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# EVIDENZREPORT ZUR S3-LEITLINIE "ATOPISCHE DERMATITIS" AWMF-REGISTER-NR.: 013 - 027, 2023

Die hier enthaltenen Dokumente wurden aus dem Evidence Report der EuroGuiDerm Atopic Eczema Guideline (teils modifiziert) übernommen. Den vollständige Bericht finden Sie unter https://www.edf.one/home/Guidelines/EuroGuiDerm-2022.html

1. ***QUESTION: What is the efficacy (improvement in short term disease control [signs and symptoms] as well as quality of life) and safety of conventional and novel systemic therapies for the treatment of AE?***

<table>
<tr><th colspan="2">What is the efficacy (improvement in short term disease control [signs and symptoms] as well as quality of life) and safety of conventional and novel systemic therapies for the treatment of AE?</th></tr>
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<tr><td>Comparison:</td><td>Direct, indirect and placebo comparisons</td></tr>
<tr><td>Main outcomes:</td><td>- Clinical signs: Eczema Area and Severity Index (EASI);<br>- Overall disease severity as measured by the composite score SCORing of Atopic Dermatitis (SCORAD) index;<br>- Patient-reported symptoms: Patient-Oriented Eczema Measure (POEM);<br>- Quality of life: Dermatology Life Quality Index (DLQI), Children’s Dermatology Life Quality Index (CDLQI), Infant's Dermatitis Quality of Life Index (IDQOL);<br>- Objective SCORAD (o-SCORAD);<br>- Patient-oriented SCORAD (PO-SCORAD);<br>- Investigator’s Global Assessment (IGA);<br>- Visual analogue scale itch (VAS-itch);</td></tr>
</table>

| | |
|---|---|
| | - Typical adverse events: clinically relevant serious adverse effects of each systemic treatment, such as infection with all agents, conjunctivitis with the new biologic agents, renal function impairment and hypertension with cyclosporine, and gastrointestinal side effects with methotrexate. |
| Setting: | Region: Europe , dermatologists and allergists in clinical practice |
| Perspective: | Clinical recommendation – population perspective |
| Background: | - New topical and systemic treatments for atopic eczema have been developed and approved.<br>- Several guidelines for the treatment of atopic eczema exist, but recommendations vary[1] and evidence-based recommendations for novel treatments are needed.<br>- Different prescribing practices between dermatologists across Europe and lack of experience in particular with systemic treatments have been reported.[2] There is therefore a need for current guidance and treatment algorithms on conventional and emerging therapies. Besides, expert consensus advice on managing patients in special circumstances such as during pregnancy or, for example, with allergic comorbidities is essential.[3]<br>- There is also a lack of clear guidance on switching patients from one systemic therapy to another and combined systemic therapy. |

## Assessment

| Problem Is the problem a priority? |
|---|
| The problem is relevant for all stakeholders. Patients with moderate to severe forms of AE maybe treated with systemic immunosuppressive or immunomodulatory treatments but only ciclosporin, dupilumab, tralokinumab, abrocitinib, baricitinib and upadacitinib are approved for this use in Europe, leaving a vast majority of affected persons with unmet medical needs that require prescriptions for off label agents.<br><br>A scoping search was carried out in MEDLINE Ovid the 17 March 2020, to identify current needs and perspectives related to AE treatment taking into account patients, caregivers and healthcare professionals. We identified 12 studies reporting on stakeholder needs, experiences and preferences.<br><br>**Patients and parents needs/preferences:**<br><br>In Germany, 1,678 AE patients indicated the following needs to be quite important/very important: 'to be free of itching' (96.0%), 'to get better skin quickly' (87.8%) and 'to be healed of all skin defects' (85.7%), 'to no longer have burning sensations on your skin' (83.0%), 'to regain control of disease' (81.9%) and 'to have confidence in therapy' (81.2%).[4] |

A cross-sectional study with 1,111 AE patients and parents from 34 countries evaluated the importance of symptoms taking into account patient´s perspectives. Ten items were evaluated as 'most important' or 'very important' by 80% or more of the participants. Of these, itch and pain/soreness were the most important items for assessing treatment response. Skin feels hot or inflamed, bleeding, involvement of visible or sensitive body sites, cracks, sleep difficulties, amount of body affected and weeping/oozing were also important.[5]

A qualitative study interviewing 32 mothers with children of one-year and then at two years of age identified the following straining factors: sudden reactions, living with scratching and pain, skin care, skin reactions during lactation, lactation stop due to allergic symptoms and child waking up at night because of itching.[6]

In the Netherlands, AE patients (n=139) and psoriasis patients (n=80) reported preference to share treatment decisions with their doctor for topical therapy (45%), phototherapy (40%) and systemic therapy (39%). Physicians (n=147) also preferred to make shared decisions for phototherapy and systemic therapy (59%). Barrier identified by patients was lack of continuity of care by the same physician (72%) and by dermatologists lack of time (38%).[7]

**Healthcare professional needs:**

The TREAT survey from 2013 reported data on prescribing practice for refractory pediatric atopic eczema and found varying prescribing practices among 343 physicians in eight European countries. The first line systemic agents of choice were at that time: ciclosporin (43.0%), oral corticosteroids (30.7%), azathioprine (21.7%), methotrexate (0.8%) and mycophenolate mofetil MMF (0.5%). Majors factors identified as discouraging were potential side effects (82.8%) and long-term organ toxicity (81.1%).[8]

Vermeulen et al. found different prescribing practices among 229 dermatologists across Europe and a lack of experience in particular with systemic treatments was reported.[2] First line systemic treatment in adults were*:* ciclosporin (n=118; 54.1%), followed by off-label oral corticosteroids (n=71; 32.6%) and methotrexate (n=67; 30.7%). Only 12 (5.5%) and four (1.8%) participants prescribed azathioprine and mycophenolic acid respectively, as first line choice of treatment.

**Indirect evidence:**

From the scoping search, five studies[9-13] were related to topical treatment with patients reporting poor adherence, not following instructions properly and phobia due to possible side effects and lack of information. Kosse et al. reported patient's preference for faster and long-lasting effects[11]. One additional study described patient's experiences of using silk garments.[14]

Desirable Effects – short term: How substantial are the desirable anticipated effects for drugs currently in use?

