women and men who want to conceive a child may need to stop mycophenolate for 3 months before trying to conceive. Women who are pregnant or breastfeeding should not use mycophenolate.

Methotrexate

Women who want to conceive a child may need to stop methotrexate for up to 6 months before trying to conceive. Men who want to conceive a child may need to stop methotrexate for up to 3 months before trying to conceive. Women who are pregnant or breastfeeding should not use methotrexate.

Dupilumab

There is not enough information yet to know about using dupilumab in women or men who want to conceive a child or in pregnant or breastfeeding women.

Systemic corticosteroids

If needed, steroids can be used for a short period of time in women and men who want to conceive a child and in pregnant or breastfeeding women. Steroids should be used with the smallest dose and for the shortest length of time.

(Reference consulted for these descriptive responses: Vestergaard 2019)

Search Summary

Number of articles screened and selected

	Screened	Selected*
1st-round (DynaMed)	27	1
2nd-round (Systematic review searches)	30	8
3rd-round (Original article searches)	5	0
4th-round (Citation tracing)	1	1
Total	*63*	*10*

*Number shown is after deduplication and does not include any consideration of full-text articles for verification or clarification of details (e.g., verification or clarification of content reported in systematic reviews)

	Articles selected for evaluation (Author Year)
Systematic reviews	9 (Drucker 2020*, Hoare 2000, Nankervis 2017, Roekevisch 2014, Schmitt 2007A, Schmitt 2007B, Wang 2018, Seger 2019, Schram 2011)
Randomized, controlled trials	1 (Goujon 2018)
Other article types	0

*Drucker 2020 was published online ahead of print on April 22, 2020. Accordingly, it was not available/included in our initial search on April 14, 2020. We only became aware of it when we re-ran our search on April 27, 2020, after we had completed Critical Appraisal and Evidence Synthesis based on the evidence we had available to us from our original searches. Drucker 2020 ultimately did not impact Evidence Synthesis.

Results – Synthesis Details

General note about the overall evidence base for this evidence report

In general, the evidence base for this evidence report is often limited by sparse, dated, and poorly-reported studies reporting on heterogeneous outcomes intended to capture the same broad clinical construct (e.g., severity of disease, quality of life). Moreover, many bodies of evidence inappropriately focus on within-group changes (from baseline) rather than between-group differences, thus making assessment of between-group differences difficult and limited in nature, often requiring consultation of the full-text of the trials in question. Additionally, in many instances, our synthesis necessarily incorporated indirect reasoning due to outcomes not being addressed or because placebo-controlled evidence was lacking. This indirect reasoning: (1) pulled on the available evidence for FAQs that one would expect to be interrelated and/or (2) invoked transitivity assumptions (e.g., if cyclosporine appears to be better than placebo, and cyclosporine and mycophenolate do not appear to have a clear difference, then in the absence of placebo-controlled evidence for mycophenolate, one might also infer mycophenolate appears to be better than placebo). However, this invariably introduces at least some degree of indirectness. Drucker 2020 was published after we completed Evidence Synthesis for the evidence available to us at the time of our original search, but Drucker 2020 ultimately does not change our conclusions. Drucker 2020 only published network estimates (no direct, pairwise estimates), and they also note the limited nature of the evidence base, stating explicitly that the "networks are sparse", "[m]ost comparisons were informed by only a single RCT and usually with a small number of patients, which led to imprecision", and that these limitations "precluded planned evaluation of consistency" between direct and indirect evidence. All these things (with additional considerations below) lead to reservation in placing emphasis on Drucker 2020's network estimates.

Additionally, the available evidence focuses heavily on continuous measures. This is not a problem in and of itself. However, communicating the meaning of continuous outcome measures to clinicians and patients is rendered difficult by the nature of the measurement. This is rendered even more difficult when different scales are used and/or if the continuous measures are reported as standard deviation units (as is the case with SMDs). Although "rules of thumb" exist for interpretation of SMDs, these are nebulous and largely serve as a "rough guide" for understanding effect sizes in the absence of a better method for contextualization. The appropriateness of the SMD also relies heavily on the extent to which the scales being combined are truly similar. Drucker 2020 explicitly note this limitation, as well as the impact that the timing of the trials could have on the apparent efficacy of any given agent: "These analyses are limited by pooling outcome measures such as peak itch and mean itch, which measure the same domain but in different ways, and their inclusion of trials only up to 16 weeks, which may favor medications with more rapid onset of action." Very limited evidence reported on dichotomous (or other categorical) measures, but it would be problematic to limit focus to such measures for at least two reasons. First – and perhaps most importantly – focusing solely on measures that happen to be reported categorically would introduce serious risk of selection bias (i.e., the evidence would no longer represent a systematic review of the available evidence). Second, if the categorical outcomes are defined by a dichotomous cut-point for underlying continuous data, this can be a problematic approach to data analysis, at least depending on the point in analysis where this dichotomization occurs and how the data are dichotomized (this is discussed further in the summary for Goujon 2018 in Critical Appraisal; if one desires to know what proportion of people would be expected to achieve a certain degree of change on a continuous scale, such estimation/analysis could instead occur at the latest possible point in analysis, such as the continuous outcome being analyzed on the continuous scale, and any estimation about the

proportion of people who might achieve some degree of change occurring after the outcome is analyzed on the continuous scale).

Considering the above, although we conducted extensive and detailed review of the available evidence for the scoped therapies for this evidence report, we do not feel it is appropriate to give quantified answers for any of the scoped FAQs. Accordingly, we have adopted a pattern of qualitative evidence synthesis throughout.

Lastly, because for FAQ 2 we pre-specified a greater interested in patient-reported outcomes but found on evidence review that (1) these were often lacking and (2) the clinician-assessed outcomes were also heterogeneous, we may broadly refer to clinician-assessed outcomes as 'sign' outcomes (i.e., those things a clinician can assess), which is intended to serve as a contrast to 'symptom' outcomes (i.e., things a patient experiences and reports).

FAQ 1: What does the treatment involve?

Therapies considered in this evidence report correspond to 'Step 4' of the German guidelines (Werfel 2016). Of note, Step 4 therapy may include concurrent use of topical therapy or UV-based therapy as "background" therapies as well as lifestyle modifications such as avoidance of triggers or general irritants. For some therapies, however (e.g., cyclosporine, azathioprine), concurrent UV therapy is *discouraged*, and UV protection is recommended.

Although not mentioned below for each individual agent, sometimes a larger initial dose is used (with the idea of more rapidly bringing the condition under control) which is followed by a scheduled reduction or recommendation for gradual dose reduction until the lowest effective dose is found. This is, in general, good practice for pharmacotherapeutics in general, but it is perhaps of additional note here given some of these agents are known to have considerable potential toxicity and a narrow therapeutic window.

Relevant comorbidities that may preclude use of a specific agent are noted for each agent, but active infection may complicate or preclude use of any of these agents (with the possible exception of dupilumab, other than perhaps for helminth infections).

Medication interactions complicating or precluding use are not considered (e.g., azathioprine and allopurinol have a serious interaction that can increase the toxicity of azathioprine).

Implications for people trying to get pregnant or who desire to get pregnant are addressed in FAQ 5: What if I am pregnant or want to become pregnant?

Given the common sources used for the therapies, we present references at the end of FAQ 1 rather than at the end of each option.

Cyclosporine

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

Cyclosporine is given daily and can be administered orally (it can also be administered intravenously, but for practicality and desirability in a typical situation, this option is unlikely and not considered in any detail here). An initial dose of 5 mg/kg/day is often used (e.g., Wollenberg 2018), but the starting dose can be as low as 2.5 mg/kg/d; for instance, the German guidelines recommend a starting dose of 2.5 to 5 mg/kg/day (Werfel 2016). The total daily dose is typically divided into two doses, with major guidelines explicitly recommending this (Werfel 2016, Wollenberg 2018). In general, cyclosporine has a relatively rapid onset (effects may be seen within 2 weeks), but it is not used as a continuous, indefinite long-term therapy due to its known toxicities; rather, continuous therapy is typically limited to a 1- or 2-year period maximum, and some suggest even shorter durations – such as intervals of 3 to 6 months – and highlight its use more as a therapy that can be used to achieve initial control with an intent to eventually transition to an agent with a slower onset, such as azathioprine. The German guidelines specifically recommend discontinuing cyclosporine therapy after 4 to 6 months, and they also recommend – as alluded to above – a reduction in the dose of cyclosporine if possible after achieving response.

Before starting this medication, a patient will need to have various testing done unless such tests are already in the patient's record based on a recent evaluation. Although the exact tests obtained may vary somewhat, testing may include:

- blood pressure*
- comprehensive metabolic panel†‡
- urinalysis with microscopy
- fasting lipid profile‡
- complete blood count with differential‡
- magnesium (not in a comprehensive metabolic panel)‡
- uric acid‡
- tuberculosis§ and infectious hepatitis¶ testing
- pregnancy test if female
- testing for HIV if an at-risk population

*will generally check this at every visit
†may instead separately order liver function, renal function, and potassium
‡may repeat this every other week for 2 to 3 months, then every month thereafter; if dose is increased, may check within 2 to 4 weeks of dose change
§may repeat tuberculosis testing annually
¶perhaps especially B and C, though hepatitis testing is not unanimously recommended

Comorbid uncontrolled hypertension, renal insufficiency, liver disease, gout, uncontrolled / poorly controlled diabetes, and malignancy may complicate or preclude use.

Cyclosporine should not be combined with UV phototherapy, and UV protection should be used while taking cyclosporine.

Descriptive Summary Results

You can take cyclosporine by mouth. You will take it every day, and you may take it twice a day. You may see it start to work within 2 weeks. In most cases, cyclosporine is not used as a long-term medicine. It may be used for about 3 to 6 months to get your eczema under control, or it may be used for up to 1 or 2 years. After that, people often change to a different medicine. You should not use ultraviolet ("UV") light therapy (often also called "phototherapy") while taking cyclosporine. You should also protect your skin from UV light while taking cyclosporine, which means avoiding things like sun tanning or tanning beds and wearing sunscreen if you will have long periods where your skin is exposed to sun light.

You will need blood tests and blood pressure checks before you start cyclosporine and while you are on cyclosporine. For people with certain conditions, cyclosporine may not be the best choice. You can discuss this more with your clinician.

Azathioprine

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

Azathioprine is given daily, taken orally, and can be used as continuous, long-term therapy (it can also be administered intravenously, but for practicality and desirability in a typical situation, this option is unlikely and not considered in any detail here). However, it has a relatively slower onset (effects may not be seen for 8 to 12 weeks). The German guidelines (Werfel 2016) recommend considering azathioprine if cyclosporine does not have sufficient effect or cannot be used (they mention contraindication specifically, but would also presumably include inability to use due to intolerance).

Before starting this medication, a patient will need to have various testing done unless such tests are already in the patient's record based on a recent evaluation. Although the exact tests obtained may vary somewhat, testing may include:

- thiopurine methyltransferase (TPMT) polymorphism/activity*
- comprehensive metabolic panel†‡
- complete blood count with differential‡
- tuberculosis§ and infectious hepatitis¶ testing
- pregnancy test if female
- testing for HIV if an at-risk population

*checked at baseline to help avoid the myelotoxicity that can be associated with azathioprine; repeat testing may occur at regular intervals to help guide dosing
†may instead separately order liver function and renal function
‡may repeat this twice per month for 2 months, monthly for 4 months, then every other month; may check again if dose is increased
§may repeat tuberculosis testing annually
¶perhaps especially B and C, though hepatitis testing is not unanimously recommended

Comorbid liver disease, renal insufficiency, malignancy, inadequate TPMT activity, myelosuppressive conditions, or cytopenias may complicate or preclude use.

Azathioprine should not be combined with UV phototherapy, and UV protection should be used while taking azathioprine.

Descriptive Summary Results

You can take azathioprine by mouth. You will take it every day. You may have to take it for 8 to 12 weeks before you start to see it work. Azathioprine can be used as a long-term medicine. You should not use ultraviolet ("UV") light therapy (often also called "phototherapy") while taking azathioprine. You should also protect your skin from UV light while taking azathioprine, which means avoiding things like sun tanning or tanning beds and wearing sunscreen if you will have long periods where your skin is exposed to sunlight.

You will need blood tests before you start azathioprine and while you are on azathioprine. For people with certain conditions, azathioprine may not be the best choice. You can discuss this more with your clinician.

Mycophenolate mofetil

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

Mycophenolate is given daily, taken orally, and can be used as continuous, long-term therapy (it can also be administered intravenously, but for practicality and desirability in a typical situation, this option is unlikely and not considered in any detail here). However, it has a relatively slower onset (effects may not be seen for 8 to 12 weeks). The German guidelines (Werfel 2016) recommend considering mycophenolate if cyclosporine does not have sufficient effect or cannot be used (they mention contraindication specifically, but would also presumably include inability to use due to intolerance).

Before starting this medication, a patient will need to have various testing done unless such tests are already in the patient's record based on a recent evaluation. Although the exact tests obtained may vary somewhat, testing may include:

- comprehensive metabolic panel*†
- complete blood count with differential†
- tuberculosis‡ and infectious hepatitis§ testing
- pregnancy test if female
- testing for HIV if an at-risk population

*may instead separately order liver function and renal function
†may repeat this every 2 weeks for 1 month, monthly for 3 months, then every 2 to 3 months thereafter
‡may repeat tuberculosis testing annually
§perhaps especially B and C, though hepatitis testing is not unanimously recommended

Comorbid renal insufficiency, myelosuppressive conditions, cytopenias (other than, perhaps, thrombocytopenia), or peptic ulcer disease may complicate or preclude use.

Descriptive Summary Results

You can take mycophenolate by mouth. You will take it every day. You may have to take it for 8 to 12 weeks before you start to see it work. Mycophenolate can be used as a long-term medicine.

You will need blood tests before you start mycophenolate and while you are on mycophenolate. For people with certain conditions, mycophenolate may not be the best choice. You can discuss this more with your clinician.

Methotrexate

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

Methotrexate is typically given weekly and can be administered subcutaneously or orally (it can also be administered intramuscularly or intravenously, but for practicality and desirability in a typical situation, this option is unlikely and not considered in any detail here). Depending on the dosing regimen used, oral administration may not require more frequent dosing than subcutaneous dosing. It can be used as continuous, long-term therapy. However, it has a relatively slower onset (effects may not be seen for 8 to 12 weeks). The German guidelines (Werfel 2016) recommend considering methotrexate if cyclosporine does not have sufficient effect or cannot be used (they mention contraindication specifically, but would also presumably include inability to use due to intolerance).

Before starting this medication, a patient will need to have various testing done unless such tests are already in the patient's record based on a recent evaluation. Although the exact tests obtained may vary somewhat, testing may include:

- comprehensive metabolic panel*†‡
- complete blood count with differential†
- tuberculosis§ and infectious hepatitis testing
- pulmonary function testing if at risk
- pregnancy test if female
- testing for HIV if an at-risk population

*may instead separately order liver function and renal function
†may repeat liver function and complete blood count with differential every week for 2 to 4 weeks, every 2 weeks for a month, and every 2 to 3 months thereafter; may check again in 1 week after a dose increase
‡may repeat renal function testing every 6 to 12 months
§may repeat tuberculosis testing annually

Comorbid alcoholism or alcoholic liver disease, chronic liver disease or liver impairment, immunosuppression, myelosuppressive conditions or bone marrow hypoplasia, significant cytopenia, abnormal renal function, chronic lung disease, peptic ulcer disease, ulcerative colitis, or diabetes may complicate or preclude use.

Descriptive Summary Results

You can take methotrexate by mouth. You can take it once a week, but some people may want to take a lower dose that they take every day. You may have to take it for 8 to 12 weeks before you start to see it work. Methotrexate can be used as a long-term medicine.

You will need blood tests before you start methotrexate and while you are on methotrexate. For people with certain conditions, methotrexate may not be the best choice. You can discuss this more with your clinician.

Dupilumab

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

Dupilumab is given subcutaneously every other week, with the first dose amounting to 2 subcutaneous injections given in different areas on day 1, and subsequent doses amounting to a single subcutaneous injection every other week. It can be used as continuous, long-term therapy. Effects may not be seen for 4 to 6 weeks. There is no monitoring required while using this medication. Although conjunctivitis is a known possible side effect (see FAQ 4: What are the risks or side effects?) and thus comorbid conditions predisposing to conjunctivitis might complicate use (e.g., Sjögren's syndrome leading to keratoconjunctivitis sicca), this is speculative; dupilumab does not have as many cautions or relative or absolute contraindications for use as do the other agents considered in this evidence report. Other biologics and small molecule agents are currently being evaluated in or have been identified as potential candidates for clinical trials, such as nemolizumab, upadacitinib, and ustekinumab.

Descriptive Summary Results

Dupilumab is given under your skin. The first time you take it, you will get two doses in different spots on your body. After that, you will need one dose every other week. You can give yourself the medicine under your skin once you learn how. You may have to take it for 4 to 6 weeks before you start to see it work. Dupilumab can be used as a long-term medicine.

People do not usually need any tests before taking dupilumab or while they are on dupilumab. Most people can take dupilumab even if they have other conditions. You can discuss this more with your clinician.

Systemic corticosteroids

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

Systemic corticosteroids can be given orally, intramuscularly, or intravenously. They are intended only for short-term use (e.g., up to 1 week, but sometimes given for 2 weeks or so depending on the situation) to rapidly bring atopic dermatitis under control. There is clear consensus that long-term use should be avoided, so long-term use is not considered here. Given the narrow scope of systemic corticosteroids, no testing may be required prior to use. However, certain comorbid conditions may complicate use based largely on systemic corticosteroids causing for excursion in blood glucose levels and retention of sodium and water (with loss of potassium); accordingly, one must use these with caution (if at all) in patients with comorbid heart failure, renal insufficiency, or poorly controlled or uncontrolled diabetes mellitus or hypertension. Accordingly, monitoring while on systemic corticosteroids may include blood pressure, electrolytes, and blood glucose (the latter two may be summarily assessed via a basic metabolic panel). Liver disease, especially cirrhosis, may result in more pronounced effects of systemic corticosteroids at a given dose due to decreased medication metabolism.

Descriptive Summary Results

You can take steroids by mouth, but they are sometimes given in your muscle or vein. Steroids are usually only used for a week or two to get eczema under control. For people with certain conditions, steroids may not be the best choice. Some people may need blood tests or blood pressure checks while they take steroids. You can discuss this more with your clinician.

(DynaMed 2018-2020, Gooderham 2017, Sidbury 2014, Vestergaard 2020, Wollenberg 2016, Wollenberg 2018)

FAQ 2: Will my skin and symptoms improve?

Efficacy scales/scores used in the literature

There are several scales/scores used in the available literature for this evidence report. To help readers understand these scales/scores better, we include below a brief description of scales/scores that appear in this FAQ. However, some studies used non-validated scales/scores and their composition was not apparent from the sources considered (e.g., van Joost 1994 as reported by the Schmitt 2007A systematic review); we do not provide further information about these scales below.

- 6 area, total body severity assessment
  - This score/scale assesses erythema, infiltration, vesicles/papules, dryness/scaling, cracking/fissuring, and excoriation/crusting on a 0 (none) to 3 (severe) scale for 6 regions of the body: head and neck; a band wrapping around the trunk that is defined anteriorly by the superior aspect of the axillary folds, the inguinal ligaments, and pubis, and posteriorly by the inferior scapular borders and gluteal folds; the elbows/mid-upper arms to mid-forearms; hands and wrists; knees/mid-thighs to mid-calves; and feet and ankles. Accordingly, the final score ranges from 0 to 108, with higher scores being worse. This is essentially a variant of the SASSAD (measuring infiltration and vesicles/papules instead of exudation and lichenification), but it generally much less used.
- Eczema Area and Severity Index (EASI)
  - This score/scale assesses the extent and severity of disease activity in 4 body regions. The 4 body regions are: head and neck, trunk and genitals, upper limbs, and lower limbs and buttocks. 'Extent' is assessed on a 0 (no activity in the region) to 6 (90% to 100% of the region is affected) scale, and 'severity' is assessed on a 0 (none) to 3 (severe) scale for the 4 components of redness/erythema/ inflammation, thickness/infiltration/induration/papulation, excoriation/scratching, and lichenification. These components are then used in a formula to derive a final score, which ranges from 0 to 72, with higher scores worse.
- Severity SCORing of Atopic Dermatitis (SCORAD)
  - This score/scale assesses three domains: area, intensity, and subjective symptoms. 'Area' has a maximum score of 100% based on the rule of 9s (head and neck are 9%, upper limbs are 9% each, lower limbs are 18% each, the anterior and posterior aspects of the trunk are 18% each, and the genitalia is 1%). 'Intensity' is scored on a 0 (none) to 3 (severe) scale for the components redness, swelling, oozing/crusting, scratch marks, lichenification, and dryness (the latter specifically assessed in noninflamed areas); the maximum score is 18. 'Subjective symptoms' is comprised of itch and loss of sleep/difficulty sleeping, each of which is assessed on a 0 (none) to 10 (worst) scale. The final SCORAD score is calculated as: (area/5) + (7*intensity/2) + subjective symptoms. Accordingly, the scale ranges from 0 to 103 (100/5 + 7*18/2 + 20), with higher scores being worse.
- Six-Area, Six-Sign Atopic Dermatitis (SASSAD)
  - This score/scale assesses erythema, dryness, cracking, excoriation, exudation, and lichenification on a 0 (none) to 3 (severe) scale for 6 regions of the body: head and neck; a band wrapping around the trunk that is defined anteriorly by the superior aspect of the axillary folds, the inguinal ligaments, and pubis, and posteriorly by the inferior scapular borders and gluteal folds; the elbows/mid-upper arms to mid-forearms; hands and wrists; knees/mid-thighs to mid-calves; and feet and ankles. Accordingly, the final score ranges from 0 to 108, with higher scores being worse. The 6 area, total body severity assessment is essentially a less-used variant of this scale/sore (measuring infiltration and vesicles/papules instead of exudation and lichenification).