Network meta-analysis based on 60 RCTs with 16,579 AE patients. For clinical relevance we presented an excerpt of effect estimates for the networks of medications currently used in clinical practice or expected to be available soon (azathioprine, methotrexate, cyclosporine, dupilumab, abrocitinib, baricitinib, tralokinumab, upadacitinib, and placebo) in adult patients receiving 8 to 16 weeks of treatment modified from Drucker et al.).[15]

**A complete overview of all analyses performed as part of the living systematic review can be found on https://eczematherapies.com/research/**

| Medication and dose (all against placebo) | Mean difference in EASI score (95% CrI[+]) | Certainty of evidence (GRADE) | Standardized mean difference in signs (95% CrI) | Certainty of evidence (GRADE) | Mean difference in POEM score (95% CrI) | Certainty of evidence (GRADE) | Mean difference in peak pruritus NRS (95% CrI) | Certainty of evidence (GRADE) | Mean difference in DLQI score (95% CrI) | Certainty of evidence (GRADE) | Standardized mean difference in QoL score (95% CrI) | Certainty of evidence (GRADE) | Standardized mean difference in itch score (95% CrI) | Certainty of evidence (GRADE) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Ranking[++] SUCRA | | Ranking SUCRA | | Ranking SUCRA | | Ranking SUCRA | | Ranking SUCRA | | Ranking SUCRA | | Ranking SUCRA | |
| Abrocitinib, 100 mg/d | -8.6 (-10.3, -6.9) SUCRA 0.76 | ⊕⊕⊕⊕ High | -0.8 (-0.9, -0.6) SUCRA 0.72 | ⊕⊕⊕⊕ High | -5 (-6, -3.9) SUCRA 0.49 | ⊕⊕⊕⊕ High | -1.6 (-2.1, -1) SUCRA 0.49 | ⊕⊕⊕⊕ High | -3.4 (-4.3, -2.5) SUCRA 0.72 | ⊕⊕⊕⊕ High | -0.6 (-0.7, -0.4) SUCRA 0.70 | ⊕⊕⊕⊕ High | -0.5 (-0.7, -0.4) SUCRA 0.46 | ⊕⊕⊕⊕ High |
| Abrocitinib, 200 mg/d | -13 (-14.7, -11.3) SUCRA 0.94 | ⊕⊕⊕⊕ High | -1.2 (-1.3, -1) SUCRA 0.91 | ⊕⊕⊕⊕ High | -8.2 (-9.2, -7.1) SUCRA 0.85 | ⊕⊕⊕⊕ High | -2.4 (-3, -1.9) SUCRA 0.74 | ⊕⊕⊕⊕ High | -5.5 (-6.4, -4.6) SUCRA 0.96 | ⊕⊕⊕⊕ High | -0.9 (-1.1, -0.7) SUCRA 0.93 | ⊕⊕⊕⊕ High | -0.9 (-1, -0.7) SUCRA 0.73 | ⊕⊕⊕⊕ High |
| Azathioprine 1-2.5 mg/kg/d | | | -0.6 (-1, -0.2) SUCRA 0.59 | ⊕⊕⊕◯ Moderate | | | | | | | -0.4 (-0.9, 0.1) Rank: SUCRA 0.53 | ⊕⊕◯◯ Low[b] | -0.6 (-1.2, 0) SUCRA 0.50 | ⊕⊕◯◯ Low[b] |
| Baricitinib, 2 mg/d | -5.6 (-7.5, -3.7) SUCRA 0.55 | ⊕⊕⊕⊕ High | -0.4 (-0.5, -0.2) SUCRA 0.38 | ⊕⊕⊕⊕ High | -3.8 (-4.9, -2.6) SUCRA 0.36 | ⊕⊕⊕⊕ High | -1.3 (-1.7, -0.9) SUCRA 0.39 | ⊕⊕⊕⊕ High | -2.3 (-3.1, -1.4) SUCRA 0.56 | ⊕⊕⊕⊕ High | -0.4 (-0.5, -0.2) SUCRA 0.51 | ⊕⊕⊕⊕ High | -0.5 (-0.7, -0.3) SUCRA 0.43 | ⊕⊕⊕⊕ High |
| Baricitinib, 4 mg/d | -7.6 (-9.6, -5.5) SUCRA 0.7 | ⊕⊕⊕⊕ High | -0.5 (-0.7, -0.4) SUCRA 0.51 | ⊕⊕⊕⊕ High | -5.4 (-6.6, -4.2) SUCRA 0.54 | ⊕⊕⊕⊕ High | -1.7 (-2.2, -1.3) SUCRA 0.50 | ⊕⊕⊕⊕ High | -3.5 (-4.4, -2.6) SUCRA 0.74 | ⊕⊕⊕⊕ High | -0.6 (-0.8, -0.4) SUCRA 0.74 | ⊕⊕⊕⊕ High | -0.6 (-0.8, -0.4) SUCRA 0.53 | ⊕⊕⊕⊕ High |
| Cyclosporine–higher dose | | | -1 (-1.6, -0.4) SUCRA 0.83 | ⊕⊕⊕◯ Moderate | | | | | | | -0.7 (-1.3, -0.1) SUCRA 0.78 | ⊕⊕⊕◯ Moderate | -0.7 (-1.5, 0.2) SUCRA 0.58 | ⊕⊕◯◯ Low[b] |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cyclosporine–lower dose | | | -0.7 (-1.4, -0.1) SUCRA 0.66 | ⊕⊕⊕◯ Moderate | | | | | | | -0.5 (-1.1, 0.2) SUCRA 0.60 | ⊕⊕◯◯ Low[b] | -0.7 (-1.6, 0.3) SUCRA 0.56 | ⊕⊕◯◯ Low[b] |
| Dupilumab, 600 mg for 1 dose, then 300 mg every 2 wk | -10.8 (-12.2, -9.5) SUCRA 0.86 | ⊕⊕⊕⊕ High | -0.9 (-1, -0.8) SUCRA 0.80 | ⊕⊕⊕⊕ High | -7.3 (-8, -6.6) SUCRA 0.72 | ⊕⊕⊕⊕ High | -2 (-2.3, -1.8) SUCRA 0.60 | ⊕⊕⊕⊕ High | -4.9 (-5.5, -4.3) SUCRA 0.9 | ⊕⊕⊕⊕ High | -0.8 (-0.9, -0.7) SUCRA 0.88 | ⊕⊕⊕⊕ High | -0.8 (-0.9, -0.7) SUCRA 0.69 | ⊕⊕⊕⊕ High |
| Methotrexate 10-22,5 mg/week | | | -0.6 (-1.3, 0) SUCRA 0.60 | ⊕⊕◯◯ Low[b] | | | | | | | -0.4 (-1.1, 0.3) SUCRA 0.53 | ⊕⊕◯◯ Low[b] | -0.5 (-1.4, 0.3) SUCRA 0.47 | ⊕⊕◯◯ Low[b] |
| Tralokinumab, 600 mg for 1 dose, then 300 mg every 2 wk | -7.3 (-9.1, -5.4) SUCRA: 0.68 | ⊕⊕⊕⊕ High | -0.6 (-0.7, -0.4) SUCRA 0.58 | ⊕⊕⊕⊕ High | -4.6 (-5.6, -3.6) SUCRA 0.44 | ⊕⊕⊕⊕ High | -1.1 (-1.4, -0.8) SUCRA 0.33 | ⊕⊕⊕⊕ High | -3 (-3.9, -2) SUCRA 0.66 | ⊕⊕⊕⊕ High | -0.4 (-0.6, -0.3) SUCRA 0.56 | ⊕⊕⊕⊕ High | -0.4 (-0.6, -0.3) SUCRA 0.38 | ⊕⊕⊕⊕ High |
| Upadacitinib, 15 mg/d | -11 (-12.5, -9.5) SUCRA 0.87 | ⊕⊕⊕⊕ High | -1.1 (-1.3, -1) SUCRA 0.90 | ⊕⊕⊕⊕ High | -7 (-11.1, -2.9) SUCRA 0.69 | ⊕⊕⊕⊕ High | -2.4 (-2.8, -2) SUCRA 0.74 | ⊕⊕⊕⊕ High | | | | | -0.7 (-0.9, -0.6) SUCRA 0.62 | ⊕⊕⊕⊕ High |
| Upadacitinib, 30 mg/d | -13.5 (-15.1, -12) SUCRA 0.95 | ⊕⊕⊕⊕ High | -1.4 (-1.5, -1.3) SUCRA 0.96 | ⊕⊕⊕⊕ High | -10.6 (-14.8, -6.6) SUCRA 0.95 | ⊕⊕⊕⊕ High | -3.4 (-3.8, -3) SUCRA 0.92 | ⊕⊕⊕⊕ High | | | | | -1 (-1.2, -0.9) SUCRA 0.83 | ⊕⊕⊕⊕ High |

**Table definitions**

[+] CrI: credible interval. Results are expressed in credible intervals as opposed to the confidence intervals since a Bayesian analysis has been conducted.

[++] Rank statistics is defined as the probabilities that a treatment out of n treatments in a network meta-analysis is the best, the second, the third and so on until the least effective treatment, and surface under the cumulative ranking curve (SUCRA) ranges from 0 to 1, the higher the SUCRA value the higher the treatment in the hierarchy according to the outcome.[16]

**Explanatory footnotes**

* Rated down for inconsistency

a. Rated down for significant issues related to risk of bias in included trials

b. Rated down for imprecision

Grades of the certainty of evidence [17]:

High ⊕⊕⊕⊕: we are very confident that the true effect lies close to that of the estimate of the effect.

Medium ⊕⊕⊕◯: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low ⊕⊕◯◯: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low ⊕◯◯◯: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

## Undesirable Effects – short term How substantial are the undesirable anticipated effects for drugs currently in use?

Network meta-analysis based on 60 RCTs with 16,579 AE patients. For clinical relevance we presented an excerpt of effect estimates for the networks of medications currently used in clinical practice or expected to be available soon (azathioprine, methotrexate, cyclosporine, dupilumab, abrocitinib, baricitinib, tralokinumab, upadacitinib, and placebo) in adult patients receiving 8 to 16 weeks of treatment modified from Drucker et al.).[15]

**A complete overview of all analyses performed as part of the living systematic review can be found on https://eczematherapies.com/research/**

| Medication and dose (all versus placebo) | Odds ratios (95% CrI)+ for serious adverse events++<br><br>Ranking+++ SUCRA | Certainty of evidence (GRADE) | Odds ratios (95% CrI) for withdrawal due to adverse events | Certainty of evidence (GRADE) |
|---|---|---|---|---|
| Abrocitinib, 100 mg/d | 1.2<br>(0.6, 2.6)<br><br>SUCRA 0.37 | ⊕◯◯◯<br>Very low [c] | 0.7<br>(0.4, 1.3)<br><br>SUCRA 0.69 | ⊕⊕◯◯<br>Low[a] |
| Abrocitinib, 200 mg/d | 0.6<br>(0.3, 1.5)<br><br>SUCRA 0.56 | ⊕◯◯◯<br>Very low[c] | 0.7<br>(0.4, 1.3)<br><br>SUCRA 0.71 | ⊕⊕◯◯<br>Low[a] |
| Azathioprine<br>1-2.5 mg/kg/d | | | | |
| Baricitinib, 2 mg/d | 0.5<br>(0.2, 1)<br><br>SUCRA 0.67 | ⊕⊕◯◯<br>Low[a] | 0.8<br>(0.3, 1.9)<br><br>SUCRA 0.66 | ⊕◯◯◯<br>Very low[c] |
| Baricitinib, 4 mg/d | 0.7<br>(0.3, 1.4)<br><br>SUCRA 0.54 | ⊕⊕◯◯<br>Low[a] | 1.5<br>(0.7, 3.4)<br><br>SUCRA 0.45 | ⊕◯◯◯<br>Very low[c] |
| Cyclosporine–lower dose | | | | |
| Cyclosporine–higher dose | | | | |
| Dupilumab, 600 mg for 1 dose,<br>then 300 mg every 2 wk | 0.5<br>(0.3, 0.8)<br><br>SUCRA 0.66 | ⊕⊕⊕◯<br>Moderate | 1<br>(0.5, 1.8)<br><br>SUCRA 0.60 | ⊕⊕◯◯<br>Low[a] |

| | | | | |
|---|---|---|---|---|
| Methotrexate | | | | |
| Tralokinumab, 600 mg for 1 dose, then 300 mg every 2 wk | 0.7 (0.4, 1.3) SUCRA 0.54 | ⊕⊕◯◯ Low[a] | 0.9 (0.5, 1.8) SUCRA 0.62 | ⊕⊕◯◯ Low[a] |
| Upadacitinib, 15 mg/d | 0.7 (0.4, 1.3) SUCRA 0.55 | ⊕⊕⊕◯ Moderate[a] | 0.6 (0.3, 1) SUCRA 0.77 | ⊕⊕⊕◯ Moderate[a] |
| Upadacitinib, 30 mg/d | 0.7 (0.3, 1.2) SUCRA 0.56 | ⊕⊕⊕◯ Moderate[a] | 0.7 (0.4, 1.3) SUCRA 0.70 | ⊕⊕◯◯ Low[a] |

**Table definitions**

[+]CrI: credible interval. Results are expressed in credible intervals as opposed to the confidence intervals since a Bayesian analysis has been conducted.