The above scores/scales are all different in certain ways, but they all generally capture the same basic concepts. Accordingly, and to help patients better understand what the bolded synthesis statements below mean, we have standardized to say "[Agent] [may/may not] help how much of your body has eczema and how bad the eczema is (things like the amount of dryness, redness, scaling, cracking, and so on) …". Being extremely specific about exact score/scale components does not seem helpful and could instead lead to confusion and spurious inferences.

Cyclosporine vs. placebo

Evidence Review

We prepared summaries of 5 SRs that addressed this comparison and reported this outcome: Drucker 2020, Hoare 2000, Roekevisch 2014, Schmitt 2007A, and Schmitt 2007B. The completeness and adequacy of methods and reporting varied across SRs, but methods or results reported incompletely or inadequately in one SR could be supplemented with information reported more completely in another SR. Roekevisch 2014 only reported trials' results as within-group (rather than between-group) differences. However, this SR provided us with an overall 'evidence picture' in terms of the number of trials addressing each scoped option as of Roekevisch 2014's search window closure of June 2012. For the comparison of cyclosporine vs. placebo, Roekevisch 2014 included four eligible trials: Munro 1994, Sowden 1991, van Joost 1994, and Wahlgren 1990. Searches for subsequent SRs and RCTs revealed no additional RCTs.

For extractable information about characteristics, quality, and between-group results from these eligible trials, we critically appraised and summarized relevant details from 3 other SRs (Hoare 2000, Schmitt 2007A, Schmitt 2007B).

The characteristics were reported in clear detail in Hoare 2000 and were extracted from there (see table below). Characteristics reported in Hoare 2000 were cross-checked with and supplemented with (as appropriate) those reported in Schmitt 2007A (as documented in footnotes of characteristics table below).

Risk of bias assessments and other study quality domains were reported in Schmitt 2007A, Schmitt 2007B, and Roekevisch 2014. However, Roekevisch 2014 reported only a summary risk of bias assessment for a comparison overall, but not for specific trials or outcomes. Therefore, we preferred to use the more detailed trial-specific risk of bias assessments as reported in Schmitt 2007A, which we crosschecked against Schmitt 2007B given it included additional information on allocation concealment which was not assessed in Schmitt 2007A. Hoare 2000 did not report risk of bias assessments, but it contributed to our overall certainty assessment because it included a table showing the heterogeneous outcome measures across the trials which precluded a meta-analysis and contributed to an inconsistency downgrade.

Results of between-group comparisons were reported for a composite index of symptom severity only in Schmitt 2007A, but these results were not meta-analyzed or otherwise quantitatively synthesized. Hoare 2000 reported results per trial and a meta-analysis of a pooled itch outcome, but we did not carry that forward to Synthesis because it focuses on a single symptom and not a composite index of disease severity.

The tables below present the simplified amalgamation of the evidence review for this FAQ and comparison. As noted in Critical Appraisal, Drucker 2020 was published after our original search, and we became aware of it only after we had completed our initial draft of Evidence Synthesis based on the information available to us at the time. Drucker 2020 ultimately did not change any of our synthesis for FAQ 2.

Characteristics of placebo-controlled randomized trials of cyclosporine treatment in adults with moderate to severe eczema*†

Study	Number of participants	Design‡	Duration	Co-treatments
Sowden 1991	33	crossover	16 weeks	topical steroids
Munro 1994	24	crossover	8 weeks	topical steroids
van Joost 1994	46	parallel	6 weeks	hydroxyzine 10 or 25 mg, emollients
Wahlgren 1990	10	crossover	10 days	1% hydrocortisone, emollients

*All trials reported an oral cyclosporine dosage of 5 mg/kg/day; Schmitt 2007A reported that dose adjustment not allowed in any of the 3 relevant trials it included (ie, all but Wahlgren 1990)

†Based on data extracted from Hoare 2000

‡For 3 crossover trials (Sowden 1991, Munro 1994, Wahlgren 1990) only the study period prior to cross-over was considered to avoid risk of bias due to carry-over effects. This was the specified analytic approach in both Schmitt 2007A and in Hoare 2000 (the latter for its meta-analysis of itch outcome).

Clinical severity outcome measurement and results for comparison of cyclosporine vs. placebo for 6 to 8 weeks in adults with severe eczema*

Study	Outcome measurement		Results (Comparative efficacy)
	Primary outcome	Components	
Sowden 1991	non-validated score	erythema, purulence, excoriation, dryness, fissuring, lichenification, extent	mean severity score with cyclosporine vs. placebo: 16.5 vs. 40.5; $p < 0.01$
Munro 1994	extent, erythema, excoriation	no composite score applied	mean extent after cyclosporine vs. placebo: 2% BSA vs. 14% BSA; $p < 0.01$
van Joost 1994	6-Area, Total Body Severity Assessment	erythema, vesiculation, excoriation, dryness, infiltration, fissures, extent	significant superiority of cyclosporine; $p < 0.05$

*Based on data extracted from Schmitt 2007A

Review authors' ratings of individual quality criteria and overall study quality*

Study	Clear case definition	Clearly defined eligibility criteria	Adequate description of study population	Double-blind treatment	Validated outcome	Follow-up rate > 80%	ITT analysis	Allocation concealment†
Sowden 1991	yes	yes	yes	yes	no	No	no	no
Munro 1994	no	no	no	yes	no	no	no	no
van Joost 1994	yes	yes	yes	yes	yes	no	yes	no

*Based on data extracted from Schmitt 2007A supplemented with assessments on allocation concealment from Schmitt 2007B. Assessments for domains reported in both Schmitt 2007A and Schmitt 2007B were cross-checked and no inconsistencies were identified. The withdrawals and dropouts reported in Hoare 2000 and extracted into that summary (see Critical Appraisal) supports incomplete outcome data.

†Allocation concealment was not included in Schmitt 2007A.

Certainty

We consider these data to permit only Very low certainty conclusions. Key concerns include risk of bias (inadequate allocation concealment, high losses to follow-up) and indirectness (outcome being clinician-assessed rather than patient-assessed). We also note the trials themselves are small and dated, and reporting on concepts pertaining to precision was often insufficient (tests of statistical significance are not a sufficient gauge of precision).

Evidence Synthesis Process

Outcome	Approach taken and justification: measure of comparative effect	Results: measure of comparative effect
signs/clinician-assessed severity	**Qualitative synthesis of available randomized trials** Because the trials used different outcome measures for severity and reported the results in different ways, it was not possible to synthesize the numerical findings. However, all trials included in Schmitt 2007A reported significant between-group differences in disease severity as assessed by a clinician. Other SRs served to generate a more complete evidence profile for this comparison as described above and in Critical Appraisal. Drucker 2020, although providing a measure of SMD as a quantified estimate, does not change this interpretation. We use a qualitative expression for synthesis for reasons stated in the above section 'General note about the overall evidence base for this evidence report', and we include phrasing about our uncertainty in the evidence synthesis statement.	**Cyclosporine may improve severity of eczema more than placebo** Certainty for the outcome is Very low (see 'Certainty' in the Evidence Review section for details)

Evidence Synthesis Results

Cyclosporine may help how much of your body has eczema and how bad the eczema is (things like the amount of dryness, redness, scaling, cracking, and so on) within the first few months of use, but the research on this is not very good. (Very low certainty; based on 5 systematic reviews: Drucker 2020, Hoare 2000, Roekevisch 2014, Schmitt 2007A, and Schmitt 2007B) **If you notice your skin get better, it may last over time, but we do not have enough research on long-term use of cyclosporine.**

Cyclosporine vs. methotrexate

Evidence Review

We identified 1 randomized trial which addressed this comparison (Goujon 2018). It compared cyclosporine vs. methotrexate for 24 weeks in 97 patients with moderate-to-severe atopic dermatitis. Outcomes were measured at weeks 4, 8, 12, 16, 20, and 24, and we extracted outcome data from week 16 and week 24 as our short-term and long-term outcomes respectively (per Scoping). The results are reported in table below.

Effects of methotrexate vs. cyclosporine on signs (responder analysis)

Outcome	Week	Methotrexate		Cyclosporine		Absolute risk difference (90% CI)
		No. Evaluated	% of patients achieving outcome	No. Evaluated	% of patients achieving outcome	
SCORAD 50 (50% improvement in SCORAD index)	16	28	42.9%	34	61.8%	-19% (95% CI -39% to 2%)
	24	23	39.1%	31	71.0%	-32% (-53% to -10%)
EASI 50 (50% improvement in EASI index)	16	27	66.7%	34	79.4%	-13% (-31% to 6%)
	24	23	87.0%	31	80.7%	6% (-10% to 23%)

As noted in Critical Appraisal, we are concerned with how the authors' attempted to analyze non-inferiority in this trial. They conducted responder analyses, defining a 'responder' as someone who achieved ≥50% improvement in the scale in consideration. However, we have concerns with this approach, as detailed in Critical Appraisal. Additionally, they calculated 90% CIs for their responder analyses (given their desire to estimate a one-sided CI bound at $\alpha = 0.05$), thus impeding analysis outside of their specific intent for non-inferiority. Accordingly, we also considered the underlying continuous data:

Effects of methotrexate vs. cyclosporine on signs (continuous)

Outcome	Methotrexate (mean±SD)	Cyclosporine (mean±SD)
SCORAD (score from 0 to 103)		
16 weeks	28.7±11.5	27.0±15.6
24 weeks	26.9±11.6	24.9±15.5
EASI (score from 0 to 72)		
16 weeks	6.3±4.6	6.1±6.9
24 weeks	5.0±3.6	5.4±5.0

As one can see from the continuous data, the groups are comparable at both time points.

Certainty
Very low due to risk of bias (no patient blinding and high/differential dropouts), imprecision (small trial), indirectness (measures are clinician-assessed rather than patient-reported), and inconsistency (only a single trial, thus precluding assessment of consistency).

Evidence Synthesis Process

Outcome	Approach taken and justification: measure of comparative effect	Results: measure of comparative effect
signs/clinician-assessed severity	**Use results from single trial that addressed this comparison, qualitative expression** Because of our concerns about the responder analyses conducted by the authors, we rely on the underlying continuous data to make inferences. We use a qualitative expression for synthesis for reasons stated in the section 'General note about the overall evidence base for this evidence report'.	
16 weeks		**There may be no clear difference between cyclosporine and methotrexate on the severity of eczema** Certainty for the outcome is Very low (see 'Certainty' in the Evidence Review section for details)
24 weeks		**There may be no clear difference between cyclosporine and methotrexate on the severity of eczema** Certainty for the outcome is Very low (see 'Certainty' in the Evidence Review section for details)

Evidence Synthesis Results
A bolded synthesis statement is not relevant for this outcome. As stated in Scoping, the comparator of interest for scoped outcomes is placebo. This comparison is included only because it indirectly informs the evidence review for methotrexate vs. placebo given the lack of placebo-controlled trials for methotrexate.

Methotrexate vs. placebo

Evidence Review and Synthesis Process

We did not identify any trials making this comparison. Accordingly, our evidence review and synthesis process relies heavily on indirect reasoning, thus lowering the certainty of evidence that is already Very low certainty.

Considering that there is Very low certainty evidence that cyclosporine may be better than placebo and Very low certainty evidence that there may be no clear difference between methotrexate and cyclosporine (as addressed in the corresponding sections above), one might indirectly infer (assuming transitivity) that there is Very low certainty evidence that methotrexate may be better than placebo. The same inferential process applies to the evidence base for azathioprine vs. placebo and methotrexate vs. azathioprine (as addressed in the corresponding sections below). Drucker 2020 provides at least some corroboration of this indirect reasoning, finding an SMD for "signs of disease" for methotrexate vs. placebo of -0.6 (95% CrI -1.1 to 0.0), and although the upper bound of the 95% CrI is a null effect, we would be hesitant to interpret that finding too strongly to avoid (1) inappropriate 'bright-line' thinking concerning research and (2) relying too heavily on the network estimate due to reasons stated above (see 'General note about the overall evidence base for this evidence report') and in Critical Appraisal. Accordingly, we still consider it reasonable to conclude – with Very low certainty – that methotrexate may help with eczema. Akin to our phrasing for cyclosporine, however, we include uncertainty as part of the synthesized result. We use a qualitative expression for synthesis for reasons stated in the above section 'General note about the overall evidence base for this evidence report'.

Evidence Synthesis Results

Methotrexate may help how much of your body has eczema and how bad the eczema is (things like the amount of dryness, redness, scaling, cracking, and so on) within the first few months of use, but the research on this is not very good. (Very low certainty; based on indirect reasoning from the evidence for cyclosporine vs. placebo and methotrexate vs. cyclosporine [see corresponding sections], indirect reasoning from the evidence for azathioprine vs. placebo and methotrexate vs. azathioprine [see corresponding sections], and indirect estimates for methotrexate vs. placebo from 1 systematic review [Drucker 2020]). **If you notice your skin get better, it may last over time, but we do not have enough research on long-term use of methotrexate.**

Cyclosporine vs. mycophenolate

Evidence Review

There was only one, small RCT reporting on this comparison (Haeck 2011, n = 50), identified via Roekevisch 2014. Roekevisch 2014 focuses on within-group differences for its conclusion that these two therapies may be similarly effective, but we consulted the full text of Haeck 2011 in an attempt to assess between-group differences. Although we found Haeck 2011 to be sub-optimally reported, we were able to obtain results for between-group difference at 30 weeks (mean difference in SCORAD score 1.3, 95% CI -4.0 to 6.6), and this corroborated Roekevisch 2014's conclusions. Consideration of other timepoints also corroborates no clear/meaningful difference in these agents. Two timepoints early in the course of treatment (3 and 6 weeks) had a statistically-significant difference, but these timepoints do not align with our prespecified timepoints for consideration (per Scoping), and the differences are of questionable clinical relevance that could be entirely attributable to the difference in expected onset of action for these agents.

Certainty

We concur with Roekevisch 2014's assessment of these results as being Very low certainty. Roekevisch assigned two downgrades for risk of bias and one downgrade for publication bias; we would add downgrades for imprecision, inconsistency, and indirectness due to the nature of this comparison coming from a single, small trial (leading to imprecision and an inability to assess consistency of findings) and the outcome being clinician-assessed rather than patient-reported (thus leading to indirectness). However, given the certainty is already Very low from the risk of bias and publication bias downgrades, these additional downgrades would not further reduce the GRADE rating of this outcome.

Evidence Synthesis Process

Outcome	Approach taken and justification: measure of comparative effect	Results: measure of comparative effect
signs/clinician-assessed severity	**Use results from single trial that addressed this comparison, qualitative expression** We use a qualitative expression for synthesis for reasons stated in the above section 'General note about the overall evidence base for this evidence report'.	**There may be no clear difference between cyclosporine and mycophenolate on the severity of eczema** The results have Very low certainty (see 'Certainty' in the Evidence Review section for details)

Evidence Synthesis Results

A bolded synthesis statement is not relevant for this outcome. As stated in Scoping, the comparator of interest for scoped outcomes is placebo. This comparison is included only because it indirectly informs the evidence review for mycophenolate vs. placebo given the lack of placebo-controlled trials for mycophenolate.

Mycophenolate vs. placebo

Evidence Review and Synthesis Process

We did not identify any trials making this comparison. Accordingly, our evidence review and synthesis process relies heavily on indirect reasoning, thus lowering the certainty of evidence that is already Very low certainty.

Considering that there is Very low certainty evidence that cyclosporine may be better than placebo and Very low certainty evidence that there may be no clear difference between mycophenolate and cyclosporine (as addressed in the corresponding sections above), one might indirectly infer (assuming transitivity) that there is Very low certainty evidence that mycophenolate may be better than placebo. Drucker 2020 does not include mycophenolate in its considerations, as the only-available trial (Haeck 2011) did not meet its inclusion criteria (it had a run-in period where all participants received cyclosporine). Akin to our phrasing for other agents, we include uncertainty as part of the synthesized result. We use a qualitative expression for synthesis for reasons stated in the above section 'General note about the overall evidence base for this evidence report'.

Evidence Synthesis Results

Mycophenolate may help how much of your body has eczema and how bad the eczema is (things like the amount of dryness, redness, scaling, cracking, and so on) within the first few months of use, but the research on this is not very good. (Very low certainty; based on indirect reasoning from the evidence for cyclosporine vs. placebo and 1 randomized trial of mycophenolate vs. cyclosporine [Haeck 2011]). **If you notice your skin get better, it may last over time, but we do not have enough research on long-term use of mycophenolate.**

Azathioprine vs. placebo

Evidence Review

Schram 2011, which was an SR on azathioprine for dermatologic conditions, included detailed methods and results for severity for the 2 placebo-controlled trials of azathioprine for severe atopic dermatitis. Searches for subsequent SRs and RCTs revealed no additional RCTs. Drucker 2020 was published after we had completed Critical Appraisal and Evidence Synthesis for the evidence available to us at the time of our original search, but it did not impact our synthesized findings.

Characteristics and results of placebo-controlled randomized trials of azathioprine in adults with atopic dermatitis*

Study	Number of patients	Design	Duration	Co-treatments	Efficacy	Withdrawals
Berth-Jones 2002	37	Crossover	6 months, where each treatment period was 3 months	topical corticosteroid	reduction in disease severity as assessed by SASSAD: azathioprine 10.2 points (26%) vs. placebo 1.0 points (3%); between groups: $p < 0.01$	12/37 during azathioprine (4 because of adverse events); 4/37 during placebo (no. because of adverse events not reported)
Meggitt 2006	61	Parallel	12 weeks	topical corticosteroid	reduction in disease severity as assessed by SASSAD: azathioprine 12.0 points (37%) vs placebo 6.6 points (20%); difference: 5.4 (95% CI, 1.4 to 9.3) and 17% (4.3% to 29%)	6/41 in azathioprine group and 1/20 in placebo group

*Daily dose was 2.5 mg/kg in Berth-Jones 2002 and 0.5 -2.5 mg/kg in Meggitt 2006

Risk of bias of placebo-controlled randomized trials of azathioprine in adults with atopic dermatitis

Study	Adequate randomization	Adequate allocation concealment	Adequate masking*	Adequate completeness of data reported	Free of selective reporting?	Free of other bias?
Berth-Jones 2002	yes	yes	yes	unclear	Yes	yes
Meggitt 2006	yes	yes	yes	yes	Yes	yes

*Both trials were reported to have adequate masking of participants, researchers, and outcome assessors

Certainty

We consider these data to permit only Very low certainty conclusions. Concerns include risk of bias (high and unequal dropouts), indirectness (clinician-assessed outcome rather than patient-assessed outcome), and imprecision (Meggitt 2006 reported a 95% CI which shows clear imprecision, such as the data being compatible with a 1.4-point difference on the 108-point SASSAD scale, and despite measures of precision not being reported for Berth-Jones 2002, the estimates reported in each group and the very small size of the trial still raises concerns about imprecision in any results obtained).

Evidence Synthesis Process

Outcome	Approach taken and justification: measure of comparative effect	Results: measure of comparative effect
signs/clinician-assessed severity	**Qualitative synthesis of available randomized trials** Both placebo-controlled trials found benefit for azathioprine vs. placebo on signs/clinician-assessed severity. We use a qualitative expression for synthesis for reasons stated in the above section 'General note about the overall evidence base for this evidence report', and we include phrasing about our uncertainty in the evidence synthesis statement.	**Azathioprine may improve severity of eczema more than placebo** Certainty for the outcome is Very low (see 'Certainty' in the Evidence Review section for details)

Evidence Synthesis Results

Azathioprine may help how much of your body has eczema and how bad the eczema is (things like the amount of dryness, redness, scaling, cracking, and so on) within the first few months of use, but the research on this is not very good. (Very low certainty; based on 5 systematic reviews: Drucker 2020, Hoare 2000, Roekevisch 2014, Schmitt 2007A, and Schmitt 2007B) **If you notice your skin get better, it may last over time, but we do not have enough research on long-term use of azathioprine.**

Azathioprine vs. methotrexate

Evidence Review

Through Roekevisch 2014, we identified 1 randomized trial which addressed this comparison (Schram 2011A). This trial compared azathioprine vs. methotrexate for 12 weeks in 42 patients with severe atopic dermatitis and reported on severity and quality of life (quality of life is addressed in FAQ 3). Roekevisch 2014 described Schram 2011A's findings as "AZA and MTX were found to be equally efficacious"; Roekevisch 2014 also reported similar percent improvements in the two groups for disease severity but did not report between group comparisons. The full text of Schram 2011A was obtained and means and SDs were extracted from each group to calculate the mean differences between groups, which showed no clear difference for disease severity as assessed by a clinician or the patient (e.g., MD for SCORAD 1.9, 95% CI -7.6 to 11.4; MD for POEM 1, 95% CI -3.3 to 5.3; and other measures were comparable).