[++]Analyses using restrictive priors on treatment effects and heterogeneity parameters

[+++]Rank statistics is defined as the probabilities that a treatment out of n treatments in a network meta-analysis is the best, the second, the third and so on until the least effective treatment and surface under the cumulative ranking curve (SUCRA) ranges from 0 to 1, the higher the SUCRA value the higher the treatment in the hierarchy according to the outcome

**Explanatory footnotes**

* Rated down for inconsistency

a. Rated down for imprecision (estimate imprecise and would suggest different conclusions at either end of the 95% Credible Intervals)

b. Rated down for imprecision (very wide credible intervals)

c. Rated down 2 levels for imprecision (estimate imprecise and would suggest different conclusions at either end of the 95% Credible Intervals and very wide credible intervals)

"…generally low rates of withdrawals owing to adverse events and serious adverse events in the included studies make our estimates unstable and preclude strong conclusions on relative safety." (Taken from Drucker et al.; discussion section, page 528)[15]

## Values: Is there important uncertainty about or variability in how much people value the main outcomes?

- *Clinical signs: Eczema Area and Severity Index (EASI);*
- *Patient-reported symptoms: Patient-Oriented Eczema Measure (POEM);*
- *Dermatology Life Quality Index (DLQI);*
- *Objective SCORAD (o-SCORAD);*
- *Visual analogue scale itch (VAS-itch);*
- *Serious adverse events;*
- *Withdrawal due to adverse events.*

Von Kobyletzki et al. evaluated the importance of symptoms taking into account patient´s perspectives. Ten items were considered "most important" or "very important" by more than 80% of the participants.[5] Of these, itch and pain/soreness were the most important items for assessing treatment response. Skin feels hot or inflamed, bleeding, involvement of visible or sensitive body sites, cracks, sleep difficulties, amount of body affected and weeping/oozing were also important. Differences were found between adult patients and parents of children with AE. Parents considered bleeding, itch and sleep difficulties as being more important and adult patients considered dry flaky skin as more important.

## Resources required: How large are the resource requirements (costs)?

Economic evaluations based on interventions in children and adults in Europe are scarce. Resource usage and costs vary according to country and health care systems, making extrapolation from one setting to another difficult.[18]

Zink et al. estimated the mean annual out of pocket costs to be € 927.12 per year.[19] 5% of the participants did not report extra expenses but for the majority of participants the mean extra spending per month was €27.26 for emollients and moisturizers, €17.74 for medication, €8.68 for doctors and hospitals, €5.69 for travel expenses, €8.68 for phototherapy and €1.94 for in-patient treatment.

A cohort study in Spain found total costs of AE patients (n=6,186) to be €9.3 million, of which 75.5% were health care costs and 24.5% were productivity loss, the average cost was €1,504 per patient per year. Patients with severe disease had higher costs than moderate and mild disease patients.[20]

In the Netherlands, in a cohort study with 90 AE patients on systemic treatment the mean total direct costs were calculated. The direct costs were €5,191 (95% CI: €4,382–6,019) per patient per year and the costs of productivity loss were calculated to have been €10,040 (95% CI €6,260–14,012) per patient per year. The total costs (direct costs plus costs of productivity loss) were €15,231 (95% CI €11,487–19,455) per patient per year. Patients with uncontrolled AE had higher costs with €20,695 vs. €11,287 for patients with controlled disease.[21]

## Cost effectiveness: Does the cost-effectiveness of the intervention favor one of the above interventions over another?

Economic evaluations based on interventions in children and adults in Europe are scarce. Resource usage and costs vary according to country and health care systems, making extrapolation from one setting to another difficult.[18]

| Equity: What would be the impact on health equity? |
|---|
| Depends on setting (availability of drugs) and populations group (adults and children).<br><br>A study from registry database in Denmark with children (n=9704) and adults (n=5558) found systemic treatments are rarely used in children: methotrexate (n= 70; 0.7% vs n=388; 7.0%), azathioprine (n= 72; 0.7% vs n=1012; 18.2%), ciclosporin (n= 37; 0.4% vs n=278; 5.0%) and corticosteroids (n= 482; 5.0% vs n=3196; 57.5%).[22]<br><br>No significant difference was found on prescribing practices on systemic treatment for adults among physicians in relation to place of work.[2] However, for systemic therapies in children, place of work and primary specialty were main factors. Possible causes stated were lack of clinical trials and drug licensing for pediatric AE.[8] |
| **Acceptability: Is the intervention acceptable to key stakeholders?** |
| The TREAT registry survey from the Netherlands on phototherapy and systemic therapy reported that most physicians prescribed systemic treatments. Not all physicians chose all treatments equally: (ciclosporin (n=201; 87.8%), methotrexate (n=199; 86.9%), oral corticosteroids (n=184; 80.3%), azathioprine (n=135; 59.0%) and mycophenolic acid (n=85; 37.1%)). Common reasons against prescribing specific systemic treatments were lack of personal experience and, for oral corticosteroids, the reason was a high potential of long-term side effects.[2]<br><br>Indirect evidence on patient´s preference:<br><br>Five studies[9-13] on topical treatment reported poor adherence, not following instructions properly and phobia due to possible side effects as well as lack of information. Kosse et al. reported patient's preference for faster and long-lasting treatment effects.[11] |
| **Feasibility: Is the intervention feasible to implement?** |
| Depends on setting (availability of drugs) and populations group (adults and children).<br><br>Physicians from the Netherlands reported the following drugs were not available in their centre in 2020: mycophenolic acid (n=25; 18.8%), ciclosporin (n= 6; 35.5%), azathioprine (n=3; 3.6%) and methotrexate (n=2; 10.5%).[2] |

| Certainty of evidence – short term summary |
|---|

*"For clinical relevance we presented effect estimates in this iteration of our study only for placebo and medications currently used in clinical practice or expected to be available soon: azathioprine, methotrexate, cyclosporine, dupilumab, abrocitinib, baricitinib, tralokinumab, upadacitinib, and placebo.*

*[…]Up to 16weeks of treatment in adults, abrocitinib, 200mg daily (MD, 2.2; 95%CrI, 0.2-4.0; high certainty) and upadacitinib, 30 mg daily (MD, 2.7; 95% CrI, 0.6-4.7; high certainty) were associated with reduced EASI scores slightly more than dupilumab, 600mg then 300mg every 2weeks. Abrocitinib, 100mg daily (MD, −2.1; 95%CrI, −4.1 to −0.3; high certainty), baricitinib, 4 mg daily (MD, −3.2; 95% CrI, −5.7 to −0.8; high certainty), baricitinib, 2 mg daily (MD, −5.2; 95% CrI, −7.5 to −2.9; high certainty), and tralokinumab, 600mg then 300mg every 2weeks (MD, −3.5; 95%CrI, −5.8 to −1.3; high certainty) reduced EASI slightly less than dupilumab and there was little or no difference between upadacitinib, 15mg daily, and dupilumab (MD, 0.2; 95%CrI, −1.9 to 2.2; high certainty). The pattern of results was similar for change in POEM, DLQI and PP-NRS."*

*[…]In SMD analyses, the relative outcomes of conventional systemic agents vs dupilumab were similar to our baseline network meta-analyses. Higher-dose cyclosporine was associated with improved clinical signs slightly better than dupilumab (SMD, −0.2; 95% CrI, −0.8 to 0.5; low certainty). Lower-dose cyclosporine (SMD, 0.2; 95%CrI, −0.5 to 0.8; low certainty), methotrexate (SMD, 0.2; 95% CrI, −0.4 to 0.9; low certainty), and azathioprine (SMD, 0.3; 95% CrI, −0.1 to 0.7; low certainty) were associated with reduced signs slightly less than dupilumab, but certainty of evidence was low owing to concerns related to risk of bias of included trials and imprecision reflected in wide credible intervals.."*

*[…]For withdrawal owing to adverse events among patients receiving abrocitinib, baricitinib, dupilumab, tralokinumab, upadacitinib, and placebo, credible intervals were wide, contributing to lower certainty evidence, so we were unable to make clinically useful conclusions."*

(Taken from Drucker et al.; methods and results section, page 525-526[15])

Table 1: Effectiveness of medications used in clinical practice or likely to be approved soon for atopic eczema (Data taken from Drucker et al.; Supplemental Online Content – published online March 2022). Lower left hand triangle: **change in signs** (standardized mean difference (95% CrI)) up to 16 weeks of treatment in adults / upper right hand triangle change in **QoL** (standardized mean difference (95% CrI)) up to 16 weeks of treatment in adults

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Abrocitinib 100 mg daily** | -0.3 (-0.5, -0.2) | 0.2 (-0.4, 0.7) | 0.2 (0, 0.4) | 0 (-0.3, 0.2) | -0.1 (-0.8, 0.5) | 0.1 (-0.6, 0.8) | -0.3 (-0.4, -0.1) | 0.2 (-0.5, 0.8) | 0.6 (0.4, 0.7) | 0.2 (-0.1, 0.4) | not in NMA | not in NMA |
| 0.4 (0.3, 0.6) | **Abrocitinib 200 mg daily** | 0.5 (0, 1.1) | 0.5 (0.3, 0.8) | 0.3 (0, 0.5) | 0.2 (-0.4, 0.8) | 0.4 (-0.3, 1.1) | 0.1 (-0.1, 0.3) | 0.5 (-0.2, 1.2) | 0.9 (0.7, 1.1) | 0.5 (0.3, 0.7) | not in NMA | not in NMA |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| -0.1 (-0.6, 0.3) | -0.6 (-1, -0.1) | **Azathioprine** | 0 (-0.5, 0.6) | -0.2 (-0.8, 0.3) | -0.3 (-1, 0.3) | -0.1 (-0.7, 0.6) | -0.4 (-1, 0.1) | 0 (-0.6, 0.5) | 0.4 (-0.1, 0.9) | 0 (-0.6, 0.5) | not in NMA | not in NMA |
| -0.4 (-0.6, -0.2) | -0.8 (-1, -0.6) | -0.2 (-0.7, 0.2) | **Baricitinib 2 mg daily** | -0.3 (-0.4, -0.1) | -0.3 (-1, 0.3) | -0.1 (-0.8, 0.5) | -0.5 (-0.7, -0.3) | 0 (-0.7, 0.6) | 0.4 (0.2, 0.5) | 0 (-0.3, 0.2) | not in NMA | not in NMA |
| -0.3 (-0.5, 0) | -0.7 (-0.9, -0.5) | -0.1 (-0.5, 0.3) | 0.1 (0, 0.3) | **Baricitinib 4 mg daily** | -0.1 (-0.7, 0.5) | 0.1 (-0.5, 0.8) | -0.2 (-0.4, 0) | 0.2 (-0.5, 0.9) | 0.6 (0.4, 0.8) | 0.2 (0, 0.4) | not in NMA | not in NMA |
| 0.3 (-0.4, 0.9) | -0.1 (-0.8, 0.5) | 0.4 (-0.2, 1) | 0.7 (0, 1.3) | 0.5 (-0.1, 1.1) | **Cyclosporine (higher dose)** | 0.2 (-0.2, 0.6) | -0.1 (-0.7, 0.5) | 0.3 (-0.3, 0.9) | 0.7 (0.1, 1.3) | 0.3 (-0.3, 0.9) | not in NMA | not in NMA |
| 0 (-0.7, 0.6) | -0.4 (-1.1, 0.2) | 0.1 (-0.5, 0.7) | 0.4 (-0.3, 1) | 0.2 (-0.4, 0.9) | -0.3 (-0.7, 0.1) | **Cyclosporine (lower dose)** | -0.3 (-1, 0.3) | 0.1 (-0.4, 0.6) | 0.5 (-0.2, 1.1) | 0.1 (-0.6, 0.8) | not in NMA | not in NMA |
| 0.1 (0, 0.3) | -0.3 (-0.4, -0.1) | 0.3 (-0.1, 0.7) | 0.5 (0.3, 0.7) | 0.4 (0.2, 0.6) | -0.2 (-0.8, 0.5) | 0.2 (-0.5, 0.8) | **Dupilumab*** | 0.4 (-0.3, 1.1) | 0.8 (0.7, 0.9) | 0.4 (0.2, 0.6) | not in NMA | not in NMA |
| -0.1 (-0.7, 0.5) | -0.5 (-1.2, 0.1) | 0 (-0.5, 0.6) | 0.3 (-0.4, 0.9) | 0.1 (-0.5, 0.8) | -0.4 (-0.9, 0.2) | -0.1 (-0.6, 0.4) | -0.2 (-0.9, 0.4) | **Methotrexate** | 0.4 (-0.3, 1.1) | 0 (-0.7, 0.7) | not in NMA | not in NMA |
| -0.8 (-0.9, -0.6) | -1.2 (-1.3, -1) | -0.6 (-1, -0.2) | -0.4 (-0.5, -0.2) | -0.5 (-0.7, -0.4) | -1 (-1.6, -0.4) | -0.7 (-1.4, -0.1) | -0.9 (-1, -0.8) | -0.6 (-1.3, 0) | **Placebo** | -0.4 (-0.6, -0.3) | not in NMA | not in NMA |
| -0.2 (-0.4, 0) | -0.6 (-0.8, -0.4) | 0 (-0.5, 0.4) | 0.2 (0, 0.4) | 0.1 (-0.1, 0.3) | -0.5 (-1.1, 0.2) | -0.2 (-0.8, 0.5) | -0.3 (-0.5, -0.1) | -0.1 (-0.7, 0.6) | 0.8 (0.1, 1.4) | **Tralokinumab*** | not in NMA | not in NMA |
| 0.4 (0.2, 0.6) | 0 (-0.2, 0.2) | 0.5 (0.1, 0.9) | 0.8 (0.6, 1) | 0.6 (0.4, 0.8) | 0.1 (-0.5, 0.7) | 0.4 (-0.2, 1) | 0.2 (0.1, 0.4) | 0.5 (-0.1, 1.1) | 1.1 (1, 1.3) | 0.6 (0.4, 0.7) | **Upadacitinib 15 mg daily** | not in NMA |
| 0.6 (0.4, 0.8) | 0.2 (0, 0.4) | 0.8 (0.3, 1.2) | 1 (0.8, 1.2) | 0.9 (0.7, 1.1) | 0.4 (-0.3, 1) | 0.7 (0, 1.3) | 0.5 (0.3, 0.7) | 0.8 (0.1, 1.4) | 1.4 (1.3, 1.5) | 0.8 (0.6, 1) | 0.3 (0.1, 0.4) | **Upadacitinib 30 mg daily** |