Certainty

Because this was a single, small trial with incomplete blinding showing no clear difference between groups, we rated it as having Very low certainty with downgrades for risk of bias, imprecision, and inconsistency.

Evidence Synthesis Process

Outcome	Approach taken and justification: measure of comparative effect	Results: measure of comparative effect
signs/clinician-assessed severity and symptoms/patient-reported severity	**Use results from single trial that addressed this comparison, qualitative expression** We use a qualitative expression for synthesis for reasons stated in the above section 'General note about the overall evidence base for this evidence report'	**There may be no clear difference between azathioprine and methotrexate on the severity of eczema** Certainty for the outcome is Low (see 'Certainty' in the Evidence Review section for details)

Evidence Synthesis Results

A bolded synthesis statement is not relevant for this outcome. As stated in Scoping, the comparator of interest for scoped outcomes is placebo. This comparison is included only because it indirectly informs the evidence review for methotrexate vs. placebo (see corresponding section above) given the lack of placebo-controlled trials for methotrexate.

Dupilumab vs. placebo

Evidence Review

One systematic review of double-blind randomized controlled trials compared dupilumab (300 mg either once weekly or every other week) vs. placebo in 6 trials with 2,447 adults with moderate-to-severe atopic dermatitis (Wang 2018). Duration of treatment ranged from 4 to 52 weeks; 1 trial each had treatment durations of 4, 12, and 52 weeks, and 3 trials had duration of 16 weeks. Severity was reported on 4 different scales assessing disease severity, all of which showed consistent benefit of dupilumab vs. placebo; we include in the table below the results reported on EASI because it has been most extensively validated. Drucker 2020 was published after we completed Critical Appraisal and Evidence Synthesis for the evidence available to use at the time of our original searches. As noted in Critical Appraisal, Drucker 2020 does not impact Evidence Synthesis for dupilumab. We include below the direct (pairwise) results from Wang 2018.

Dupilumab vs. placebo on severity (Wang 2018)

Outcome	No. Studies	No. Patients		Standardized mean difference (95% CI)*	Certainty (downgrade)
		dupilumab	placebo		
EASI	6	1,481	1,634	-0.89 (95% CI -1.0 to -0.78)	Moderate (publication bias)[1]

*There was no clear evidence for heterogeneity of treatment effect for: (1) a regimen of 300 mg weekly vs. a regimen of 300 mg every 2 weeks or (2) the effect size of the 52-week trial vs. the trials of a shorter duration.

[1] All outcomes were downgraded for risk of publication bias because Wang 2018 note "7 potentially relevant RCTs which had been published as an abstract only were excluded owing to data unavailable". Review authors did not identify any (other) risk of bias. Although the EASI is clinician-assessed, we did not downgrade for indirectness (as we have elsewhere) given the consistent benefit for dupilumab vs. placebo shown across all scales measured, including patient-reported outcome measures like the DLQI (addressed in FAQ 3: Will my quality of life improve?), and one would not expect the DLQI to show benefit if the patient did not also experience benefit in patient-reported outcomes gauging disease severity.

Evidence Synthesis Process

Outcome	Approach taken and justification: measure of comparative effect	Results: measure of comparative effect
signs/clinician-assessed severity	**Meta-analysis already done, qualitative expression** We use a qualitative expression for synthesis for reasons stated in the above section 'General note about the overall evidence base for this evidence report'.	**Dupilumab may improve severity of eczema more than placebo** Certainty for short-term effectiveness is Moderate due to risk of publication bias. For long-term effectiveness, we also consider the findings to have Moderate certainty. Although only one trial assessed long-term effects, we did not assign an additional downgrade due to the estimate coming from a single trial (inability to assess consistency in effects) because our downgrade for concerns of publication bias already addresses the possibility that additional data could change this finding; accordingly, downgrading due to concerns for publication bias and concerns over the finding coming from a single trial would be unduly punitive.

Evidence Synthesis Results

Dupilumab may help how much of your body has eczema and how bad the eczema is (things like the amount of dryness, redness, scaling, cracking, and so on) within the first few months of use, and this may last for a year or more. (Moderate certainty; based on 1 systematic review with pairwise meta-analysis [Wang 2018] and 1 systematic review with network meta-analysis [Drucker 2020])

Systemic corticosteroids

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

We noted in Scoping that we would give a descriptive summary of the use of systemic corticosteroids. We do that below.

Descriptive Summary Results

There is not much research on using steroids in eczema, but they can be used for a short time to get eczema under control quickly. Because of side effects with long-term use, they should not be used for long-term control.

(See FAQ 1 for references, especially the references to major guidelines)

FAQ 3: Will my quality of life improve?

Efficacy scales/scores used in the literature

There are several scales/scores used in the available literature for this evidence report. To help readers understand these scales/scores better, we include below a brief description of scales/scores that appear in this FAQ.

- Dermatology Life Quality Index (DLQI)
    - This score/scale assess the extent to which atopic dermatitis and/or treatment has affected the patient over the previous week. This is assessed via 10 questions scored from 0 ('not at all' or 'not relevant') to 3 ('very much'). The questions assess itching, soreness, stinging, and pain; embarrassment and self-consciousness; interference with shopping or tending to the home or garden; influence on choice of clothes to wear; impact on social or leisure activity; impact on sport/recreation; impact on working or studying (a 3 here is specifically noted to be actual prevention of work or studying rather than posing a certain degree of problem with respect to work or studying); impact on relationships with partner, close friends, and relatives; impact on sex life; and the degree to which treatment is a problem, including such things as causing messes or taking up time. The final score is a simple sum and thus ranges from 0 to 30, with higher scores being worse.
- Eczema Disability Index (EDI)
    - This score/scale assesses the extent to which atopic dermatitis and/or treatment has affected the patient over the previous month. This is assessed via 15 questions scored from 1 ('not at all') to 7 ('very much') within 5 categories: daily activity (5 questions), work/school (3 questions), personal relationships (2 questions), leisure (4 questions), and treatment (1 question). The score is a simple sum and thus ranges from 15 to 105, with higher scores being worse.
- UK Sickness Impact Profile (UKSIP)
    - This score/scale is the UK version of the American Sickness Impact profile. It is comprised of 136 questions that are grouped into 12 areas of function: body care and movement, mobility, and ambulation (subgrouped as being pertinent to the 'physical dimension', with 45 questions); emotional behavior, social interaction, alertness behavior, and communication (subgrouped as being pertinent to the 'psychosocial dimension', with 48 questions); and sleep and rest, home management, work, recreation/pastime, and eating (each considered an independent subgroup, with 7, 10, 9, 8, and 9 questions, respectively). It also assesses 'overall health' on a scale ranging from 'very good' to 'very poor'. Final scores are calculated based on weighted sums that are converted into a percentage.

The UKSIP is not disease-specific, so we do not afford it much consideration in this report (we include it for completeness). Considering the disease-specific quality of life scales DLQI and EDI, they are different in certain ways, but they generally capture the same basic concepts. Accordingly, and to help patients better understand what the bolded synthesis statements below mean, we have standardized to say "[Agent] [may/may not] help improve your quality of life (things like how much your eczema gets in the way of daily activities, how much you worry about what others think about your eczema, how much you find treatment to be a problem, and so on) …". Being extremely specific about exact score/scale components does not seem helpful and could instead lead to confusion and spurious inferences.

Cyclosporine vs. placebo

Evidence Review and Synthesis Process

As described in FAQ 2 (Will my skin and symptoms improve?), we identified 4 relevant trials for this comparison and only one reported quality of life (Salek 1993 [n = 33], a follow-up publication of Sowden 1991). None of the systematic reviews directly reported between-group differences in quality of life for Salek 1993, but we incorporated these results into our summary of Hoare 2000. Salek 1993 was poorly reported and focused on within-group changes rather than between-group differences. However, they do report means ± standard errors for two quality of life scales in the placebo and cyclosporine groups at the 8-week point:

- UK Sickness Impact Profile (UKSIP; 0-100 scale): 5.6±1.8 vs. 4.8±1.9
- Eczema Disability Index (EDI; 15-105 scale): 29.1±4.8 vs. 16.1±5.3
    - if calculating a mean difference (and accounting for the fact that the authors report standard errors, not standard deviations), one finds a mean difference of 13 (95% CI -1.6 to 27.6)

The results for the UKSIP are comparable between groups, while the results for the EDI suggest a possibly-meaningful difference, albeit limited by imprecision (among other concerns pertaining to certainty).

We consider these results to have Very low certainty, with downgrades for risk of bias (high loss to follow-up, no intention-to-treat analysis), imprecision (small trial), and inconsistency (inability to assess consistency given only trial for this comparison to report on quality of life and having some signal of internal inconsistency as well). Although the EDI is more disease-specific (the UKSIP is more generic), it is not among the validated measurements we mentioned in Scoping. However, one may speculate that the EDI would be better able to detect a difference in quality of life if one existed (compared to a generic quality of life instrument), and indeed this is a central idea behind developing disease-specific quality of life instruments. This – coupled with the observations for FAQ 2 (Will my skin and symptoms improve?) for this comparison – might lead one to tentatively conclude that cyclosporine may have a beneficial effect on quality of life compared to placebo. However, signals of benefit for disease severity should not be assumed to have full transitivity for inferences about quality of life, as quality of life encompasses many other facets, such as the possible impact of side effects or the burden of treatment *per se*. Additionally, we note the results for EDI suffer from imprecision (as evidenced by the 95% CI).

Drucker 2020 was published after we completed Evidence Synthesis for the evidence available to us at the time of our original search, and although they do not report direct results for a between-group difference from Salek 1993, they do include network estimates for cyclosporine vs. placebo measured on the SMD scale. They stratify their analysis according to higher- (>3 mg/kg/d and ≤5 mg/kg/d and 300 mg/d) and lower-dose (≤3 mg/kg/d and 150 mg/d) cyclosporine. The higher-dose analysis corresponds more to recommended dosing for atopic dermatitis (Wollenberg 2018). The results are less clear for lower-dose cyclosporine, but both suffer from imprecision; even the higher-dose analysis has a 95% CrI upper bound of 0. We consider these results consistent with those directly observed in Salek 1993, and for reasons stated above (see 'General note about the overall evidence base for this evidence report') and in Critical Appraisal, we are concerned about placing emphasis on the network estimates from Drucker 2020, perhaps especially for the network estimates on the SMD scale.

Considering the above, we believe it is reasonable to infer that cyclosporine might improve a person's quality of life, but that this will likely depend on the degree to which a person experiences side effects. Setting aside considerations of evidence, this statement is broadly true in general, namely that the degree to which a person's quality of life might be impacted by a given intervention is likely a function of the degree to which the intervention has its intended beneficial effect and the degree to which the intervention yields harm (with "harm" here including both adverse effects and things like medication burden and cost regardless of whether the medication causes adverse effects). For simplicity in evidence synthesis statements, we call these harms "side effects".

We use a qualitative expression for synthesis for reasons stated in the above section 'General note about the overall evidence base for this evidence report', and we include phrasing about our uncertainty in the evidence synthesis statement.

Evidence Synthesis Results

Cyclosporine may help improve your quality of life (things like how much your eczema gets in the way of daily activities, how much you worry about what others think about your eczema, how much you find treatment to be a problem, and so on), but the effect may be small, and the evidence is uncertain. (Very low certainty; based on 1 randomized trial [Salek 1993] and indirect reasoning from the evidence for FAQ 2 [Will my skin and symptoms improve?]). **How your quality of life might change while taking cyclosporine probably depends a lot on how well cyclosporine works for you and if you have side effects from cyclosporine.**

Cyclosporine vs. methotrexate

Evidence Review

We identified 1 randomized trial which addressed this comparison (Goujon 2018). It compared cyclosporine vs. methotrexate for 24 weeks in 97 patients with moderate-to-severe atopic dermatitis. Outcomes were measured at weeks 4, 8, 12, 16, 20, and 24, and we extracted quality of life outcome data from week 16 and week 24 as our short-term and long-term outcomes respectively (per our criteria in scoping). The results are reported in table below.

Effects of methotrexate vs. cyclosporine on quality of life

Outcome	Week	Methotrexate		Cyclosporine		Absolute risk difference (90% CI)
		No. Evaluated	% of patients achieving outcome	No. Evaluated	% of patients achieving outcome	
DLQI (post-treatment score of ≤ 5)	16	28	60.7%	34	77.1%	-16% (-36% to 3%)
	24	23	65.2%	31	80.6%	-15% (-35% to 5%)

As noted in Critical Appraisal, we are concerned with how the authors' attempted to analyze non-inferiority in this trial. They conducted responder analyses, defining a 'responder' as someone who achieved a DLQI of ≤5 after treatment. However, we have concerns with this approach, as detailed in Critical Appraisal. Additionally, they calculated 90% CIs for their responder analyses (given their desire to estimate a one-sided CI bound at $\alpha = 0.05$), thus impeding analysis outside of their specific intent for non-inferiority. Accordingly, we also considered the underlying continuous data:

Effects of methotrexate vs. cyclosporine on signs and quality of life, continuous data

Outcome	Methotrexate (mean±SD)	Cyclosporine (mean±SD)
DLQI		
16 weeks	5.1±3.5	4.3±5.4
24 weeks	5.0±4.6	3.3±4.4

As one can see from the continuous data, the groups are comparable at both time points

Certainty

Very low due to risk of bias (no patient blinding and high/differential dropouts), imprecision (small trial), and inconsistency (only a single trial, thus precluding assessment of consistency).

Evidence Synthesis Process

Outcome	Approach taken and justification: measure of comparative effect	Results: measure of comparative effect
quality of life	**Use results from single trial that addressed this comparison, qualitative expression** Because of our concerns about the responder analyses conducted by the authors, we rely on the underlying continuous data to make inferences. We use a qualitative expression for synthesis for reasons stated in the section 'General note about the overall evidence base for this evidence report'.	
16 weeks		**There may be no clear difference between cyclosporine and methotrexate on quality of life** Certainty for the outcome is Very low (see 'Certainty' in the Evidence Review section for details)
24 weeks		**There may be no clear difference between cyclosporine and methotrexate on quality of life** Certainty for the outcome is Very low (see 'Certainty' in the Evidence Review section for details)

Evidence Synthesis Results

A bolded synthesis statement is not relevant for this outcome. As stated in Scoping, the comparator of interest for scoped outcomes is placebo. This comparison is included only because it indirectly informs the evidence review for methotrexate vs. placebo given the lack of placebo-controlled trials for methotrexate.

Methotrexate vs. placebo

Evidence Review and Synthesis Process

We did not identify any trials making this comparison. Accordingly, our evidence review and synthesis process relies heavily on indirect reasoning, thus lowering the certainty of evidence that is already Very low certainty.

Considering that there is Very low certainty evidence that cyclosporine may be better than placebo and Very low certainty evidence that there may be no clear difference between methotrexate and cyclosporine (as addressed in the corresponding sections above), one might indirectly infer (assuming transitivity) that there is Very low certainty evidence that methotrexate may be better than placebo. The same inferential process applies to the evidence base for azathioprine vs. placebo and methotrexate vs. azathioprine (as addressed in the corresponding sections below). Drucker 2020 only provides an estimate for quality of life on the SMD scale for methotrexate vs. placebo, with the estimate suffering from considerable imprecision (but compatible with possibly-important improvement or worsening of quality of life). Due to reasons stated above (see 'General note about the overall evidence base for this evidence report') and in Critical Appraisal, we are concerned about relying too heavily on the network estimate, perhaps especially on the SMD scale. However, the alternative here still relies on very indirect reasoning with evidence of Very low certainty. Accordingly, it is not clear which approach is better. Irrespective of that difficulty, however, we consider it reasonable to conclude with Very low certainty that – similar to cyclosporine – the impact methotrexate has on quality of life may depend heavily on the degree to which it has its intended beneficial effect and the degree to which it yields harm (again, "harm" here includes both adverse effects and things like medication burden and cost regardless of whether the medication causes adverse effects, but for simplicity in evidence synthesis statements, we call these harms "side effects"). We use a qualitative expression for synthesis for reasons stated in the above section 'General note about the overall evidence base for this evidence report', and we include uncertainty as part of the synthesized result.

Evidence Synthesis Results

Methotrexate may help improve your quality of life (things like how much your eczema gets in the way of daily activities, how much you worry about what others think about your eczema, how much you find treatment to be a problem, and so on), but the effect may be small, and the evidence is uncertain. (Very low certainty; based on indirect reasoning from the evidence for cyclosporine vs. placebo and methotrexate vs. cyclosporine [see corresponding sections], indirect reasoning from the evidence for azathioprine vs. placebo and methotrexate vs. azathioprine [see corresponding sections], and indirect estimates for methotrexate vs. placebo from 1 systematic review [Drucker 2020]). **How your quality of life might change while taking methotrexate probably depends a lot on how well methotrexate works for you and if you have side effects from methotrexate.**

Cyclosporine vs. mycophenolate

Evidence Review

The single RCT reporting on this comparison (Haeck 2011, n = 50) was identified via Roekevisch 2014. Although Haeck 2011 nominally discuss the categorization of patients in three DLQI categories, they "did not formally analyze differences" and data are not reported in a readily-interpretable manner. We also consider their decision to trichotomize the results into three categories (rather than report the results in their native form) questionable. Accordingly, we did not appraise and will not synthesize these results. We instead rely on indirect reasoning from the data on the SOCRAD scale (see FAQ 2: Will my skin and symptoms improve?), namely that there may be no difference between these two therapies.

Evidence Synthesis Process

As above-noted, given the extremely limited information for this outcome for this comparison, we rely on indirect reasoning from the data on the SCORAD scale (see FAQ 2: Will my skin and symptoms improve?), which suggest there may be no difference between these two therapies (albeit with Very low certainty, further reduced here due to further indirectness).

Evidence Synthesis Results

A bolded synthesis statement is not relevant for this outcome. As stated in Scoping, the comparator of interest for scoped outcomes is placebo. This comparison is included only because it indirectly informs the evidence review for mycophenolate vs. placebo given the lack of placebo-controlled trials for mycophenolate.

Mycophenolate vs. placebo

Evidence Review and Synthesis Process

We did not identify any trials making this comparison. Accordingly, our evidence review and synthesis process relies heavily on indirect reasoning, thus lowering the certainty of evidence that is already Very low certainty.

Considering that there is Very low certainty evidence that cyclosporine may be better than placebo and Very low certainty evidence that there may be no clear difference between mycophenolate and cyclosporine (as addressed in the corresponding sections above), one might indirectly infer (assuming transitivity) that there is Very low certainty evidence that mycophenolate may be better than placebo. Drucker 2020 does not include mycophenolate in its considerations, as the only-available trial (Haeck 2011) did not meet its inclusion criteria (it had a run-in period where all participants received cyclosporine). Akin to our phrasing for other agents, we include uncertainty as part of the synthesized result. We use a qualitative expression for synthesis for reasons stated in the above section 'General note about the overall evidence base for this evidence report'. We adopt the same general structure for expressing quality of life impact as for cyclosporine and methotrexate (see corresponding sections above for these agents vs. placebo).

Evidence Synthesis Results

Mycophenolate may help improve your quality of life (things like how much your eczema gets in the way of daily activities, how much you worry about what others think about your eczema, how much you find treatment to be a problem, and so on), but the effect may be small, and the evidence is uncertain. (Very low certainty; based on indirect reasoning from the evidence for cyclosporine vs. placebo and 1 randomized trial of mycophenolate vs. cyclosporine [Haeck 2011]). **How your quality of life might change while taking mycophenolate probably depends a lot on how well mycophenolate works for you and if you have side effects from mycophenolate.**

Azathioprine vs. placebo

Evidence Review

Schram 2011, which was an SR on azathioprine for dermatologic conditions, included detailed information on methods and results for severity outcome for the 2 placebo-controlled trials of azathioprine for severe atopic dermatitis (Berth-Jones 2002, Meggitt 2006) but it did not report on quality of life. We therefore consulted the full text of each of these two trials and found that Berth-Jones 2002 did not report quality of life but Meggitt 2006 did. We include a table below summarizing the characteristics and quality of life outcome results of Meggitt 2006. Because the risk of bias of Meggitt 2006 had already been extracted from Schram 2011, we have included those assessments below.