A positive effect estimate in a given cell favors the row-defining treatment. A negative effect estimate in a given cell favors the column-defining treatment

red = ⊕⊕◯◯ low certainty evidence

yellow = ⊕⊕⊕◯ moderate certainty evidence

green = ⊕⊕⊕⊕ high certainty evidence

white = no further data available

*Dose of dupilumab and tralokinumab is 600 mg then 300 mg every 2 weeks

Table 2: Effectiveness of medications used in clinical practice or likely to be approved soon for atopic eczema (Data taken from Drucker et al.; Supplemental Online Content – published online March 2022). Lower left hand triangle: change in **EASI** (mean difference (95% CrI)) up to 16 weeks of treatment in adults / upper right hand triangle change in **POEM** (mean difference (95% CrI)) up to 16 weeks of treatment in adults

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Abrocitinib 100 mg daily** | -3.2 (-4.2, -2.2) | not in NMA | 1.2 (-0.4, 2.7) | -0.5 (-2.1, 1.1) | not in NMA | not in NMA | -2.3 (-3.5, -1.2) | not in NMA | 5 (3.9, 6) | 0.4 (-1.1, 1.8) | -2 (-6.3, 2.2) | -5.6 (-10, -1.5) |
| 4.3 (2.7, 6) | **Abrocitinib 200 mg daily** | not in NMA | 4.4 (2.9, 5.9) | 2.7 (1.2, 4.3) | not in NMA | not in NMA | 0.9 (-0.2, 2) | not in NMA | 8.2 (7.1, 9.2) | 3.6 (2.1, 5) | 1.2 (-3, 5.4) | -2.4 (-6.7, 1.7) |
| not in NMA | not in NMA | **Azathioprine** | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA |
| -3.1 (-5.6, -0.5) | -7.4 (-9.9, -4.8) | not in NMA | **Baricitinib 2 mg daily** | -1.6 (-2.8, -0.5) | not in NMA | not in NMA | -3.5 (-4.8, -2.2) | not in NMA | 3.8 (2.6, 4.9) | -0.8 (-2.3, 0.7) | -3.2 (-7.5, 1.1) | -6.8 (-11.1, -2.6) |
| -1.1 (-3.7, 1.6) | -5.4 (-8, -2.7) | not in NMA | 2 (-0.1, 4.1) | **Baricitinib 4 mg daily** | not in NMA | not in NMA | -1.9 (-3.2, -0.5) | not in NMA | 5.4 (4.2, 6.6) | 0.8 (-0.7, 2.4) | -1.5 (-5.8, 2.8) | -5.2 (-9.5, -1) |
| not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | **Cyclosporine (higher dose)** | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA |
| not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | **Cyclosporine (lower dose)** | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA |
| 2.1 (0.3, 4.1) | -2.2 (-4, -0.2) | not in NMA | 5.2 (2.9, 7.5) | 3.2 (0.8, 5.7) | not in NMA | not in NMA | **Dupilumab*** | not in NMA | 7.3 (6.6, 8) ) | 2.7 (1.5, 3.9) | 0.3 (-3.9, 4.5) | -3.3 (-7.6, 0.8) |
| not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | **Methotrexate** | not in NMA | not in NMA | not in NMA | not in NMA |
| -8.6 (-10.3, -6.9) | -13 (-14.7, -11.3) | not in NMA | -5.6 (-7.5, -3.7) | -7.6 (-9.6, -5.5) | not in NMA | not in NMA | -10.8 (-12.2, -9.5) | not in NMA | **Placebo** | -4.6 (-5.6, -3.6) | -7 (-11.1, -2.9) | -10.6 (-14.8, -6.6) |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| -1.4 (-3.9, 1.1) | -5.7 (-8.2, -3.2) | not in NMA | 1.7 (-1, 4.3) | -0.3 (-3, 2.4) | not in NMA | not in NMA | -3.5 (-5.8, -1.3) | not in NMA | 7.3 (5.4, 9.1) | **Tralokinumab*** | -2.4 (-6.6, 1.8) | -6 (-10.3, -1.9) |
| 2.3 (0.1, 4.7) | -2 (-4.3, 0.3) | not in NMA | 5.4 (2.9, 7.9) | 3.4 (0.8, 6) | not in NMA | not in NMA | 0.2 (-1.9, 2.2) | not in NMA | 11 (9.5, 12.5) | 3.7 (1.4, 6.1) | **Upadacitinib 15 mg daily** | -3.7 (-7.7, 0.4) |
| 4.9 (2.6, 7.2) | 0.6 (-1.7, 2.9) | not in NMA | 7.9 (5.5, 10.4) | 5.9 (3.4, 8.5) | not in NMA | not in NMA | 2.7 (0.6, 4.7) | not in NMA | 13.5 (12, 15.1) | 6.3 (3.9, 8.6) | 2.5 (1, 4) | **Upadacitinib 30 mg daily** |

A positive effect estimate in a given cell favors the row-defining treatment. A negative effect estimate in a given cell favors the column-defining treatment
red = ⊕⊕◯◯ low certainty evidence
yellow = ⊕⊕⊕◯ moderate certainty evidence
green = ⊕⊕⊕⊕ high certainty evidence
white = no further data available
*Dose of dupilumab and tralokinumab is 600 mg then 300 mg every 2 weeks

Table 3: Effectiveness of medications used in clinical practice or likely to be approved soon for atopic eczema (Data taken from Drucker et al.; Supplemental Online Content – published online March 2022). Lower left hand triangle: change in **DLQI** (mean difference (95% CrI)) up to 16 weeks of treatment in adults / upper right hand triangle change in **peak pruritus NRS** (mean difference (95% CrI)) up to 16 weeks of treatment in adults

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Abrocitinib 100 mg daily** | -0.8 (-1.3, -0.4) | not in NMA | 0.3 (-0.4, 0.9) | -0.1 (-0.9, 0.6) | not in NMA | not in NMA | -0.4 (-1, 0.2) | not in NMA | 1.6 (1, 2.1) | 0.5 (-0.2, 1.1) | -0.8 (-1.5, -0.2) | -1.8 (-2.5, -1.1) |
| 2.1 (1.1, 2.9) | **Abrocitinib 200 mg daily** | not in NMA | 1.1 (0.4, 1.8) | 0.7 (0, 1.4) | not in NMA | not in NMA | 0.4 (-0.2, 1) | not in NMA | 2.4 (1.9, 3) | 1.3 (0.6, 1.9) | 0 (-0.7, 0.7) | -1 (-1.7, -0.3) |
| not in NMA | not in NMA | **Azathioprine** | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA |
| -1.1 (-2.4, 0.1) | -3.2 (-4.5, -2) | not in NMA | **Baricitinib 2 mg daily** | -0.4 (-0.8, 0.1) | not in NMA | not in NMA | -0.7 (-1.2, -0.2) | not in NMA | 1.3 (0.9, 1.7) | 0.2 (-0.3, 0.7) | -1.1 (-1.7, -0.5) | -2.1 (-2.7, -1.5) |
| 0.1 (-1.2, 1.4) | -1.9 (-3.3, -0.6) | not in NMA | 1.3 (0.3, 2.2) | **Baricitinib 4 mg daily** | not in NMA | not in NMA | -0.3 (-0.8, 0.2) | not in NMA | 1.7 (1.3, 2.2) | 0.6 (0.1, 1.1) | -0.7 (-1.3, -0.1) | -1.7 (-2.3, -1.1) |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | **Cyclosporine (higher dose)** | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA |
| not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | **Cyclosporine (lower dose)** | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA |
| 1.5 (0.5, 2.5) | -0.6 (-1.5, 0.4) | not in NMA | 2.6 (1.6, 3.7) | 1.4 (0.3, 2.5) | not in NMA | not in NMA | **Dupilumab*** | not in NMA | 2 (1.8, 2.3) | 0.9 (0.5, 1.3) | -0.4 (-0.9, 0.1) | -1.4 (-1.9, -0.9) |
| not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | **Methotrexate** | not in NMA | not in NMA | not in NMA | not in NMA |
| -3.4 (-4.3, -2.5) | -5.5 (-6.4, -4.6) | not in NMA | -2.3 (-3.1, -1.4) | -3.5 (-4.4, -2.6) | not in NMA | not in NMA | -4.9 (-5.5, -4.3) | not in NMA | **Placebo** | -1.1 (-1.4, -0.8) | -2.4 (-2.8, -2) | -3.4 (-3.8, -3) |
| -0.4 (-1.8, 0.8) | -2.5 (-3.8, -1.2) | not in NMA | 0.7 (-0.6, 2) | -0.6 (-1.9, 0.8) | not in NMA | not in NMA | -2 (-3.1, -0.8) | not in NMA | 3 (2, 3.9) | **Tralokinumab*** | -1.3 (-1.8, -0.8) | -2.3 (-2.8, -1.8) |
| not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | **Upadacitinib 15 mg daily** | -1 (-1.4, -0.6) |
| not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | **Upadacitinib 30 mg daily** |

A positive effect estimate in a given cell favors the row-defining treatment. A negative effect estimate in a given cell favors the column-defining treatment
yellow = ⊕⊕⊕◯ moderate certainty evidence
green = ⊕⊕⊕⊕ high certainty evidence
white = no further data available
*Dose of dupilumab and tralokinumab is 600 mg then 300 mg every 2 weeks

Table 4: Effectiveness of medications used in clinical practice or likely to be approved soon for atopic eczema (Data taken from Drucker et al.; Supplemental Online Content – published online March 2022). Lower left hand triangle: **change in itch** (standardized mean difference (95% CrI)) up to 16 weeks of treatment in adults