Characteristics and results of placebo-controlled randomized trial of azathioprine in adults with atopic dermatitis reporting on quality of life

Study	Number of patients	Design	Efficacy	Withdrawals
Meggitt 2006	61	parallel, dosed according to thiopurine methyltransferase (TPMT) activity	mean difference in change between groups on DLQI quality of life scale (range from 0 to 30) was 3.5 (95% CI 0.3 to 6.7)	6/41 in azathioprine group and 1/20 in placebo group

Risk of bias domains for Meggitt 2006 extracted from Schram 2011

Study	Adequate randomization	Adequate allocation concealment	Adequate masking	Adequate completeness of data reported	Free of selective reporting?	Free of other bias?
Meggitt 2006	Yes	yes	yes	yes	yes	yes

Drucker 2020 was published after we completed Evidence Synthesis for the evidence available to us at the time of our original search, but Drucker 2020 ultimately did not add to the above evidence. It reports a network estimate for "TPMT adjusted" azathioprine vs. placebo (this is what Meggitt 2006 did, as above noted) that is highly consistent with the above direct estimate (albeit more imprecise). We favor using the evidence directly from Meggitt 2006.

Certainty

Very low, with downgrades for risk of bias (unequal dropouts), imprecision (small trial, wide CI), and inconsistency (single trial precludes assessment of consistency in effect)

Evidence Synthesis Process

Considering the above, we believe it is reasonable to infer that azathioprine might improve a person's quality of life, but that this will likely depend on the degree to which a person experiences side effects. As noted above (see section on cyclosporine vs. placebo), if one sets aside considerations of evidence, this statement is broadly true in general, namely that the degree to which a person's quality of life might be impacted by a given intervention is likely a function of the degree to which the intervention has its intended beneficial effect and the degree to which the intervention yields harm (with "harm" here including both adverse effects and things like medication burden and cost regardless of whether the medication causes adverse effects). For simplicity in evidence synthesis statements, we call these harms "side effects". We use a qualitative expression for synthesis for reasons stated in the above section 'General note about the overall evidence base for this evidence report', and we include phrasing about our uncertainty in the evidence synthesis statement.

Evidence Synthesis Results

Azathioprine may help improve your quality of life (things like how much your eczema gets in the way of daily activities, how much you worry about what others think about your eczema, how much you find treatment to be a problem, and so on), but the effect may be small, and the evidence is uncertain. (Very low certainty; based on 1 randomized trial [Meggitt 2006]). **How your quality of life might change while taking azathioprine probably depends a lot on how well azathioprine works for you and if you have side effects from azathioprine.**

Azathioprine vs. methotrexate

Evidence Review

Through Roekevisch 2014, we identified 1 randomized trial which addressed this comparison (Schram 2011). This trial compared azathioprine vs. methotrexate for 12 weeks in 42 patients with severe atopic dermatitis and reported on severity and quality of life. Roekevisch 2014 reported "AZA and MTX were found to be equally efficacious" and reported similar percent improvements in the two groups for the quality of life measure (Skindex) but did not report between-group comparisons. The full text of Schram 2011 was obtained and means and SDs were extracted from each group to calculate the mean difference between groups: 3.7 (95% CI -3.6 to 11.0).

Certainty

Because this was a single, small trial with incomplete blinding that showed no clear difference between groups, we rated it as having Very low certainty with downgrades for risk of bias, imprecision, and inconsistency (single trial precludes evaluation of consistency in effect).

Evidence Synthesis Process

Outcome	Approach taken and justification: measure of comparative effect	Results: measure of comparative effect
quality of life	**Use results from single trial that addressed this comparison, qualitative expression** We use a qualitative expression for synthesis for reasons stated in the above section 'General note about the overall evidence base for this evidence report'	**There may be no clear difference between azathioprine and methotrexate on quality of life** Certainty for the outcome is Very low (see 'Certainty' in the Evidence Review section for details)

Evidence Synthesis Results

A bolded synthesis statement is not relevant for this outcome. As stated in Scoping, the comparator of interest for scoped outcomes is placebo. This comparison is included only because it indirectly informs the evidence review for methotrexate vs. placebo given the lack of placebo-controlled trials for methotrexate.

Dupilumab vs. placebo

Evidence Review

One systematic review of double-blind randomized controlled trials compared dupilumab (300 mg once weekly and every 2 weeks) vs. placebo in 6 trials with 2,447 adults with moderate-to-severe atopic dermatitis (Wang 2018). Duration of treatment ranged from 4 to 52 weeks; 1 trial each had treatment durations of 4, 12, and 52 weeks, and 3 trials had duration of 16 weeks. Quality of life was reported using the DLQI. The results are reported in the table below. As noted in Critical Appraisal, Drucker 2020 does not impact Evidence Synthesis for dupilumab. We include below the direct (pairwise) results from Wang 2018.

Dupilumab vs. placebo on quality of life (Wang 2018)

Outcome	No. Studies	No. Patients		Standardized mean difference (95% CI)*	Certainty (downgrade)
		dupilumab	placebo		
DLQI	5	1,405	1,570	-0.78 (95% CI -0.89 to -0.66)	Moderate (publication bias)[1]

*There was no clear evidence for heterogeneity of treatment effect for: (1) a regimen of 300 mg weekly vs. a regimen of 300 mg every 2 weeks or (2) the effect size of the 52-week trial vs. the trials of a shorter duration.

[1] All outcomes were downgraded for risk of publication bias because SR authors noted that "7 potentially relevant RCTs which had been published as an abstract only were excluded owing to data unavailable". Review authors did not identify any (other) risk of bias downgrades (risk of bias summary figure shows low risk of bias for all included trials for all risk of bias domains).

Evidence Synthesis Process

Outcome	Approach taken and justification: measure of comparative effect	Results: measure of comparative effect
quality of life	**Meta-analysis already done, qualitative expression** We use a qualitative expression for synthesis for reasons stated in the section 'General note about the overall evidence base for this evidence report'.	**dupilumab may improve quality of life of eczema patients more than placebo** Certainty for the outcome is Moderate (see 'Certainty' in the Evidence Review section for details)

Because of the general truth that quality of life is likely a function of the degree to which the intervention has its intended beneficial effect and the degree to which the intervention yields harms/drawbacks, we include that phrasing for dupilumab as well (this helps maintains parallelism in phrasing for comparative purposes). However, certainty for improvement in quality of life is also considerably higher for dupilumab than for any of the other agents, and we think this should be somehow reflected. Accordingly, we use different phrasing when discussing dupilumab than we do for the other agents considered in this report; specifically, we do not include direct mentioning of uncertainty in the synthesis statement (despite the presence of some degree of uncertainty, this seems substantially less than for the other agents), nor do we note that the effect may be small.

Evidence Synthesis Results

Dupilumab may help improve the quality of your life (things like how much your eczema gets in the way of daily activities, how much you worry about what others think about your eczema, how much you find treatment to be a problem, and so on). (Moderate certainty; based on 1 systematic review with pairwise meta-analysis [Wang 2018] and 1 systematic review with network meta-analysis [Drucker 2020]) **How your quality of life might change while taking dupilumab probably depends a lot on how well dupilumab works for you and if you have side effects from dupilumab.**

Systemic corticosteroids

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

We noted in Scoping that we would give a descriptive summary of the use of systemic corticosteroids. We do that below. In consideration of our descriptive summaries for FAQ 2 (Will my skin and symptoms improve?) and FAQ 4 (What are the risks or side effects?), we consider it reasonable to infer that the degree to which a person's quality of life might be impacted is a function of the degree to which systemic corticosteroids improve a person's atopic dermatitis and the degree to which the systemic corticosteroids cause adverse effects.

Descriptive Summary Results

Steroids might improve your quality of life by helping improve your eczema more quickly. But some people have side effects from steroids. How your quality of life might change while taking steroids probably depends a lot on how well the steroids work for you and if you have side effects from steroids.

(See FAQ 1 for references, especially the references to major guidelines; the statement above is based on consideration of the possibility of steroids helping with eczema control and the possibility for side effects, not based on actual language included in any of the references)

FAQ 4: What are the risks or side effects?

Evidence capturing serious adverse events or withdrawals due to adverse events was limited, so we ultimately rely heavily on descriptive summaries for this FAQ. However, we include below the comparative evidence that does exist, followed by the descriptive evidence that we use for our synthesis statements.

Comparative evidence

Evidence Review and Synthesis Process

For transparency and completeness, we include below a brief review of the adverse event data available in the different sources appraised for this evidence report. Unfortunately, data were very sparse. This is well in line with Drucker 2020, who also noted this rather directly: "Given low adverse event rates, robust, interpretable relative safety estimates, particularly among medications currently in use, are not possible. Many of the studies reported 0 events for 1 or more treatments, which generates results that cannot be estimated or results with high uncertainty, even in our analyses with more informative priors" (they used Bayesian methods for analysis). For example, in many cases the nature of the empirical evidence suggests no difference from placebo or even (at least nominally) lower rates of serious adverse events or withdrawal due to adverse events in the intervention group. We consider such findings implausible and more likely reflective of the nature of an evidence base largely dominated by small, short studies and the larger and well-known problem of underreporting of harms in much of the medical literature. Accordingly, although we provide below a brief review of this evidence, our synthesis statements are wholly comprised of descriptive summaries.

- ***Cyclosporine***
  - ***vs. placebo***

    The Roekevisch 2014 SR reported both adverse events and withdrawals due to adverse events for this comparison. The Schmitt 2007B SR also reported both outcomes, and the Schmitt 2007A SR reported only on the adverse events leading to discontinuation outcome. We extracted the outcome data from Roekevisch 2014 because it is the most current of the 3 SRs, reported both outcomes, and reported the outcome for all 4 randomized trials comparing cyclosporine vs. placebo. For serious adverse events, Roekevisch 2014 reported rates of 0% in 2 trials (Munro 1994, Wahlgren 1990) and rates in the cyclosporine group that were lower than (Sowden 1991/Salek 1993) or equal to (van Joost 1994) the placebo group for the other 2 trials ('serious adverse events' was not defined by Roekevisch 2014, and Roekevisch 2014 may thus have relied on the original trials' definition of such). Two of the placebo-controlled trials reported on withdrawals because of adverse events; both reported rates of 0% (Salek 1993, Wahlgren 1990).

  - ***vs. methotrexate***

    One trial we summarized addressed this comparison (Goujon 2018, n = 97). It reported serious adverse events in 0 patients in methotrexate group and in 1 patient in cyclosporine group, and treatment-related adverse events leading to discontinuation in 2 patients in methotrexate group and in 1 patient in cyclosporine group.

- ***vs. mycophenolate***

  Roekevisch 2014 included 1 trial that addressed this comparison (Haeck 2011, n = 50). It reported for this trial a rate of 0% for serious adverse events and a rate of 0.3% for both the mycophenolate and cyclosporine groups for withdrawals because of adverse events.

- ***Azathioprine***
  - ***vs. placebo***

    Schram 2011, an SR on azathioprine for dermatologic conditions, included 2 placebo-controlled trials of azathioprine in patients with severe atopic dermatitis and reported that both trials had zero serious adverse events (Berth-Jones 2002, Meggitt 2006). Withdrawals due to adverse events were not reported (except for in the azathioprine arm only of the Berth-Jones 2002 trial in which 4 out of 37 patients were reported to have withdrawn for this reason).

  - ***vs. methotrexate***

    Roekevisch 2014 included 1 trial that addressed this comparison (Schram 2011, n = 42). It reported a rate of 0% for serious adverse events and a rate of 0.2% (azathioprine) vs. 0.4% (methotrexate) for withdrawals because of adverse events.

- ***Dupilumab***
  - ***vs. placebo***

    One systematic review compared dupilumab vs. placebo in 6 randomized trials, but it did not report either severe adverse events or adverse events leading to discontinuation (Wang 2018)

Descriptive evidence

Because the above-noted evidence was not sufficient to provide meaningful insight into the risks and side effects of the options scoped for this evidence report, we present below descriptive summaries based on an examination of drug monographs and major guidelines, including the helpful guideline from the American Academy of Dermatology (Sidbury 2014), which is also referenced by the 2017 International Eczema Council expert panel statement (Simpson 2017). The side effects and risks below are not intended to be an exhaustive account of all possible side effects or risks (which would not be feasible for the scope of this evidence report); rather, the descriptive content below reflects a consideration of adverse events that are common or serious and consistently reported across different sources while also attempting to account for the fact that adverse events may be specific to or influenced by the indication/population. Accordingly, although we are keen for patients to be well-informed about the possible harms of the interventions they are considering (in addition to the possible benefits), we did not report certain side effects or risks in some cases because of the context in which they seemed to occur. For instance, the drug monograph for cyclosporine lists seizure as a possible adverse event. However, this risk was observed in clinical trials where cyclosporine was being used as an anti-rejection agent post-transplant. It is thus very unclear how/if this risk applies to its use in atopic dermatitis. Additionally, seizure was not included among the common or serious adverse events with cyclosporine when consulting references specific to atopic dermatitis. Putting these observations together, we did not include seizure as a possible risk with cyclosporine for this evidence report. It is worth explicitly noting this example – and the broader concept it brings to light – because for many of the scoped options for this evidence report, the use is off-label, with the agents being labeled for use in another condition (and/or other off-label uses). As noted above, depending on the context in which these agents are used, important variables could be different that could impact adverse events, and we attempted to take this into consideration when preparing descriptive summaries below.

Cyclosporine

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

Side effects may include:

- Headache
- Tremor
- Paresthesia
- Hypertrichosis
- Gingival hyperplasia
- Nausea, vomiting, diarrhea
- Flu-like symptoms (e.g., myalgia, fatigue)
- Increased blood pressure
- Increased triglycerides

Risks may include:

- Nephrotoxic effects with structural damage and functional impairment
- Electrolyte disturbances
- Infection (including from the JC virus leading to progressive multifocal leukoencephalopathy)
- Malignancy (lymphoproliferative or dermatologic)

Descriptive Summary Results

Side effects may include:

- **Headache**
- **Shaking ("tremor")**
- **Feeling like certain body parts are numb, tingly, or have a "pins and needles" feeling**
- **Growing hair or more hair in places where you usually do not have hair or a lot of hair**
- **Your gums getting bigger and more sensitive (they may bleed more easily)**
- **Nausea, vomiting, diarrhea**
- **Flu-like symptoms**
- **Increased blood pressure**
- **Increased triglycerides**

Risks may include:

- **Damage to the kidneys**
- **Problems with things like sodium and potassium in your blood**
- **Infection, including serious infection**
- **Skin cancer or blood cancer**

The risks can be kept as low as possible by the tests you will have while taking this medication (see "What does the treatment involve?").

Azathioprine

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

Side effects may include:

- Nausea, vomiting, diarrhea

Risks may include:

- Bone marrow suppression, cytopenias
- Hepatitis
- Pancreatitis
- Infection (including from the JC virus leading to progressive multifocal leukoencephalopathy)
- Malignancy (lymphoproliferative or dermatologic)

Different hypersensitivity reactions have also been described, ranging from mild (e.g., arthralgia, myalgia, back pain, fever, chills, nausea, vomiting, diarrhea, rash, fatigue) to more serious (associated with hypotension – which may be severe, pancreatitis, and/or vasculitis)

Descriptive Summary Results

Side effects may include:

- **Nausea, vomiting, diarrhea**

Risks may include:

- **Your bone marrow not working like it should, which can lead to not having enough red blood cells, white blood cells, or plate lets**
- **Hepatitis**
- **Pancreatitis**
- **Infection, including serious infection**
- **Skin cancer or blood cancer**

Some people who take azathioprine also have an allergic reaction to it. This can be mild or serious. Mild cases have symptoms like join and muscle pain, fever, chills, nausea, and vomiting. More serious cases can have low blood pressure that is dangerous, pancreatitis, or inflammation in the blood vessels.

The risks can be kept as low as possible by the tests you will have while taking this medication (see "What does the treatmen t involve?").

Mycophenolate mofetil

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

Side effects may include:

- Nausea, vomiting, diarrhea, abdominal cramps
- Dysuria and/or urinary urgency and frequency
- Fever, headache, and myalgia
- Difficulty sleeping
- Peripheral edema
- Increased blood pressure
- Increased cholesterol

Risks may include:

- Bone marrow suppression, cytopenias
- Electrolyte disturbances
- Pancreatitis
- Infection (including from the JC virus leading to progressive multifocal leukoencephalopathy)
- Malignancy (lymphoproliferative or dermatologic)

Descriptive Summary Results

Side effects may include:

- **Nausea, vomiting, diarrhea, stomach cramps**
- **Pain when you urinate, feeling like you need to urinate often or suddenly**
- **Flu-like symptoms**
- **Difficulty sleeping**
- **Fluid buildup in your feet, ankles, or legs**
- **Increased blood pressure**
- **Increased cholesterol**

Risks may include:

- **Your bone marrow not working like it should, which can lead to not having enough red blood cells, white blood cells, or platelets**
- **Problems with things like sodium and potassium in your blood**
- **Pancreatitis**
- **Infection, including serious infection**
- **Skin cancer or blood cancer**

The risks can be kept as low as possible by the tests you will have while taking this medication (see "What does the treatment involve?").

Methotrexate

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

Side effects may include:

- Nausea, vomiting, diarrhea
- Ulcerative stomatitis
- Malaise, fatigue, chills, and/or fever
- Dizziness
- Photosensitivity
- Burning sensation on the skin
- Alopecia
- Abnormal liver function tests

Risks may include:

- Bone marrow suppression, cytopenias
- Hepatotoxicity
- Interstitial pneumonitis, pulmonary fibrosis
- Peptic ulcer disease and bleeding
- Infection (including from the JC virus leading to progressive multifocal leukoencephalopathy)
- Malignancy (lymphoproliferative or dermatologic)

Descriptive Summary Results

Side effects may include:

- **Nausea, vomiting, diarrhea, stomach cramps**
- **Painful ulcers in your mouth**
- **Flu-like symptoms**
- **Dizziness**
- **Your skin being sensitive to light**
- **Your skin feeling burned**
- **Hair loss**
- **Liver test numbers being too high or too low**

Risks may include:

- **Your bone marrow not working like it should, which can lead to not having enough red blood cells, white blood cells, or plate lets**
- **Problems with the liver**
- **Inflammation and scarring in your lungs**
- **An ulcer in your stomach or intestines, which may bleed**
- **Infection, including serious infection**
- **Skin cancer or blood cancer**

The risks can be kept as low as possible by the tests you will have while taking this medication (see "What does the treatment involve?").

Dupilumab

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

Side effects may include:

- Injection site reactions
- Conjunctivitis, blepharitis, keratitis, xerophthalmia, ocular pruritus
- Pain in throat and/or mouth
- Headaches
- Infection (mainly herpes simplex infections

Risks may include:
We note drug monographs for dupilumab make variable note of a possibility for arterial thromboembolism/cardiovascular events (hereafter CV events). Of note, based on data available from the FDA (FDA 2019), this comes from the trial evidence for dupilumab in 3 different conditions: asthma, atopic dermatitis, and chronic rhinosinusitis with nasal polyposis (CRSNP).

A 1-year trial randomized patients with asthma to receive 200 mg dupilumab (n = 631), 300 mg dupilumab (n = 633), or matching placebo (n = 638). CV events occurred in 1/631 (0.2%), 4/633 (0.6%), and 2/638 (0.3%), respectively. Neither group was clearly different from placebo. though power here is obviously very limited.

A 1-year trial randomized patients with atopic dermatitis to receive dupilumab 300 mg every other week, dupilumab 300 mg every week, or placebo, with all groups receiving topical corticosteroids. CV events occurred in 0.9%, 0.0%, and 0.3%, respectively. The pattern of these results raises questions about whether this is "signal" or "noise". For instance, the risk is nominally *higher* in the placebo group versus the dupilumab 300 mg every week group. Additionally, the rate is nominally *higher* in the dupilumab 300 mg every other week group vs. the dupilumab 300 mg every week group, but this too is counterintuitive, because there does not seem to be any reason to believe that a *lower* exposure to dupilumab (300 mg every other week) would result in a *higher* risk of CV events than a *higher* exposure to dupilumab (300 mg every week) unless dupilumab had a protective effect on CV events, but the overall results from this trial do not suggest this, either (if there were some dose-response protective effect, one would expect the *highest* risk to occur in the placebo group, followed by the dupilumab 300 mg every other week group, and then the dupilumab 300 mg weekly group). However, one must be very careful about interpreting these data in general given the aforementioned risks for this trial are based on a total of 2 events (1 in the dupilumab 300 mg every other week group and 1 in the placebo group).

A 24-week trial randomized patients with CRSNP to receive dupilumab 300 mg every other week or placebo. CV events were reported in 1 (0.7%) in the dupilumab group and 0 (0.0%) in the placebo group. These risks cannot be meaningfully distinguished from each other due to the low power of this trial (n = 143 for dupilumab and 133 for placebo). In another 24-week trial in patients with CRSNP (total n = 448), no CV events were reported.

Considering all of this, we do not include CV events among the possible risks with dupilumab.

Descriptive Summary Results

Side effects may include:

- **Injection site reactions**
- **Different symptoms or problems with the eyes or eyelids, such as pain, itchiness, redness, dryness, tearing, feeling like something is in your eye, sensitivity to light, and decreased or blurry vision**
- **Pain in throat or mouth**

Risks may include:

- **Infection, mostly herpes simplex infections**

Systemic corticosteroids

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

As systemic corticosteroids are only considered appropriate for short-term use in atopic dermatitis, we limit our consideration of potential adverse effects to short-term use. Again, as stated elsewhere in this Evidence Report, the avoidance of long-term use of systemic corticosteroids is due to their limited evidence base for efficacy and well-known adverse event profile with long-term use.

Side effects with short-term use may include:

- hyperglycemia or impaired glucose tolerance
- sodium and water retention and potassium loss
- immunosuppression, especially if a large dose is used
- behavioral effects such as euphoria, insomnia, labile mood, depression, anxiety, and psychosis

In general, corticosteroids are often avoided in patients who have recently had a myocardial infarction due to a possible association with free-wall rupture of the left ventricle, although causality is not clear.

Descriptive Summary Results

Side effects may include:

- **increased blood sugar**
- **your body holding on to water**
- **your immune system not being as strong as it usually is**
- **feeling happier, sadder, angrier, more agitated, more energetic, or more anxious than usual**
- **difficulty sleeping**

Risks with short-term use are usually low as long as people do not have other health issues that might put them at risk. However, some people may have problems with things like sodium and potassium in the blood. Some people may have a bad reaction to the steroids. These people may have problems thinking, make poor choices, see or hear things that are not there, or believe things that are not true.

(DynaMed 2018-2020, FDA 2019, Gooderham 2017, Ou 2018, Sidbury 2014, Vestergaard 2020, Wollenberg 2016, Wollenberg 2018)

FAQ 5: What if I am pregnant or want to get pregnant?

As described in Scoping, our considerations here come from the dedicated position statement from the European Task Force on Atopic Dermatitis (ETFAD) on the treatment of atopic dermatitis in women and men who wish to conceive or are pregnant or breastfeeding (Vestergaard 2019).

Cyclosporine

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

Before and during attempts to conceive, the ETFAD do not recommend any restrictions on the use of cyclosporine for women or men. For women who are pregnant or breastfeeding, the ETFAD suggests cyclosporine may be used under "strict indications", and based on the context of their reporting, it appears these "strict indications" refer to cases where topical treatment and UV-based therapy have proven insufficient, there "is a clear need for better long-term disease control", and "all restrictions for non-pregnant females are considered". They also note the FDA labeling for this medication states cyclosporine "should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the foetus", but that cyclosporine is considered the first-line choice for long-term control while a woman is pregnant if she meets these "strict indications".

Descriptive Summary Results

Women and men can take cyclosporine before trying to conceive a child. Women who are pregnant or breastfeeding can use cyclosporine if creams, ointments, and similar treatments have not helped enough. Pregnant or breastfeeding women should let their clinicians know about all medicines they are taking or are thinking about taking.

Azathioprine

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

Before and during attempts to conceive, the ETFAD do not recommend any restrictions on the use of azathioprine for women or men. The ETFAD suggest azathioprine may be continued during pregnancy in women already receiving azathioprine under "strict indications", and based on the context of their reporting, it appears these "strict indications" are akin to those delineated for cyclosporine *plus* the inability to use cyclosporine for some reason. If a safer alternative exists, they recommend that "AZA [azathioprine] use during pregnancy should be avoided". They do not recommend *starting* azathioprine after conception, and they also note the FDA labeling for this medication states "Azathioprin [sic] (IMURAN) should not be given during pregnancy without careful weighing of risk versus benefit. Whenever possible, the use of Azathioprine (IMURAN) in pregnant patients should be avoided". If it is used, the ETFAD recommend a 50% reduction in dose. For breastfeeding mothers, ETAFD suggest azathioprine can be used, but that mothers should discard milk produced within 4 hours of taking azathioprine.

Descriptive Summary Results

Women and men can take azathioprine before trying to conceive a child. For pregnant women, cyclosporine is preferred to azathioprine. Breastfeeding women can use azathioprine, but they should not use any breastmilk they make within 4 hours of taking azathioprine. Pregnant or breastfeeding women should let their clinicians know about all medicines they are taking or are thinking about taking.

Mycophenolate mofetil

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

The ETFAD recommends stopping mycophenolate 3 months before trying to conceive for women and men. Mycophenolate is known to be teratogenic and is thus considered absolutely contraindicated in pregnancy. The ETFAD also note the FDA label states "women of childbearing potential must receive contraceptive counselling and use effective contraceptive while and for [sic] 3 months after stopping therapy". The ETFAD also recommend never using mycophenolate while breastfeeding.

Descriptive Summary Results

Women and men who want to conceive a child may need to stop mycophenolate for 3 months before trying to conceive. Women who are pregnant or breastfeeding should not use mycophenolate.

Methotrexate

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

The ETFAD recommends stopping methotrexate 6 months before trying to conceive for women and 3 months before trying to conceive for men. They also note there are discrepancies in recommendations. For example, the European Medicines Agency recommends women stop methotrexate "at least six months" before trying to conceive, the European League Against Rheumatism recommends stopping methotrexate 1 to 3 months prior to trying to conceive, and "labels in different countries" recommend stopping methotrexate between 1 month and 6 months prior to trying to conceive. Accordingly, the ETFAD also recommends that local/national guidelines on the matter take precedence over their guidance. Methotrexate is known to be teratogenic and is considered absolutely contraindicated in pregnancy and breastfeeding.

Descriptive Summary Results

Women who want to conceive a child may need to stop methotrexate for up to 6 months before trying to conceive. Men who want to conceive a child may need to stop methotrexate for up to 3 months before trying to conceive. Women who are pregnant or breastfeeding should not use methotrexate.

Dupilumab

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

The ETFAD suggest there is no evidence pointing to dupilumab having teratogenic potential. However, given the "ample experience" with cyclosporine, azathioprine, and systemic corticosteroids, they recommend attempting to use these agents prior to using dupilumab "until more experience is available". Their recommendation holds for pregnant and breastfeeding women. They do not make any recommendations for men. They also note the FDA label states "there are no available data on DUPIXENT [the brand name for dupilumab] use in pregnant women to inform any drug associated risk" and the European summary of product characteristics states "Dupixent should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus".

Descriptive Summary Results

There is not enough information yet to know about using dupilumab in women or men who want to conceive a child or in pregnant or breastfeeding women.

Systemic corticosteroids

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

For all relevant populations (women or men interested in trying to conceive, pregnant women, and breastfeeding women), the ETFAD suggests systemic corticosteroids can be used for short periods of time (akin to their use in atopic dermatitis in general). For pregnant women specifically, the ETFAD notes systemic corticosteroids might be used for 2 to 3 weeks, but the dose should not exceed 0.5 mg/kg/day and (in line with their use in general), they should be used as sparingly as possible.

Descriptive Summary Results

If needed, steroids can be used for a short period of time in women and men who want to conceive a child and in pregnant or breastfeeding women. Steroids should be used with the smallest dose and for the shortest length of time.

(Vestergaard 2019)

Evidence report for systemic treatment of patients with moderate to severe atopic eczema

Search and Selection

EBSCO Information Services

May 12, 2020

Prepared by EBSCO Health Innovations and EBM Development Department:

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Methods

First-round searching will consist of searching DynaMed Plus summaries pertinent to the topic. The search starts with DynaMed Plus because DynaMed Plus content is based on a thorough, systematic search and active literature surveillance system.

> Systematic literature surveillance (SLS) has been a cornerstone of creating DynaMed content since its inception. Currently, the SLS team works closely with members of McMaster University's Department of Health Research Methods, Evidence, and Impact to define and refine optimal search strategies, utilizing search terms for methodology and for clinical concepts (especially diagnosis and treatment) for each journal. These filters for PubMed searches are derived from PubMed Clinical Queries, McMaster University Hedges system, and DynaMed search filters and were found to capture >95% of relevant valid articles for use in DynaMed.[1]
> [1]Alper BS, Iorio A. Optimising search filters for active literature surveillance: a concordance study. Global Evidence Summit. Cape Town, South Africa; September 2017.
>
> The SLS team, in collaboration with McMaster University, continually evaluates and improves these filters to keep abreast of the ever-changing medical literature landscape. PubMed searches are performed daily. Each article is assessed by an external screener for clinical relevance, then reviewed by internal staff for both clinical relevance and validity. Any disagreements are settled by the Deputy Editor of the SLS team.
> In addition, the SLS team continually monitors the Journal source list against the list of journals catalogued in MEDLINE and existing DynaMed content to determine the set of journals that provide the highest yield for valid, clinically relevant content. As of November 2018, 507 Journals are systematically searched (see http://dynamed.com/home/content/content-sources). The journal selection threshold leads to routine adjustments to the number of journals selected.

Second-round searching will involve PubMed/MEDLINE® searches for intervention-specific systematic reviews or guidelines that involve a systematic review that are more recent than those identified in first-round searching.

Third-round searching will involve searches for original evidence reports. Such searching will be limited to areas considered insufficiently addressed by earlier searches, such as focused concepts published after search dates in systematic reviews.

Fourth-round searching will involve citation tracing from sources found in the preceding rounds of searching. This may be done to identify additional evidence sources if the results from the preceding rounds of searching are insufficient.

Additional selective searching, such as tracing citations from articles found or seeking related articles, may be done for additional concepts discovered.

Additional evidence updates may also be added continuously from feedback from any source.

FAQ Summary

Results

First-round searching – DynaMed

DynaMed subsection	Number of article citations	Number of unique references included
Atopic Dermatitis > Management > Medications > Systemic immunomodulating agents > Cyclosporine (April 14, 2020)	6	1 (Schmitt 2007A)*
Atopic Dermatitis > Management > Medications > Systemic immunomodulating agents > Dupilumab (April 14, 2020)	11	0†
Atopic Dermatitis > Management > Medications > Systemic immunomodulating agents > Azathioprine (April 14, 2020)	3	0‡
Atopic Dermatitis > Management > Medications > Systemic immunomodulating agents > Mycophenolate (April 14, 2020)	5	0
Atopic Dermatitis > Management > Medications > Systemic immunomodulating agents > Comparisons of systemic immunomodulating agents (April 14, 2020)	2	0§

*Schmitt 2010 also included in this section, but we address this trial and how we will handle systemic corticosteroids in Scoping, so it is not counted here as being included

†Beck 2014, Blauvelt 2017, Simpson 2016, and Thaçi 2016 are all addressed via ≥1 systematic review in 2nd-round searching

‡Meggitt 2006 addressed via ≥1 systematic review in 2nd-round searching

§Haeck 2011 and Schram 2011 are addressed via ≥1 systematic review in 2nd-round searching

Second-round searching – searches for intervention-specific systematic reviews

Database	Search string	Number of search results	Number of unique references included
PubMed April 14, 2020; last checked April 27, 2020	(atopic dermatitis OR eczema) AND (cyclosporine OR cyclosporin OR methotrexate OR mycophenolate OR azathioprine OR dupilumab) AND systematic[sb]	29 on April 14, 2020 30 on April 27, 2020	8 (Drucker 2020*, Hoare 2000, Nankervis 2017, Roekevisch 2014, Schmitt 2007B, Wang 2018, Seger 2019, Schram 2011)†‡

*Drucker 2020 was published online ahead of print on April 22, 2020. Accordingly, it was not available/included in our initial search on April 14, 2020. We only became aware of it when we re-ran our search on April 27, 2020, after we had completed Critical Appraisal and Evidence Synthesis based on the evidence we had available to us from our original searches. Drucker 2020 ultimately did not impact Evidence Synthesis.

†This search also captures Schmitt 2007A

‡Han 2017 appeared potentially relevant, but full-text review revealed it was published as a letter to the editor and was less comprehensive than Wang 2018 (e.g., a total of 1,965 patients vs. 2,447 patients) while also including non-standard doses of dupilumab (e.g., 75 mg every week, 100 mg every 4 weeks); accordingly, Han 2017 was not considered beyond Search and Selection

PARSE Mapping

PARSE Name	Search string	Number of search results	Number of new references selected for inclusion
EvRep AtopicDerm second round string #1	(atopic dermatitis OR eczema) AND (cyclosporine OR cyclosporin OR methotrexate OR mycophenolate OR azathioprine OR dupilumab) AND systematic[sb])	29 on April 14, 2020 30 on April 27, 2020	Not applicable for first run 1 (Drucker 2020)

Third-round searching – searches for original evidence reports

Database	Search string	Number of search results	Number of unique references included
PubMed April 14, 2020; last checked on April 27, 2020	(atopic dermatitis OR eczema) AND (cyclosporine OR cyclosporin OR methotrexate OR mycophenolate OR azathioprine OR dupilumab) AND randomized controlled trial[pt] AND ("2018/07/01"[EDAT] : "3000/12/31"[EDAT])	5 on April 14, 2020 5 on April 14, 2020	0*

*Lake 2019 is a commentary on the Simpson 2016 trial program (already accounted for by Wang 2018). Guttman-Yassky 2019 is a small trial of dupilumab focused on surrogate outcomes.

PARSE Mapping*

PARSE Name	Search string	Number of search results	Number of new references selected for inclusion
EvRep AtopicDerm third round string #1	(atopic dermatitis OR eczema) AND (cyclosporine OR cyclosporin OR methotrexate OR mycophenolate OR azathioprine OR dupilumab) AND randomized controlled trial[pt] AND ("2018/07/01"[EDAT] : "3000/12/31"[EDAT])	5 on April 14, 2020 5 on April 14, 2020	Not applicable for first run 0 on April 27, 2020

*The Drucker 2020 systematic review stated an intent for their work to be a living systematic review, where they will update results every 4 months. This could potentially be used as an alternate or supplemental source for currency tracking.

Fourth-round searching – citation tracing

Source	Tracing	Number of unique references included
Seger 2019	Tracing for additional RCTs published since Roekevisch 2014	1 (Goujon 2018)

Search summary:

Number of articles screened and selected

	Screened	Selected*
1st-round (DynaMed)	27	1
2nd-round (Systematic review searches)	30	8
3rd-round (Original article searches)	5	0
4th-round (Citation tracing)	1	1
Total	*63*	*10*

* Number shown is after deduplication and does not include any consideration of full-text articles for verification or clarification of details (e.g., verification or clarification of content reported in systematic reviews)

	Articles selected for evaluation (Author Year)
Systematic reviews	9 (Drucker 2020*, Hoare 2000, Nankervis 2017, Roekevisch 2014, Schmitt 2007A, Schmitt 2007B, Wang 2018, Seger 2019, Schram 2011)
Randomized, controlled trials	1 (Goujon 2018)
Other article types	0

*Drucker 2020 was published online ahead of print on April 22, 2020. Accordingly, it was not available/included in our initial search on April 14, 2020. We only became aware of it when we re-ran our search on April 27, 2020, after we had completed Critical Appraisal and Evidence Synthesis based on the evidence we had available to us from our original searches. Drucker 2020 ultimately did not impact Evidence Synthesis.

Evidence report for systemic treatment of patients with moderate to severe atopic eczema

Critical Appraisal

EBSCO Information Services

May 12, 2020

Prepared by EBSCO Health Innovations and EBM Development Department:

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Methods

For each study selected for critical appraisal, we assessed for criteria needed for Level 1 [likely reliable] evidence ratings in DynaMed's Levels of Evidence criteria in which evidence quality is labeled in 1 of 3 levels:

- **(level 1 [likely reliable] evidence)** for studies with clinical outcomes and minimal risk of bias;
- **(level 2 [mid-level] evidence)** for studies with clinical outcomes and significant methodological or statistical limitations; and
- **(level 3 [lacking direct] evidence)** for reports that do not include scientific analysis of clinical outcomes or for study types that do not include comparisons between groups.

The specific concepts we critically assessed are fully mapped to cover all the criteria used in GRADE. We summarized key concerns identified that reduce the certainty of evidence in categories used for GRADE methods (i.e., risks of bias, indirectness, imprecision, inconsistency, and other considerations if relevant). In the study-level summaries inconsistency assessment was applied to consistency of within-study results – this applies to consistency across related outcomes for both original studies and for systematic reviews, and also applies to consistency across studies when applied to systematic reviews.

FAQ Summary

Results

Characteristics and Results of Critically Appraised Studies/Sources

General note: Because for FAQ 2 we pre-specified a greater interested in patient-reported outcomes but found on evidence review that (1) these were often lacking and (2) the clinician-assessed outcomes were also heterogeneous), we may broadly refer to clinician-assessed outcomes as 'sign' outcomes (i.e., those things a clinician can assess), which is intended to serve as a contrast to 'symptom' outcomes (i.e., things a patient experiences and reports).

DRUCKER 2020

Drucker AM, Ellis AG, Bohdanowicz M, Mashayekhi S, Yiu ZZN, Rochwerg B, Di Giorgio S, Arents BWM, Burton T, Spuls PI, Küster D, Siegels D, Schmitt J, Flohr C. Systemic Immunomodulatory Treatments for Patients With Atopic Dermatitis: A Systematic Review and Network Meta-analysis. JAMA Dermatol. 2020 Apr 22. [Epub ahead of print] PubMed

This SR was published electronically ahead of print on Apr 22. We conducted our original search on Apr 14; thus, this SR was not available to us at the time of our original search. We re-ran our searches on Apr 27 as we were approaching the end of Evidence Synthesis (based on the evidence we found with our original search), and our Apr 27 search captured this SR. This SR included detailed reporting of methods and results in the published journal supplement and in an additional online supplement that reported trial characteristics and arm-level outcome data. We used it as a check of the robustness of our findings in Evidence Synthesis based on the information previously available to us. We first compared the trials included in Drucker 2020 vs. the trials that we had previously identified and included for each comparison and summarized any discrepancies in the Results section of this summary. We then reported results of pre-specified issues that we checked in assessing whether Drucker 2020 would affect our overall synthesized finding for a given comparison and FAQ.

Relevant to FAQ2, FAQ3

- **Study design:** systematic review and network meta-analysis of randomized trials
- **Population:** children and adults with moderate to severe atopic eczema
- **Intervention:** systemic immunomodulatory medications
- **Comparison:** any
    - most comparisons were vs. placebo

- **Study inclusion criteria:**
    - English-language report
    - ≥ 8 weeks treatment duration
    - did not use a run-in period where all participants received a systemic immunomodulatory agent

- **Number of studies:** 39 trials overall, including scoped and non-scoped interventions
    - many trials were of dupilumab (a scoped agent) or of investigational agents
- **Number of participants:** 6,360
    - see related point above about composition of evidence
- **Results:**

- for scoped interventions, we compared the trials included in Drucker 2020 (listed in the Excel file they provide via an online supplement with trial characteristics and arm-level outcome data) vs. trials that we had previously identified and extracted for each comparison and report discrepancies below:
  - cyclosporine
    - vs. placebo
      - trials previously included/extracted
        - Sowden 1991/Salek 1993
        - Wahlgren 1990
        - Munro 1994
        - van Joost 1994
      - trials in Drucker 2020
        - Sowden 1991/Salek 1993
        - Munro 1994
      - discrepancies
        - previously identified and not in Drucker 2020
          - Wahlgren 1990
            - not included in Drucker 2020 because it did not meet the Drucker 2020 study inclusion criterion of ≥ 8 weeks treatment duration
          - van Joost 1994
            - not included in Drucker 2020 because it did not meet the Drucker 2020 study inclusion criterion of ≥ 8 weeks treatment duration
    - vs. methotrexate
      - trials previously included/extracted
        - Goujon 2018
      - trials in Drucker 2020
        - Goujon 2018
    - vs. mycophenolate
      - trials previously included/extracted
        - Haeck 2011
      - trials in Drucker 2020
        - none
      - discrepancies
        - previously identified and not in Drucker 2020
          - Haeck 2011
            - not included in Drucker 2020 because it utilized a run-in period where all participants received cyclosporine
  - azathioprine
    - vs. placebo
      - trials previously included/extracted
        - Berth-Jones 2002
        - Meggitt 2006
      - trials in Drucker 2020
        - Berth-Jones 2002
        - Meggitt 2006

- vs. methotrexate
  - trials previously included/extracted
    - Schram 2011A
  - trials in Drucker 2020
    - Schram 2011A
- mycophenolate mofetil
  - only identified trial was Haeck 2011 which compared cyclosporine vs. mycophenolate and which was not included in Drucker 2020 as described under cyclosporine heading above
- methotrexate
  - only identified trials are vs. cyclosporine (Goujon 2018) and vs. azathioprine (Schram 2011A) described under respective outline headings above
- dupilumab vs. placebo
  - trials previously included/extracted (all from Wang 2018)
    - Beck 2014 M12
    - Beck 2014 4C
    - Thaci 2016
    - Simpson 2016 SOLO 1
    - Simpson 2016 SOLO 2
    - Blauvelt 2017
  - trials previously identified but excluded
    - Blauvelt 2018
    - Guttman-Yassky 2019
  - trials in Drucker 2020
    - Beck 2014 M12
    - Thaci 2016
    - Simpson 2016 SOLO 1
    - Simpson 2016 SOLO 2
    - Blauvelt 2017
    - Blauvelt 2018
    - de Bruin-Weller 2018
    - Guttman-Yassky 2019
    - Paller 2019
  - discrepancies
    - previously identified and not in Drucker 2020
      - Beck 2014 4C
        - not included in Drucker 2020 because it did not meet the Drucker 2020 study inclusion criterion of > 8 weeks treatment duration
    - trials in Drucker 2020 that were not previously identified
      - de Bruin-Weller 2018
        - this may not have been identified for inclusion in Seger 2019 because it focused on patients with poor response to or inability to take cyclosporine (thus raising possible questions about representativeness for the general population)
      - Paller 2019
        - only adolescents, so ineligible for this evidence report

        - trials in Drucker 2020 previously identified and considered ineligible on review of title or abstract
            - Blauvelt 2018 title suggests intent is to examine "correlates of vaccine-induced immunity"
            - Guttman-Yassky 2019 abstract suggests a focus on surrogate measures

- **Summary of findings for checks of trials we had previously included/extracted vs. trials in Drucker 2020**
    - trials in Drucker 2020 that we had not previously included/extracted
        - 1 trial of dupilumab vs. placebo focused on patients who did not respond to or could not take cyclosporine due to intolerance or contraindication (de Bruin-Weller 2018); reason for exclusion/being missed in Seger 2019 is not clear (but may be due to questions about representativeness)
        - 1 trial of dupilumab vs. placebo in adolescents (Paller 2019); not eligible for consideration for this evidence report
        - 2 trials of dupilumab vs. placebo focusing on surrogate outcomes (Blauvelt 2018, Guttman-Yassk 2019); excluded in screening of titles/abstracts
    - trials we had previously included/extracted that were not in Drucker 2020
        - 2 trials of cyclosporine vs. placebo (van Joost 1994, Wahlgren 1990), 1 trial of cyclosporine vs. mycophenolate (Haeck 2011), and 1 trial of dupilumab vs. placebo (Beck 2014 4C) because they did not meet Drucker 2020 inclusion criteria (details above)
- **Key questions checked in assessing whether Drucker 2020 SR results would affect our overall synthesized finding for a given comparison and FAQ**
    - Were there additional trials contributing to any of our comparisons that we had not previously identified and included in Evidence Synthesis?
        - if so, and if these trials appeared to have the potential to affect our overall findings for a given comparison and FAQ, we would consider the data from the new trials and incorporate into Evidence Synthesis as appropriate
    - **Results:** as reported in greater detail above, the only additional trials in Drucker 2020 concerned dupilumab
        - results were consistent with the pooled analysis from Wang 2018 in showing benefit of dupilumab vs. placebo on disease severity and quality of life outcomes; accordingly, Drucker 2020 does not affect our findings for these FAQs for this comparison, so we did not undertake any additional review
    - Were there any trials that we included but did not include for a specific outcome and for which Drucker 2020 reported data?
        - if so, we would consider the outcome from the previously not included trial and incorporate into Evidence Synthesis as appropriate
            - we made these checks by comparing
                - eligible trials listed as reporting signs (FAQ2), symptoms (FAQ2), or QoL (FAQ3) in Drucker 2020 trial characteristics and arm-level outcome data Excel spreadsheet
                - trials contributing to FAQ2 or FAQ3 in comparisons included in Evidence Synthesis
        - **Results:** no new outcomes were identified from Drucker 2020 for trials that we included but did not include for a specific outcome relevant to our review

- Were our previously extracted and summarized results for the relevant comparisons and outcomes consistent with the corresponding results reported by Drucker 2020?
  - Because Drucker 2020's meta-analytic estimates are limited to network estimates (rather than also presenting pairwise estimates where possible), we made these assessments of consistency based on their network estimates; of note, Drucker 2020 note explicitly that they were unable to evaluate coherence of their network (i.e., consistency between the direct and indirect components of their network) due to the sparse nature of the data.
    - if we found inconsistency, we would further examine the sources and attempt to identify the reason(s) for inconsistency
    - if there was no inconsistency, we would not further examine the sources nor attempt to identify an explanation for such discrepancies; we did not consider minor differences in quantified estimates to signal inconsistency
  - **Results:**
    - **signs outcome**
      - consistent
        - Drucker 2020 reported benefits vs. placebo for cyclosporine, azathioprine, and dupilumab (Figure 3A and 3B)
          - our previously extracted and summarized results for cyclosporine, azathioprine, and dupilumab had also shown benefit for cyclosporine, azathioprine, and dupilumab
        - for other scoped options of mycophenolate and methotrexate, the only available trials are head-to-head trials against other active agents, and the inferences one can draw are consistent
          - Drucker does not report on mycophenolate for this outcome, because the only trial available (Haeck 2011) did not meet their eligibility criteria as noted above
          - Drucker reports an SMD of -0.6 (95% CrI -1.1 to 0.0) for methotrexate vs. placebo
            - there are no trials of methotrexate vs. placebo, so this estimate suffers from indirectness
            - we do not consider the upper bound of the 95% CrI to signal inconsistency with the indirect inference one can make from the available head-to-head trials (namely that since the comparator agents may have efficacy vs. placebo and since there is no clear difference between the comparator agents and methotrexate, that methotrexate may have efficacy vs. placebo); suggesting these results are inconsistent would seem to invoking bright-line rules that would fail to capture the nuance of the available evidence and general uncertainty in quantified estimates (irrespective of the low quality data at hand)
    - **quality of life outcome**

- Drucker 2020 reported results for change in QoL on SMD scale for azathioprine, cyclosporine, methotrexate, and dupilumab in eTable 2. Drucker also reports results for change in DLQI on MD scale for TPMT adjusted azathioprine (this is Meggitt 2006) and dupilumab in Fig 3D (we focus our attention on the dose approved for use, namely 600 mg for 1 dose, then 300 mg every other week).
  - dupilumab showed benefit vs. placebo on both scales
  - other agents showed various degrees of imprecision
- Our results from direct comparisons were consistent with
  - benefit of dupilumab vs. placebo
- Our results from direct comparisons for other trials are limited to cyclosporine vs. placebo (Salek 1993), azathioprine vs. placebo (Meggitt 2006), methotrexate vs. azathioprine (Schram 2011A), and methotrexate vs. cyclosporine (Goujon 2018)
  - The network estimates for these comparisons often suffered from greater imprecision (perhaps especially for the network estimates of the SMD), although this imprecision is not a *per se* signal of inconsistency with the direct estimates available from trials. Full assessment of this would require calculation of SMDs for the direct evidence, but we gave preference to the direct estimates given we are not able to fully evaluate the nature of Drucker 2020's network estimates.
    - cyclosporine vs. placebo – direct evidence for a disease-specific instrument suffers from imprecision, but suggests a possible benefit (Salek 1993)
    - azathioprine vs. placebo – direct evidence for a disease-specific instrument suffers from imprecision, but suggests a possible benefit (Meggitt 2006, as addressed within Schram 2011B)
    - no clear difference for head-to-head trials of methotrexate vs. azathioprine (Schram 2011A, as addressed in Roekevisch 2014) or methotrexate vs. cyclosporine (Goujon 2018)

- Was there consistency between our overall risk of bias assessments for a comparison/outcome and the overall risk of bias assessments for a comparison/outcome based on the risk of bias assessments of the contributing trials from Drucker 2020
  - if discrepancies in risk of bias assessments would potentially change our overall risk of bias assessment for the overall certainty rating for a comparison/outcome, we would further examine the sources to attempt to identify an explanation for the discrepancies
  - if discrepancies in risk of bias assessments would not change our overall risk of bias assessment for the overall certainty rating, we would not further examine the sources nor attempt to identify an explanation for the discrepancies
  - **Results:**
    - signs
      - for comparison of cyclosporine vs. placebo

        - we based our overall risk of bias assessment on 4 trials and Drucker 2020 included only 2 of these trials so the overall risk of bias assessments are not directly comparable
    - for comparison of cyclosporine vs. methotrexate
        - a single trial (Goujon 2018) contributed to this comparison/FAQ for which we judged risk of bias for the domains blinding and high/differential dropouts based on our review of the full-text of the article, and Drucker 2020 judged similar risk of bias ('high' for blinding and 'unclear' for incomplete outcome data)
    - for comparison of azathioprine vs. placebo
        - although some individual domains in both contributing trials (Berth-Jones 2002, Meggitt 2006) were rated low risk of bias in our assessments extracted from Schram 2011B and high or unclear in Drucker 2020 risk of bias table, we had still provided a single downgrade for risk of bias for the overall evidence which would not be changed based on a review of the Drucker 2020 risk of bias assessments
    - for comparison of azthioprine vs. methotrexate
        - a single trial (Schram 2011A) contributed to this comparison/FAQ for which we judged risk of bias for the domain of blinding; Drucker 2020 also considered this trial to have a risk of bias due to blinding ('high' for Blinding of participants and personnel and 'unclear' for Blinding of outcome assessment)
    - for comparison of dupilumab vs. placebo
        - relevant dupilumab trials were assessed to have low risk of bias in both Wang 2018 and Drucker 2020
- quality of life
    - for comparison of cyclosporine vs. placebo
        - a secondary publication of a single trial (Salek 1993, which was secondary publication of Sowden 1991) contributed to this comparison/FAQ for which we judged risk of bias due to high loss to follow-up based on our review of the full-text of the article and Drucker 2020 judged similar risk of bias ('high' for incomplete outcome data)
    - for comparison of cyclosporine vs. methotrexate
        - a single trial (Goujon 2018) contributed to this comparison/FAQ for which we assigned risk of bias downgrade due to differential dropouts (higher dropouts in azathioprine group) based on a full-text review of the article and Drucker 2020 assigned as 'unclear' for incomplete outcome data (Drucker 2020 also assigned as 'unclear' for allocation concealment but we did not because the randomization was performed centrally)
    - for comparison of azathioprine vs. placebo
        - a single trial (Meggitt 2006) contributed to this comparison/FAQ for which we assigned risk of bias downgrade due to differential dropouts (higher dropouts in azathioprine group) based on a full-text review of the article and Drucker 2020 assigned as

'unclear' for incomplete outcome data (Drucker 2020 also assigned as 'unclear' for allocation concealment but we did not because the randomization was performed "by an independent clinician" which suggests randomization was adequately concealed)

- for a comparison of azathioprine vs. methotrexate
  - a single trial (Schram 2011A) contributed to this comparison/FAQ for which we did not assign a risk of bias downgrade and for which Drucker 2020 assigned risk of bias as 'high' for 'Blinding of participants and personnel'
    - although patients were not blinded in this trial, we did not consider lack of patient blinding an important risk of bias because two different active drugs were compared, and it seems unlikely that patients would have prior expectations for one to be better than the other
- for comparison of dupilumab vs. placebo
  - relevant dupilumab trials were assessed to have low risk of bias in both Wang 2018 and Drucker 2020

- Was there additional information reported about patient-reported outcome measures in Drucker 2020 that would impact our reporting of FAQ 2
  - we had prespecified in scoping of 'FAQ 2: Will my skin and symptoms improve?' that we would preferentially seek patient-reported outcome measures over clinician-assessed outcome measures
    - however, we ultimately reported on clinician-assessed outcome measures because patient-reported outcome measures were inadequately reported
  - **Results:** check of Drucker 2020 'eFigure 1. Network Plot of Arms Included in the Network Meta-analysis of Change in POEM Score up to 16 Weeks of Treatment – Main Analysis' showed that direct comparison only available for dupilumab vs. placebo so Drucker 2020 does not impact our need to use clinician-assessed outcome measures for reporting FAQ 2

- **Other considerations**
  - In addition to Drucker 2020's inclusion criteria leading to exclusion of certain trials, we also note – as can be appreciated from their Fig 2a and eFigs 1 and 2 – their networks are fairly dominated by trials of dupilumab (for which there is already a large body of direct evidence from placebo-controlled trials in Wang 2018) and investigational agents for EASI, POEM, and DLQI. Their networks for SMDs are limited to agents currently in use (Fig 2b, eFig3).
    - Drucker 2020 speaks to this in the discussion of limitations, stating explicitly that the "networks are sparse" and "[m]ost comparisons were informed by only a single RCT and usually with a small number of patients, which led to imprecision"
  - Although Drucker 2020 provides estimates for the SMD in an attempt to provide quantified estimates in spite of the heterogeneous outcome measurements used, they also explicitly note a limitation of their analysis, namely (1) the validity of the SMD relying heavily on the extent to which the scales being combined are truly similar and (2) the extent to which the timing of the trials might impact the apparent efficacy of any given agent: "These analyses are limited by pooling outcome measures such as peak itch

and mean itch, which measure the same domain but in different ways, and their inclusion of trials only up to 16 weeks, which may favor medications with more rapid onset of action."

Risk of bias assessments of included trials that addressed scoped comparisons

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
cyclosporine vs. placebo							
Sowden 1991	unclear	unclear	low	low	high	unclear	low
Munro 1994	unclear	unclear	low	unclear	high	unclear	unclear
cyclosporine vs. methotrexate							
Goujon 2018	low	low	high	low	unclear	low	low
azathioprine vs. placebo							
Berth-Jones 2002	low	unclear	low	unclear	high	unclear	high
Meggitt 2006	low	unclear	low	unclear	unclear	unclear	low
azathioprine vs. methotrexate							
Schram 2011A	low	low	high	unclear	low	low	low
dupilumab vs. placebo							
Beck 2014 (M12)	low	low	low	low	low	low	low
Thaci 2016	low	low	low	low	low	low	low
Simpson 2016 SOLO1	low	low	low	low	low	low	low
Simpson 2016 SOLO2	low	low	low	low	low	low	low
Blauvelt 2017	low	low	low	low	low	low	low
de Bruin-Weller 2018	low	low	low	low	low	low	low

GOUJON 2018

Goujon C, Viguier M, Staumont-Sallé D, Bernier C, Guillet G, Lahfa M, Ferrier Le Bouedec MC, Cambazard F, Bottigioli D, Grande S, Dahel K, Bérard F, Rabilloud M, Mercier C, Nicolas JF. Methotrexate Versus Cyclosporine in Adults with Moderate-to-Severe Atopic Dermatitis: A Phase III Randomized Noninferiority Trial. J Allergy Clin Immunol Pract. 2018 Mar - Apr;6(2):562-569.e3. PubMed

Relevant to FAQ2, FAQ3

- **Study design:** randomized trial

  - phase 3 noninferiority trial with noninferiority margin selected as 20% less efficacy in methotrexate arm vs. cyclosporine arm
- **Population:** moderate-to-severe atopic dermatitis
  - per diagnostic criteria of UK Working Party
    - score of > 15 on SCORAD index
    - presented an inadequate response to regimen of topical corticosteroids or tacrolimus
  - severe disease (SCORAD index >40) present in ≥ 80% of patients
  - median duration of disease was 23 years
- **Intervention:** methotrexate
  - 15 mg/week
  - increased to 25 mg for remaining 16 weeks if at week 8 primary end point was not achieved (increased in 56% of patients)
- **Comparison:** cyclosporine
  - 2.5 mg/kg/day
  - increased to 5 mg for remaining 16 weeks if at week 8 primary end point was not achieved (increased in 49% of patients)

- **Study inclusion criteria:**
  - no use of use of systemic corticosteroids or an immunosuppressive treatment within 4 weeks before inclusion

- **Number of participants:** 97
- **Duration of follow-up:** 24 weeks
  - outcomes measured at weeks 4, 8, 12, 16, 20, and 24
    - short-term outcome extracted for 16 weeks in line with Scoping
    - long-term outcome extracted at 24 weeks in line with Scoping

- **Results:**

Effects of methotrexate vs. cyclosporine on signs and quality of life, responder analysis

Outcome	Week	Methotrexate		Cyclosporine		Absolute risk difference (90% CI)
		No. Evaluated	% of patients achieving outcome	No. Evaluated	% of patients achieving outcome	
SCORAD 50 (50% improvement in SCORAD index)	16	28	42.9%	34	61.8%	-19% (95% CI -39% to 2%)
	24	23	39.1%	31	71.0%	-32% (-53% to -10%)
EASI 50 (50% improvement in EASI index)	16	27	66.7%	34	79.4%	-13% (-31% to 6%)
	24	23	87.0%	31	80.7%	6% (-10% to 23%)

Dermatology Life Quality index (post-treatment score of ≤ 5)	16	28	60.7%	34	77.1%	-16% (-36% to 3%)
	24	23	65.2%	31	80.6%	-15% (-35% to 5%)

Effects of methotrexate vs. cyclosporine on signs and quality of life, continuous data*

Outcome	Methotrexate (mean±SD)	Cyclosporine (mean±SD)
SCORAD		
16 weeks	28.7±11.5	27.0±15.6
24 weeks	26.9±11.6	24.9±15.5
EASI		
16 weeks	6.3±4.6	6.1±6.9
24 weeks	5.0±3.6	5.4±5.0
DLQI		
16 weeks	5.1±3.5	4.3±5.4
24 weeks	5.0±4.6	3.3±4.4

*The authors did not formally analyze these outcome data. Although these data do make possible the calculation of mean differences, we did not do this given the obviously-comparable nature of the data.

Effects of methotrexate vs. cyclosporine on adverse events

Outcome	Methotrexate	Cyclosporine
serious adverse events*	0	1†
treatment-related adverse events leading to discontinuation‡	2	1†

* Defined as a life-threatening event and events that resulted in death, hospitalization, disability, or permanent damage
† Serious adverse event was hospitalization for severe eczema flare at week 12 in patient on 2.5 mg/kg/d cyclosporine
‡ One patient on 15 mg/wk methotrexate discontinued study at week 8 because of elevation in liver enzymes (4 times normal limit) and another patient on 25 mg/wk methotrexate discontinued at week 12 because of lymphopenia (900 cells/mL vs 1500 cells/mL as normal count)

- **Certainty**
  - general concern about certainty in results pertaining to analysis of noninferiority
    - although the authors specify an intent to evaluate noninferiority via responder analysis, there are potential issues with this approach
      - the responder analysis requires setting a threshold to define a "responder" (e.g., 50% improvement in EASI index), and irrespective of how one arrives at the given threshold, this dichotomizes continuous data early in the stage of analysis (rather than at the end of the analysis); this results in a loss of information and is often considered a less-than-ideal approach to analysis of continuous data
      - the responder analysis treats anyone below the threshold as a non-responder when these people may still have meaningful responses (e.g., someone who has a 40%, 45%, or 48% improvement would still be

categorized as a non-responder); this demonstrates that responder analyses can be very sensitive to the thresholds used in the analysis
- although conceptually measuring different things, the continuous data reported suggest a much greater degree of comparability than do the responder data; for example, consider the data at 24 weeks for methotrexate vs. cyclosporine (values are mean±SD):
- accordingly, we rely on the continuous outcome measures more than the dichotomized variants

- signs outcome
  - at 16 weeks (short-term)
    - Very low certainty with following downgrades
      - risk of bias
        - no patient blinding
        - high and differential dropouts (Fig 1)
          - dropouts were reported at 8, 12, and 24 weeks only and dropouts at week 16 would be between those at weeks 12 and 24
            - week 12 dropouts in methotrexate vs. cyclosporine groups
              - 11/50 vs. 6/47
            - week 24 dropouts in methotrexate vs. cyclosporine groups
              - 27/50 vs. 14/47
      - imprecision
        - single, small trial
      - inconsistency
        - only single trial making comparison (cannot assess consistency)
      - indirectness
        - clinician-assessed rather than patient-reported outcome
  - at 24 weeks (long-term)
    - Very low certainty with following downgrades
      - risk of bias
        - no patient blinding
        - high and differential drop-outs (details above)
      - imprecision
        - single, small trial
      - inconsistency
        - only single trial making comparison (cannot assess consistency)
      - indirectness
        - clinician-assessed rather than patient-reported outcome
- quality of life outcome
  - at 16 weeks (short-term)
    - Very low certainty with following downgrades

            - risk of bias
                - no patient blinding
                - high and differential drop-outs (details above)
            - imprecision
                - single, small trial
            - inconsistency
                - only single trial making comparison (cannot assess consistency)
        - at 24 weeks (long-term)
            - Very low certainty with following downgrades
                - risk of bias
                    - no patient blinding
                    - high and differential drop-outs (details above)
                - imprecision
                    - single, small trial
                - inconsistency
                    - only single trial making comparison (cannot assess consistency)
    - for adverse events related outcomes, Certainty was not assessed because of insufficient evidence
- **Other considerations**
    - CIs presented in the table above for the absolute risk difference for the authors' responder outcomes are 90% CIs. Of note, 95% CIs would be wider.
    - The abstract for this article focuses on outcomes at 8 weeks, and specifically claims that methotrexate "was inferior" to cyclosporine at week 8. However:
        - we have concerns about how the authors assessed (non-)inferiority as described above. If instead considering the continuous data in their original form for methotrexate vs. cyclosporine:
            - SCORAD (0 to 103 scale): mean difference 12.1 (95% CI 5.4 to 18.8)
            - EASI (0 to 72 scale): mean difference 4.8 (95% CI 1 to 8.6)
            - DLQI (0 to 30 scale): mean difference 4.3 (95% CI 1.3 to 7.3)
            - these fairly modest differences could be entirely attributable to cyclosporine having a quicker onset of action

HOARE 2000

Hoare C, Li Wan Po A, Williams H. Systematic review of treatments for atopic eczema. Health Technol Assess. 2000;4(37):1-191. PubMed

Relevant to FAQ2

- **Study design:** systematic review of randomized trials
- **Population:** patients with atopic eczema of any age
- **Intervention:** interventions used in the prevention and treatment of patients with atopic eczema
    - cyclosporine reviewed in 'Chapter 10. Systemic immunomodulatory agents'
    - other scoped interventions not covered

  - azathioprine, methotrexate, and mycophenolate mofetil were each listed as 'Therapeutic interventions currently in practice for which no RCTs could be found' (Chapter 13. Discussion, Table 38)
- **Comparison:** placebo
  - SR also included head-to-head trials but the only relevant head-to-head trial of cyclosporin was published after this SR (Haeck 2011 head-to-head trial vs. mycophenolate sodium)

- **Study inclusion criteria:** no additional

- **Number of studies:** 4
  - 4 placebo-controlled trials of cyclosporin summarized below
- **Number of participants:** 113
  - number included in 4 placebo-controlled trials of cyclosporin
- **Duration of follow-up:** 8 to 16 weeks (see table below)

- **Results:**

Placebo-controlled randomized trials of cyclosporine treatment in adults with severe eczema and withdrawals and dropouts *

Study	Number of participants	Duration	Severity	Co-treatments	Withdrawals and dropouts
Sowden 1991†	33	16 weeks	severe	topical steroids	Four crossed over prematurely (placebo to cyclosporine) Six did not complete second phase (cyclosporine to placebo)
Munro 1994	24	8 weeks	chronic	topical steroids	Five‡
van Joost 1994	46	6 weeks	not reported	hydroxyzine 10 or 25 mg, emollients	18 because of lack of response from trial medication
Wahlgren 1990	10	10 days	stable, moderate or severe	1% hydrocortisone, emollients	none

* all trials reported an oral cyclosporine dosage of 5 mg/kg/day
† Table 31 also includes Salek 1993, secondary publication of Sowden 1991, and it has identical information for withdrawals and dropouts because they are the same trial
‡ no further information reported

Outcome measures and scales used in placebo-controlled randomized trials of cyclosporine treatment in adults with severe eczema

Study	Outcome measure	Scale

Sowden 1991*	clinician-assessed disease activity of erythema, purulence, excoriation or crusting, dryness or scaling, cracking or fissuring, and lichenification at six defined body sites .	0-to-3 scale
	clinician-assessed extent of disease	Rule of Nines
	patient-assessed itch and sleep loss	0 to 100 mm
	patient and clinician global assessments	5-point scale
Salek 1993*	patient-assessed health-related quality of life (results reported by Sowden 1991 not repeated here)	UK Sickness Impact Profile and Eczema Disability Index
Munro 1994	composite scale for erythema, excoriation, lichenification using rule of nines	0-to-3 scale
	itch and sleep loss	10 cm VAS
van Joost 1994	clinician-assessed severity in six regions for erythema, infiltration, vesicles and papules, dryness and scaling, cracking and fissuring, excoriation and crusting	0-to-3 scale
	lichenification scored separately	0-to-3 scale
	clinician-assessed extent of disease	Rule of Nines
	clinician-assessed itching and sleep loss	0-to-3 scale
	patient-assessed global assessment	4-point scale
Wahlgren 1990	patient-assessed itch	Symtrack
	patient-assessed itch	100 mm VAS
	clinician-assessed severity at 20 areas (no details)	0-to-3 scale

*These are two publications from the same RCT, with Salek 1993 focusing on quality of life.

Estimates of mean difference in itch scores* in placebo-controlled randomized trials of cyclosporine treatment in adults with severe eczema

Study	**No. patients**		**Mean difference (95% CI)†**
	cyclosporine	**placebo**	
Munro 1994	12	12	19.9 (2.66 to 37.14)
Sowden 1991	17	16	24.1 (12.49 to 35.70)‡
Wahlgren 1990	10	10	8.0 (–2.33 to 18.33)
Total			16.70 (5.87 to 27.54)§

*Meta-analysis was done for itch scores (only) because this outcome used consistent VAS measure for scoring itch in 3 trials.
†Mean difference for each of the three cross-over trials as well as the pooled estimate were estimated based on only the first phase of these trials to reduce risk of confounding by carry-over effects.
‡It is not clear how the trial-level result for Sowden 1991 was calculated, because the corresponding values for the cyclosporine and placebo groups were 27.7 and 36, respectively. One would thus expect this value to be about 8.3 (not 24.1).
§Pooled mean difference using random effects model. Consistent results using fixed effects model (15.92, 95% CI 8.87 to 22.96)

- **Other considerations:**
  - We did not carry forward to Evidence Synthesis the meta-analysis of the pooled itch outcome because it focuses on a single symptom and not a composite measure of disease severity
  - Authors also note van Joost 1994 reported 15/19 (78.9%) patients in the cyclosporine group reported "at least a moderate" improvement in disease severity at the end of the 6-week trial compared with 6/19 (31.6%) patients in the placebo group. They report an

estimated absolute risk difference of 39% (95% CI 10% to 62%), but it is not clear how this estimate was obtained based on the reported results in each group. Recalculating this estimate based on the reported data, one finds an absolute risk difference of 47.4% (95% CI 15.8% to 67.9%). However, we do not carry this outcome forward to Evidence Synthesis as it represents a responder analysis from only one of the trials and does not serve to substantively impact Evidence Synthesis.

- Authors do not mention the quality of life outcomes reported by Salek 1993. Salek 1993 (n = 33) was poorly reported and focused on within-group changes rather than between-group differences. However, they do report means ± standard errors for two quality of life scales in the placebo and cyclosporine groups at the 8-week point:
  - UK Sickness Impact Profile (0-100 scale): 5.6±1.8 vs. 4.8±1.9
  - Eczema Disability Index (15-105 scale): 29.1±4.8 vs. 16.1±5.3
    - if calculating a mean difference (and accounting for the fact that the authors report standard *errors*, not standard *deviations*), one finds a mean difference of 13 (95% CI -1.6 to 27.6)
  - The results for the UK Sickness Impact Profile are comparable, while the results for the Eczema Disability Index suggest a possibly-meaningful difference, albeit limited by imprecision
  - We consider these results to have Very low certainty, with downgrades for risk of bias (high loss to follow-up, no intention-to-treat analysis), imprecision (small trial), and inconsistency (inability to assess consistency given only trial for this comparison to report on quality of life and having some signal of internal inconsistency as well)

NANKERVIS 2017

Nankervis H, Thomas KS, Delamere FM, Barbarot S, Smith S, Rogers NK, Williams HC. What is the evidence base for atopic eczema treatments? A summary of published randomized controlled trials. Br J Dermatol. 2017 Apr;176(4):910-927. PubMed

Relevance to FAQs not applicable

This study seemed potentially relevant for this evidence report because it is a review and summary of the evidence base for atopic dermatitis treatments. However, this was primarily a scoping review, and given there were 92 treatments reviewed across 541 randomized trials in any severity of atopic dermatitis in any age, only general information could be provided for each specific treatment. The authors grouped treatments into 3 tables, 2 of which included scoped interventions and cite and briefly summarize the latest relevant systematic reviews on these topics where they exist:

- Table 1. Evidence of benefit: at least one good quality randomized controlled trial or a large body of evidence and a clinically useful finding*
  - cyclosporine vs. placebo cited Schmitt 2007A
  - azathioprine vs. placebo cited Schram 2011B
- Table 2. Evidence of no benefit: at least one good quality randomized controlled trial (RCT) or several less well reported RCTs that consistently failed to show a convincing benefit on overall disease activity*
  - no scoped interventions included in this table
- Table 3. Treatments that require more research

- oral prednisolone, methotrexate, mycophenolate mofetil, and biological therapies included in this table

*Review authors defined a 'good quality' trial as one that was well-designed and well-reported and had a magnitude of benefit deemed by the original trial authors to be clinically relevant; review authors defined a 'large body of evidence' as enough trials with consistent evidence of clinically relevant benefit, despite some limitations in reporting.

Although risk of bias was assessed for the included trials, the results were only reported at a summary level (eg, proportion of included trials that were high, low, or unclear for specific domain) and not at the individual trial level.

Although this SR had limited direct relevance for our purposes, it was helpful because it cited 2 previous reports that were key citations:

- Hoare 2000, which was an HTA from the National Institutes of Health Research, which included an SR of treatments for atopic eczema and which provided detailed information about the placebo-controlled trials evaluating cyclosporine for severe atopic dermatitis.
- Schram 2011B, which was an SR on azathioprine for dermatologic conditions, and included detailed methods and results on the 2 placebo-controlled trials of azathioprine for moderate-to-severe atopic dermatitis.

ROEKEVISCH 2014

Roekevisch E, Spuls PI, Kuester D, Limpens J, Schmitt J. Efficacy and safety of systemic treatments for moderate-to-severe atopic dermatitis: a systematic review. J Allergy Clin Immunol. 2014 Feb;133(2):429-38. PubMed

Relevant to FAQ2, FAQ3, FAQ4

- **Study design:** systematic review of randomized trials
  - open-label extensions of randomized trials were also included
- **Population:** patients with moderate-to-severe atopic dermatitis
  - because of absence of established definition of moderate-to-severe atopic dermatitis, trials were eligible when including patients defined as follows
    - "patients with moderate-to-severe AD [atopic dermatitis]"
    - "patients with non-adequately controlled AD despite the use of topical anti-inflammatory therapy"
    - patients with moderate-to-severe AD according to severity criteria
      - Rajka and Langeland score > 4.52
      - SCORAD score > 20%
      - total body surface area > 10%
  - trials including mixed population of different dermatologic conditions were only included if results from subgroup of AD patients were reported separately
- **Intervention:** immunomodulating systemic treatments
- **Comparison:** placebo or any other intervention
  - not mentioned in Eligibility criteria but inferred from trials included

- **Study inclusion criteria:**

- trial reported "clinical outcome" (clinical signs) or patient-reported outcome
- published before June 2012 (search window close date)

- **Number of studies:** 34
  - 34 is total number of trials evaluating all systemic treatments
  - 16 trials evaluated scoped treatments
    - 13 evaluated cyclosporine all of which reported short-term outcomes only
      - 4 placebo-controlled
        - 3 included only adults
          - Munro 1994 (ref 27)
          - Sowden 1991 (ref 37)
            - Salek 1993 (ref 32) is a secondary publication of Sowden 1991 which reports the quality of life outcome
              - Roekevisch 2014 did not note that Salek 1993 and Sowden 1991 were the same trial and therefore reported that cyclosporine was "...compared to placebo in 5 RCTs..." but it was only 4
          - Wahlgren 1990 (ref 41)
            - not clear why this trial was not included (or mentioned) in either Schmitt 2007A or 2007B
        - 1 included both adolescents and adults, but mostly adults
          - van Joost 1994 (ref 39)
            - reported by Roekevisch 2014 to include "Adults + children" but majority adults based on
              - age range is 17 to 68 (Table E3)
      - 5 were head-to-head comparisons with other treatments
        - enteric-coated mycophenolate sodium in 1 trial in adults (Haeck 2011, ref 18)
        - prednisolone in 1 trial in adults (Schmitt 2010, ref 33)
          - as noted in scoping, we are providing descriptive responses only for the systemic corticosteroid option
        - non-scoped option for 3 other trials
          - immunoglobulin IV, UV phototherapy, tacrolimus
      - 1 compared new vs. old cyclosporine formulation
      - 3 were dose finding studies
        - GRADE table Conclusion (and GRADE rating)
          - Higher dosages of CsA are more effective than lower dosages of CsA in patients with severe AD. Further research is very unlikely to change our confidence in the estimate of effect." (rated as High quality)
    - 3 evaluated azathioprine
      - 2 placebo-controlled trials, which included both children and adults but mostly adults
        - Berth-Jones 2002 (ref 12)
          - reported by Roekevisch 2014 to include "Adults + children" but mostly adults based on

                - 'Inclusion criteria' for 'Age' was "≥ 16 years" (Table E3)
                - abstract, which says mean (range) of included participants was 38 (17 to 73)
            - Meggitt 2006 (ref 26)
                - reported by Roekevisch 2014 to include "Adults + children" but mostly adults based on
                    - mean age of 30 (azathioprine group) to 36 (placebo group) (Table E3)
                    - 'Inclusion criteria' for 'Age' was "16-65 years" (Table E3)
        - 1 head-to-head comparison with methotrexate in adults
            - Schram 2011A (ref 34)
- **Number of participants:** 1,653
    - 1,653 is total number of participants across all 34 trials
- **Duration of follow-up:** 41 to 48 weeks maximum
    - Table E2 'Trial duration' column
        - 41 weeks for placebo-controlled trials relevant to this evidence report (Wahlgen 1990, ref 41)
        - 48 weeks for head-to-head trials comparing treatments relevant to this evidence report (Haeck 2011, ref 18)
        - 52 weeks for 3 non-relevant trials of cyclosporine (2 comparing different cyclosporine regimens, 1 comparing cyclosporine to UV phototherapy)

- **Results:**
    - Efficacy
        - Although this review authors stated an intent to meta-analyze (via a random-effects model) if RCTs were "qualitatively homogeneous", they do not present any such results, and this is consistent with the heterogeneous nature of the evidence seen in this SR and others summarized in Critical Appraisal (e.g., Hoare 2000).
        - This review provides a useful summary of the available trials for our scoped options and the outcomes they report but it does not provide optimal reporting of efficacy outcome data for extraction
            - Table II (main paper) and Table E4 (Supplement) report within-group differences but no indication of between-group differences
                - Table II reports results for clinical sign outcomes only (those assessed by a clinician, such as SCORAD and SASSD) and Table E4 reports other outcomes (including some patient-assessed outcomes)
            - Results text provides no additional information beyond tables
        - Efficacy of agents vs. placebo/control
            - Various within-group differences are reported as above-noted
            - GRADE table Conclusion (and GRADE rating)
                - cyclosporine
                    - "CsA [cyclosporine A] is effective in patients with moderate-to-severe AD. Further research is likely to have an important effect on our confidence in the

estimate of effect and might change our recommendation." (rated as "Moderate quality")
        - azathioprine
            - "AZA is effective in many patients with moderate-to-severe AD. Any estimate of effect in future research is very uncertain." (rated as Very low quality)
- Two small trials reported head-to-head comparison between scoped options, and both were reported to show no difference in Results text, Results tables, and GRADE table
    - Comparison of cyclosporine vs. mycophenolate (Haeck 2011, n = 50)
        - Results text described findings as "...CsA [cyclosporine A] was... similarly efficacious as EC-MPS [enteric-coated mycophenolate sodium]"
        - Table E4 shows mean improvements in SCORAD scores of 17% vs. 0% at the maintenance phase (0 to 30 weeks) for cyclosporine vs. mycophenolate, but these were within-group differences, thus not clearly supporting comparability
            - full-text was obtained, which confirmed no clear difference at 30 weeks as assessed by the between-group mean difference (95% CI) for the SCORAD score (Fig 2): 1.3 (-4.0 to 6.6)
                - the remainder of the pattern of the data do not suggest clear/meaningful differences; statistically-significant differences at the 3- and 6-week period are of questionable importance, do not align with our pre-specified timepoints in Scoping, and could be entirely attributable to the expected onset of action for these agents (see 'Other considerations' below)
            - Haeck 2011 also "presented the number of patients in [one of three DLQI] categories", but they report they "did not formally analyze differences"; they nominally discuss some of these results, but do not provide data that are readily interpretable for meaningful analysis, and their presentation of trichotomized groups of the DLQI is questionable (as opposed to reporting the DLQI data in their native form)
        - GRADE table Conclusion (and GRADE rating)
            - "CsA and EC-MPS might be equally effective as a maintenance treatment in some patients with severe AD, but our confidence in the effect is very low. Any estimate of effect in future research is very uncertain." (rated as "Very low quality")
                - Downgrades from Roekevisch include risk of bias (two downgrades) and publication bias (one downgrade). We would add downgrades for imprecision, inconsistency, and indirectness due to the nature of this comparison coming

from a single, small trial (leading to imprecision and an inability to assess consistency of findings) and the outcome being clinician-assessed rather than patient-reported (thus leading to indirectness). However, given the certainty is already Very low from the risk of bias and publication bias downgrades, these additional downgrades would not further reduce the GRADE rating of this outcome.

- Comparison of azathioprine vs. methotrexate (Schram 2011A, n = 42)
  - Results text described findings as "AZA and MTX were found to be equally efficacious"
  - Table E4 shows within-group % mean improvements SCORAD and quality of life (Skindex) at 12 weeks
    - % mean improvement SCORAD score at 12 weeks 39% vs. 42%
      - full text obtained for means and SDs from which to compute a between-groups mean difference (95% CI), which yielded 1.9 (95% CI -7.6 to 11.4)
    - % mean improvement Skindex score at 12 weeks 20% vs. 26%
      - full text obtained for means and SDs from which to compute a between-groups mean difference (95% CI), which yielded 3.7 (95% CI -3.6 to 11.0)
    - Schram 2011A also reports POEM scale outcomes:
      - full text obtained for means and SDs from which to compute a between-groups mean difference (95% CI), which yielded 1 (95% CI -3.3 to 5.3)
    - Schram 2011A also reports outcomes for the EASI scale, VAS itch score, and VAS sleeplessness score, all showing no clear difference
  - GRADE table Conclusion (and GRADE rating)
    - "MTX and AZA are both equally effective in patients with severe AD and might be considered as a treatment option. Further research is likely to have an important effect on our confidence in the estimate of effect and might change our recommendation." "(Moderate quality)"
      - We disagree with this rating and assess the certainty as Very low, with downgrades due to risk of bias (incomplete blinding), imprecision (small trial), and inconsistency (cannot assess consistency given a single trial)

- Adverse events
  - cyclosporine
    - any serious adverse event (weekly rate)
      - 0% in 9 included studies

        - one study was comparing different regimens of cyclosporine and had one arm with a 0% rate and one arm with a 0.10% rate
        - four were studies addressing scoped comparisons: Haeck 2011 ref 18, Munro 1994 ref 27, Schmitt 2010 ref 33, Wahlgren 1990 ref 41
      - 2.2% in 1 study which addressed scoped comparison (also reported 2.2% in the placebo group): van Joost 1994 ref 39
      - 2 studies did not report serious adverse events
      - remainder of studies reported serious adverse events in <1%, and only remaining placebo-controlled trial (Sowden 1991/Salek 1993) had a higher reported risk in the placebo group
    - withdrawals because of adverse events (weekly rate)
      - 0% in 8 included studies
        - one study was comparing different doses of cyclosporine and reported 0% in the lower-dose arm and 0.7% in the higher-dose arm
        - one study was comparing a short course to a continuous course of cyclosporine and reported 0.0% in the continuous course and 0.2% in the short course
        - two were studies addressing scoped comparisons: Salek 1993 ref 32/Sowden 1991 ref 37 and Wahlgren 1990 ref 41
      - 2% in one study which addressed scoped comparison (vs. 3.6% in the corticosteroid arm): Schmitt 2010 ref 33
      - 1 study did not report withdrawal due to adverse events
      - remainder of studies were all ≤0.5% (not including the one study aforementioned with a rate of 0.7%)
        - this includes Haeck 2011, which reported 0.3% for both the mycophenolate and cyclosporine groups
  - azathioprine
    - any serious adverse event (weekly rate)
      - 0% in 2 trials (Berth-Jones 2002 ref 12, Schram 2011A ref 34)
      - not reported in 1 trial (Meggitt 2006 ref 26)
    - withdrawals because of adverse events
      - weekly rate
        - 0.2% in 1 trial (Schram 2011A ref 34)
          - vs. 0.4% in methotrexate arm
        - 0.4% in 1 trial (Meggitt 2006 ref 26)
          - vs. 0.10% in placebo arm
      - not reported in 1 trial (Berth-Jones 2002 ref 12)
      - reported to be 9% at 24 weeks, but unclear which trial(s) informed this statement

- **Other considerations:**
  - Among the 16 trials that evaluated scoped treatments (summarized above), only 1 head-to-head trial qualified as "long-term", defined by review authors as active treatment of ≥ 16 weeks duration

        - head-to-head comparison of cyclosporine vs. enteric-coated mycophenolate sodium in adults (Haeck 2011, ref 18)
    - Haeck 2011 (comparison of cyclosporine vs. enteric-coated mycophenolate sodium) was interpreted by Roekevisch 2014 as suggesting no clear difference in the treatments. The abstract of Haeck 2011 highlighted "higher" SCORAD scores in the mycophenolate group during "the first 10 weeks" of treatment. However, we do not consider that focus to be the best reflection of the totality of data in Haeck 2011 (i.e., we agree with the assessment of Roekevisch 2014 of no clear difference). Although there were statistically-significant mean differences at the 3- and 6-week timepoints, these differences are of questionable clinical significance, and perhaps more importantly, all other timepoints (10, 14, 18, 22, 26, and 30 weeks) fail to demonstrate any clear difference. Additionally, focusing on the 3- and 6-week timepoints simply because they happened to be statistically significant would not only run the risk of selective outcome reporting / outcome interpretation, but it would also contradict our pre-defined approach for addressing outcomes at the short- and long-term. These differences could also be entirely attributable to the expected onset of action for these agents
    - Schmitt 2007B was a systematic review of systemic treatments for patients with severe eczema
        - included only 1 of the trials of azathioprine (Berth-Jones 2002) but did not include the other two because they were published after the review's search window close (Schram 2011A, Meggitt 2006)
        - provided no additional information about cyclosporine trials (see Schmitt 2007A summary, 'Other considerations'

SCHMITT 2007A
Schmitt J, Schmitt N, Meurer M. Cyclosporin in the treatment of patients with atopic eczema – a systematic review and meta-analysis. J Eur Acad Dermatol Venereol. 2007 May;21(5):606-19. PubMed

Relevant to FAQ2, FAQ4

- **Study design:** systematic review of randomized trials and observational studies
    - summary focuses only on the 3 placebo-controlled randomized trials
- **Population:** patients with severe atopic eczema
    - "severe" is mentioned in Introduction only (not in Methods)
- **Intervention:** cyclosporin
- **Comparison:** placebo
    - review included randomized trials comparing cyclosporin vs. placebo and alternative interventions (ie, topical tacrolimus only) and different dosages and formulations of cyclosporine, but only the data from the 3 placebo-controlled trials were extracted

- **Study inclusion criteria:**
    - > 4 patients

- **Number of studies:** 3
    - 3 placebo-controlled randomized trials
        - 15 studies overall
- **Number of participants:** 103
    - summed number of participants in 3 placebo-controlled trials

- **Duration of follow-up:** 6 to 8 weeks for 3 placebo-controlled trials
  - 6 weeks in van Joost 1994
  - 8 weeks in Sowden 1991 and Munro 1994

- **Results:**

Characteristics of 3 placebo-controlled randomized trials of cyclosporine treatment of 6 to 8 weeks in adults with severe eczema*

Study	Number of participants	Inclusion criteria regarding severity of atopic eczema	Concurrent treatment
Sowden 1991	33	inadequately controlled by conventional therapies	topical steroids
Munro 1994	24	no definition of severity of atopic eczema	topical steroids
van Joost 1994	46	resistant to conventional therapies	antihistamines

* All 3 trials used an initial dose of 5 mg/kg bodyweight and none allowed dose adjustment

Clinical severity outcome measurement and results for comparison of cyclosporine vs. placebo for 6 to 8 weeks in adults with severe eczema

Study*	Outcome measurement		Results
	Primary Outcome	Components	Comparative efficacy
Sowden 1991	non-validated score	erythema, purulence, excoriation, dryness, fissuring, lichenification, extent	mean severity score with cyclosporine vs. placebo: 16.5 vs. 40.5; $p < 0.01$
Munro 1994	extent, erythema, excoriation	no composite score applied	mean extent after cyclosporine vs. placebo: 2% BSA vs. 14% BSA; $p < 0.01$
van Joost 1994	6-Area, Total Body Severity Assessment	erythema, vesiculation, excoriation, dryness, infiltration, fissures, extent	significant superiority of cyclosporine; $p < 0.05$

*2 trials had crossover design (Sowden 1991, Munro 1994) but Methods specified that only the study period prior to cross-over was considered to avoid risk of bias due to carry-over effects

Review authors' ratings of individual quality criteria and overall study quality

Study	Clear case Definition	Clearly Defined Eligibility Criteria	Adequate Description Of study Population	Double blind Treatment	Validated Outcome	Follow-up Rate > 80%	ITT analysis	Overall study quality*
Sowden 1991	yes	yes	yes	yes	no	no	no	moderate
Munro 1994	no	no	no	yes	no	no	no	poor
van Joost 1994	yes	yes	yes	yes	yes	no	yes	good

* Good: 6–7 quality criteria were appropriately met; Moderate: 4–5 quality criteria were appropriately met; Poor: 0–3 quality criteria were appropriately met. This method of evaluating study quality was devised by the review authors and has not been validated.

Withdrawals due to adverse events*

Study	Withdrawals due to adverse events in intervention group (n/% per month of treatment)
Sowden 1991	0
Munro 1994	1/2.1%
van Joost 1994	1/2.9%

* Withdrawal numbers in Table 4 were reported for the intervention group only for these 3 placebo-controlled trials. Table 4 also reported this outcome from the non-placebo-controlled trials (eg, comparison of different doses for which numbers were reported for both arms). We did not extract this data from Schmitt 2007A and instead extracted it from Roekevisch 2014, which was a more current SR that reported both withdrawals due to adverse events and serious adverse events (not a reported outcome in Roekevisch 2014). Both SRs of randomized trials consistently reported low rates.

SCHMITT 2007B

Schmitt J, Schäkel K, Schmitt N, Meurer M. Systemic treatment of severe atopic eczema: a systematic review. Acta Derm Venereol. 2007;87(2):100-11. PubMed

Relevant to FAQ4

- **Study design:** systematic review of randomized trials and observational studies
  - review included 3 placebo-controlled randomized trials of scoped agents
    - 2 for cyclosporine - Sowden 1991 and van Joost 1994
      - did not include or mention
        - Munro 1994 (included in both Schmitt 2007A and Roekivisch 2014)
        - Wahlgren 1990 (included in Roekivisch 2014 but not included or mentioned in Schmitt 2007A)
    - 1 for azathioprine – Berth-Jones 2002
      - The other placebo-controlled trial of azathioprine (Meggitt 2006) was published after closure of search window
- **Population:** patients with severe atopic eczema ("could not be controlled adequately with conventional topical therapies")
- **Intervention:** cyclosporine and azathioprine
  - scoped interventions included in this SR
- **Comparison:** placebo or another scoped agent
  - included only placebo-controlled trials of scoped agents cyclosporine and azathioprine
  - 3 head-to-head trials of scoped agents were published later (Schram 2011A, Haecke 2011, Schmitt 2010)

- **Study inclusion criteria:**
  - no additional

- **Number of studies:** 3

  - 3 relevant trials of scoped agents
- **Number of participants:** 116
  - n = 79 combined from 2 trials of cyclosporine (Sowden 1991 [n = 33] and van Joost 1994 [n = 46])
  - n = 37 in trial of azathioprine (Berth-Jones 2002)
- **Duration of follow-up:** 6 to 12 weeks for 3 placebo-controlled trials
  - 6 weeks in van Joost 1994
  - 8 weeks in Sowden 1991
  - 12 weeks in Berth-Jones 2002

- **Results:**
  - This SR reported limited information about the 3 trials of interest and was mainly used to cross-check whether any new or different methods or outcomes were reported in this SR that had not been reported (or had been reported differently) in Schmitt 2007A or Roekevisch 2014 for cyclosporine and in Schram 2011B or Roekevisch 2014 for azathioprine.
    - for 3 relevant trials, the results were reported only as % reduction in intervention group and not as between group differences so this SR was not useful for outcome data extraction
    - serious adverse events and withdrawals due to adverse events were reported in Table II and these were compared against the outcomes previously extracted into other summaries (when available)
      - for the 2 cyclosporine trials, both outcomes reported in Table II were identical to those previously included in Schmitt 2007A summary
      - for azathioprine trial (for which adverse events were not previously extracted), serious adverse events were "not reported" and withdrawals due to adverse events were reported as n = 4 and 3.6% per month of treatment
    - Table III. Summary of study quality
      - discrepancies
        - randomization concealment reported as not adequate for all 3 trials in Schmitt 2007B but Schram 2011B reported this as adequate for Berth-Jones 2002 in their Table 4. Risk of Bias of Included Randomized Controlled Trials
        - validated outcome for van Joost 1994 reported as not met in Schmitt 2007B but as met in Schmitt 2007A

SCHRAM 2011B

Schram ME, Borgonjen RJ, Bik CM, van der Schroeff JG, van Everdingen JJ, Spuls PI; Off-Label Working and Project Group of Dutch Society of Dermatology and Venereology. Off-label use of azathioprine in dermatology: a systematic review. Arch Dermatol. 2011 Apr;147(4):474-88. PubMed

Relevant to FAQ2, FAQ4

- **Study design:** systematic review of randomized trials and observational studies
  - included randomized controlled trials, cohorts, and case series

    - we used this SR specifically to extract information about the 2 placebo-controlled trials of azathioprine in patients with severe atopic dermatitis
- **Population:** patients with severe atopic dermatitis
    - dermatology patients for SR overall; population above is our population of interest
- **Intervention:** azathioprine
    - used in an off-label dermatologic setting
- **Comparison:** placebo or another treatment

- **Study inclusion criteria:**
    - > 5 patients

- **Number of studies:** 2 randomized trials in patients with severe atopic dermatitis relevant for our research question
    - 43 studies total included in review
- **Number of participants:** 98
    - n = 37 in Berth-Jones 2002 crossover design trial
    - n = 61 in Meggitt 2006 parallel design trial
- **Duration of follow-up:**
    - Berth-Jones 2002 – crossover trial with total treatment duration of 6 months, where each treatment period was 3 months
    - Meggitt 2006 – parallel trial with treatment duration of 3 months; results reported in table below are from end of treatment

- **Results:**

Results of placebo-controlled randomized trials of azathioprine in adults with atopic dermatitis*

Study	Number of patients	Efficacy	Serious adverse events	Withdrawals
Berth-Jones 2002 (crossover trial)	37	reduction in disease severity as assessed by SASSAD: azathioprine 10.2 points (26%) vs. placebo 1.0 points (3%); between groups: p < 0.01	0	12/37 during azathioprine (4 because of adverse events); 4/37 during placebo (no. because of adverse events not reported)
Meggitt 2006 (parallel trial)	61	reduction in disease severity as assessed by SASSAD: azathioprine 12.0 points (37%) vs placebo 6.6 points (20%); difference: 5.4 (95% CI, 1.4 to 9.3) and 17% (4.3% to 29%)	0	6/41 in azathioprine group and 1/20 in placebo group

* Both trials used topical corticosteroid co-intervention; daily dose was 2.5 mg/kg in Berth-Jones 2002 and 0.5-2.5 mg/kg in Meggitt 2006 (Meggitt 2006 dosed according to thiopurine methyltransferase activity)

Risk of bias of placebo-controlled randomized trials of azathioprine in adults with atopic dermatitis

Study	Adequate randomization	Adequate allocation concealment	Adequate masking*	Adequate completeness of data reported	Free of selective reporting?	Free of other bias?
Berth-Jones 2002	yes	yes	yes	unclear	yes	yes
Meggitt 2006	yes	yes	yes	yes	yes	yes

* Both trials were reported to have adequate masking of participants, researchers, and outcome assessors

- **Other considerations:**
  - Schram 2011B only reported the disease severity outcome as above-noted, so we also assessed the trials for quality of life information. Meggitt 2006 also assessed DLQI (scale from 0 to 30) and reported differences from baseline in each group and a difference in differences from baseline among the 53 patients completing treatment (35/41 in the azathioprine group and 18/20 in the placebo group): 5.9 vs 2.4, mean difference 3.5 (95% CI 0.3 to 6.7).
    - Meggitt 2006 did not conduct a "standard" randomized trial in the typical sense of the principle. Instead, they used a method called minimization, which does not rely solely on random allocation, but instead uses a technique (called minimization) to help ensure baseline differences are minimized.

SEGER 2019

Seger EW, Wechter T, Strowd L, Feldman SR. Relative efficacy of systemic treatments for atopic dermatitis. J Am Acad Dermatol. 2019 Feb;80(2):411-416.e4. PubMed

Relevance to FAQs not applicable

- **Study design:** systematic review of randomized trials
- **Population:** patients with moderate-to-severe atopic dermatitis
  - reported to be defined as per criteria as described by Hanifin and Rajka (Hanifin 1980)
- **Intervention:** systemic treatments
- **Comparison:** any
  - not specified and assumed to be any

- **Study inclusion criteria:**
  - reported information on treatment efficacy using validated outcome measures

- **Number of studies:** 41
  - 41 trials of 17 systematic treatments included in review but no studies for scoped options had useful, extractable data
- **Number of participants:** 4,938

Results:

No relevant data could be extracted for included trials because although the authors describe a systematic search process and document the results of that search with respect to the included studies, the results from those studies were not clearly reported in a systematic or transparent manner, thus

bringing into question the reliability of the reported results from the studies. For example, for results reporting of cyclosporine, the Results text reported the results of the SASSD outcome in the intervention group for only 2 trials, neither of which were among the 4 placebo-controlled trials included in Hoare 2000 summary. Although Seger 2019's methods state a focus on validated outcome measurements (which could explain why some of the trials in Hoare 2000 are not mentioned in this section), it seems Seger 2019 may have missed outcomes; for instance, they appear to have missed the outcome from Sowden 1991, which reported disease activity on the SASSD scale despite not explicitly calling it such. Additionally, *Table I. Drug efficacy in adult placebo-controlled trials* did not include references, so it was not clear which studies the data reported in this table were compiled from, they do not report if pooling was done (and if so, how), and they also reported data for the "most efficacious dose" for many treatments (thus possibly introducing a biased estimate).

However, Seger 2019 was helpful in that it served as a source for citation tracing, which identify a trial comparing cyclosporine vs. methotrexate which had not previously been identified (Goujon 2018).

WANG 2018

Wang FP, Tang XJ, Wei CQ, Xu LR, Mao H, Luo FM. Dupilumab treatment in moderate-to-severe atopic dermatitis: A systematic review and meta-analysis. J Dermatol Sci. 2018 May;90(2):190-198 PubMed

Relevant to FAQ2, FAQ3

- **Study design:** systematic review of double-blind randomized controlled trials
- **Population:** adults with moderate-to-severe atopic dermatitis ≥ 3 years before screening visit
    - based on either cutoff of scores on disease severity scales or documented history of inadequate response to topical treatments ≤ 6 months before screening
- **Intervention:** dupilumab subcutaneous
    - SR authors reported that they only analyzed the effects of dupilumab 300 mg once weekly and 300 mg every 2 weeks (as reported in 6 trials) because these were the most common dosages among the trials
        - 2 trials included only dupilumab 300 mg once weekly
        - 4 trials included dupilumab 300 mg once weekly and dupilumab 300 mg every 2 weeks arms
        - the approved maintenance dose is 300 mg every 2 weeks (if <60 kg, 200 mg every 2 weeks)
    - 2 of the 6 trials used a topical corticosteroid cointervention
- **Comparison:** placebo

- **Study inclusion criteria:**
    - reported the following outcomes
        - Eczema Area and Severity Index
        - Investigator's Global Assessment
        - Pruritus numeric rating scale
        - Percent body surface area affected with AD
        - Dermatology Life Quality Index
        - Adverse events

- SR authors reported that trials published only in abstract form "were excluded because the data could not be fully analyzed"

- **Number of studies:** 6
  - 7 trials reported only in abstract form were excluded
- **Number of participants:** 2,447
- **Duration of follow-up:**
  - duration of treatment ranged from 4 to 52 weeks
    - 1 trial each had treatment durations of 4, 12, and 52 weeks
    - 3 trials had treatment duration of 16 weeks

- **Results and certainty:**

Dupilumab vs. placebo on reported outcomes

Outcome	No. Studies	No. Patients		Effect size (95% CI)*	Certainty (downgrade)
		dupilumab	placebo		
Eczema Area and Severity Index	6	1,481	1,634	SMD -0.89 (95% CI -1.0 to -0.78)	Moderate (publication bias)[1]
Investigator's Global Assessment†	6	1,481	1,634	RR 3.82 (95% CI 3.23 to 4.51)	Moderate (publication bias)[1]
Percentage body surface area affected with AD	6	1,481	1,634	SMD -0.83 (95% CI -0.90 to -0.75)	Moderate (publication bias)[1]
Pruritus numeric rating scale	6	1,481	1,634	SMD -0.81 (95% CI -0.96 to -0.66)	Moderate (publication bias)[1]
Dermatology Life Quality Index	5	1,405	1,570	SMD -0.78 (95% CI -0.89 to -0.66)	Moderate (publication bias)[1]

RR = risk ratio; SMD = standardized mean difference

* No evidence of heterogeneity of treatment effect for 300 mg weekly vs. every 2 weeks in any of the outcomes reported here or for the effect size of the 52-week trial vs. the trials of a shorter duration

† defined as proportion of patients achieving Investigator's Global Assessment of response which was clear (score of 0) or almost clear (score of 1)

1 All outcomes were downgraded for risk of publication bias because Wang 2018 note "7 potentially relevant RCTs which had been published as an abstract only were excluded owing to data unavailable." Review authors did not identify any (other) risk of bias downgrades. Although many of the scales are clinician-assessed (e.g., Eczema Area and Severity Index, Investigator's Global Assessment), we did not downgrade for indirectness given the consistent benefit shown across all scales measured, including patient-reported outcome measures like the Dermatology Life Quality Index (and one would not expect the Dermatology Life Quality Index scale to show benefit if the patient did not also experience benefit in patient-reported outcomes gauging disease severity).

- **Other considerations:**
  - The single long-term (52-week) trial included in this meta-analysis is LIBERTY AD CHRONOS (Blauvelt 2017). As one can see from the weights in the meta-analyses, the meta-analytic estimates are largely comprised of the data from LIBERTY AD CHRONOS and the 2 SOLO trials (each of 16 weeks' duration; Simpson 2016); this is not surprising given these 3 trials contributed 86.6% of the 2,447 patients included in this systematic review. In an attempt to evaluate whether the effects from LIBERTY AD CHRONOS suggested an attenuation in efficacy over time, we considered the effects of LIBERTY AD CHRONOS and the SOLO trials against each other and against the overall meta-analytic

estimates. To facilitate this comparison, we include below the SMD (95% CI) results for these trials for the analysis of dupilumab 300 mg every other week; this dose matches clinical use, though as above-noted, there was no heterogeneity for treatment effect in the overall meta-analytic estimates based on weekly or every other week dosing.

- EASI
  - LIBERTY AD CHRONOS: -0.75 (-0.99 to -0.50)
  - SOLO 1: -0.77 (-0.97 to -0.58)
  - SOLO 2: -0.90 (-1.09 to -0.71)
- Investigator's Global Assessment (RR, not SMD)
  - LIBERTY AD CHRONOS: 2.88 (1.88 to 4.39)
  - SOLO 1: 3.62 (2.37 to 5.53)
  - SOLO 2: 4.30 (2.73 to 6.75)
- Percentage body surface area affected with AD
  - LIBERTY AD CHRONOS: -0.99 (-1.24 to -0.74)
  - SOLO 1: -0.76 (-0.95 to -0.56)
  - SOLO 2: -0.87 (-1.06 to -0.68)
- Pruritus numeric rating scale
  - LIBERTY AD CHRONOS: -0.68 (-0.93 to -0.43)
  - SOLO 1: -0.54 (-0.73 to -0.35)
  - SOLO 2: -0.79 (-0.97 to -0.60)
- Dermatology Life Quality Index
  - LIBERTY AD CHRONOS: -0.92 (-1.17 to -0.67)
  - SOLO 1: -0.54 (-0.73 to -0.35)
  - SOLO 2: -0.84 (-1.03 to -0.66)

As a result of the above, we considered LIBERTY AD CHRONOS to provide evidence that efficacy may last up to 52 weeks, and we did not consider the available data to provide clear evidence of attenuation in efficacy over time.

- for adverse events
  - severe adverse events and adverse events leading to discontinuation were not reported
  - "most common" adverse events were reported to be "nasopharyngitis, exacerbation of atopic dermatitis, headache, and upper respiratory tract infection"
- all included trials were funded by pharmaceutical company
- time point used for analysis not reported but assumed to be end of treatment

Evidence report for systemic treatment of patients with moderate to severe atopic eczema

Reference list

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May 12, 2020

Prepared by EBSCO Health Innovations and EBM Development Department:

Martin Mayer, DMSc, MS, PA-C, Clinical Evidence Synthesizer

Eric Manheimer, PhD, EBM Editor

Brian S. Alper, MD, MSPH, FAAFP, FAMIA, Chief Medical Knowledge Officer

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