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Abrocitinib 100 mg daily** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0.3 (0.2, 0.5) | **Abrocitinib 200 mg daily** | | | | | | | | | | | |
| 0 (-0.6, 0.7) | -0.3 (-0.9, 0.4) | **Azathioprine** | | | | | | | | | | |
| 0 (-0.3, 0.2) | -0.4 (-0.6, -0.1) | -0.1 (-0.7, 0.5) | **Baricitinib 2 mg daily** | | | | | | | | | |
| 0.1 (-0.2, 0.3) | -0.2 (-0.5, 0) | 0 (-0.6, 0.7) | 0.1 (-0.1, 0.3) | **Baricitinib 4 mg daily** | | | | | | | | |
| 0.2 (-0.7, 1) | -0.2 (-1, 0.7) | 0.1 (-1, 1.1) | 0.2 (-0.7, 1.1) | 0.1 (-0.8, 0.9) | **Cyclosporine (higher dose)** | | | | | | | |
| 0.1 (-0.8, 1.1) | -0.2 (-1.1, 0.8) | 0.1 (-1.1, 1.2) | 0.2 (-0.8, 1.1) | 0.1 (-0.9, 1) | 0 (-0.4, 0.4) | **Cyclosporine (lower dose)** | | | | | | |
| 0.3 (0.1, 0.5) | 0 (-0.2, 0.1) | 0.2 (-0.4, 0.8) | 0.3 (0.1, 0.5) | 0.2 (0, 0.4) | 0.1 (-0.7, 1) | 0.1 (-0.8, 1.1) | **Dupilumab*** | | | | | |
| 0 (-0.9, 0.9) | -0.3 (-1.2, 0.5) | 0 (-0.7, 0.6) | 0 (-0.8, 0.9) | -0.1 (-1, 0.8) | -0.2 (-1.4, 1.1) | -0.2 (-1.4, 1.2) | -0.3 (-1.2, 0.6) | **Methotrexate** | | | | |
| -0.5 (-0.7, -0.4) | -0.9 (-1, -0.7) | -0.6 (-1.2, 0) | -0.5 (-0.7, -0.3) | -0.6 (-0.8, -0.4) | -0.7 (-1.5, 0.2) | -0.7 (-1.6, 0.3) | -0.8 (-0.9, -0.7) | -0.5 (-1.4, 0.3) | **Placebo** | | | |
| -0.1 (-0.3, 0.1) | -0.4 (-0.6, -0.2) | -0.1 (-0.8, 0.5) | -0.1 (-0.3, 0.2) | -0.2 (-0.4, 0.1) | -0.3 (-1.1, 0.6) | -0.2 (-1.2, 0.7) | -0.4 (-0.6, -0.2) | -0.1 (-1, 0.8) | 0.4 (0.3, 0.6) | **Tralokinumab*** | | |
| 0.2 (0, 0.4) | -0.1 (-0.4, 0.1) | 0.2 (-0.5, 0.8) | 0.2 (0, 0.5) | 0.1 (-0.1, 0.4) | 0 (-0.8, 0.9) | 0.1 (-0.9, 1) | -0.1 (-0.3, 0.1) | 0.2 (-0.7, 1.1) | 0.7 (0.6, 0.9) | 0.3 (0.1, 0.5) | **Upadacitinib 15 mg daily** | |
| 0.5 (0.3, 0.7) | 0.2 (-0.1, 0.4) | 0.4 (-0.2, 1.1) | 0.5 (0.3, 0.8) | 0.4 (0.2, 0.7) | 0.3 (-0.5, 1.2) | 0.3 (-0.6, 1.3) | 0.2 (0, 0.4) | 0.5 (-0.4, 1.4) | 1 (0.9, 1.2) | 0.6 (0.4, 0.8) | 0.3 (0.1, 0.4) | **Upadacitinib 30 mg daily** |

A positive effect estimate in a given cell favors the row-defining treatment. A negative effect estimate in a given cell favors the column-defining treatment

red = ⊕⊕◯◯ low certainty evidence

yellow = ⊕⊕⊕◯ low certainty evidence

green = ⊕⊕⊕⊕ high certainty evidence

white = no further data available

*Dose of dupilumab and tralokinumab is 600 mg then 300 mg every 2 weeks

Table 5: Safety of medications used in clinical practice or likely to be approved soon for atopic eczema (Data taken from Drucker et al.; Supplemental Online Content – published online March 2022) Lower left hand triangle: odds ratios (95% CrI) **withdrawals from adverse events** up to 16 weeks of treatment in adults / upper right hand triangle: odds ratios (95% CrI) **serious adverse events** up to 16 weeks of treatment in adults

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Abrocitinib 100 mg daily** | 0.5 (0.2, 1.1) | not in NMA | 0.4 (0.1, 1.1) | 0.6 (0.2, 1.7) | not in NMA | not in NMA | 0.4 (0.2, 0.9) | not in NMA | 0.8 (0.4, 1.7) | 0.6 (0.2, 1.5) | 0.6 (0.2, 1.5) | 0.6 (0.2, 1.5) |
| 1.1 (0.6, 1.8) | **Abrocitinib 200 mg daily** | not in NMA | 0.7 (0.2, 2.2) | 1.1 (0.3, 3.4) | not in NMA | not in NMA | 0.7 (0.3, 1.9) | not in NMA | 1.5 (0.7, 3.7) | 1.1 (0.4, 3.1) | 1.1 (0.4, 3) | 1 (0.4, 3) |
| not in NMA | not in NMA | **Azathioprine** | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA |
| 0.9 (0.3, 2.5) | 0.9 (0.3, 2.4) | not in NMA | **Baricitinib 2 mg daily** | 1.6 (0.6, 4) | not in NMA | not in NMA | 1 (0.4, 2.8) | not in NMA | 2.2 (1, 5) | 1.5 (0.6, 4.3) | 1.5 (0.6, 4.2) | 1.5 (0.5, 4.1) |
| 0.5 (0.2, 1.3) | 0.5 (0.2, 1.3) | not in NMA | 0.5 (0.2, 1.3) | **Baricitinib 4 mg daily** | not in NMA | not in NMA | 0.7 (0.3, 1.7) | not in NMA | 1.4 (0.7, 3.1) | 1 (0.4, 2.6) | 1 (0.4, 2.6) | 0.9 (0.4, 2.5) |
| not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | **Cyclosporine (higher dose)** | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA |
| not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | **Cyclosporine (lower dose)** | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA |
| 0.8 (0.4, 1.7) | 0.7 (0.3, 1.6) | not in NMA | 0.9 (0.3, 2.4) | 1.6 (0.6, 4.5) | not in NMA | not in NMA | **Dupilumab*** | not in NMA | 2.1 (1.2, 3.9) | 1.5 (0.6, 3.5) | 1.4 (0.6, 3.4) | 1.4 (0.6, 3.4) |
| not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | not in NMA | **Methotrexate** | not in NMA | not in NMA | not in NMA | not in NMA |
| 0.7 (0.4, 1.3) | 0.7 (0.4, 1.3) | not in NMA | 0.8 (0.3, 1.9) | 1.5 (0.7, 3.4) | not in NMA | not in NMA | 1 (0.5, 1.8) | not in NMA | **Placebo** | 0.7 (0.4, 1.3) | 0.7 (0.4, 1.3) | 0.7 (0.3, 1.2) |
| 0.8 (0.3, 2) | 0.8 (0.3, 1.9) | not in NMA | 0.9 (0.3, 2.6) | 1.7 (0.6, 4.7) | not in NMA | not in NMA | 1.1 (0.4, 2.6) | not in NMA | 1.1 (0.6, 2.1) | **Tralokinumab*** | 1 (0.4, 2.3) | 1 (0.4, 2.3) |
| 1.3 (0.6, 3) | 1.2 (0.5, 2.9) | not in NMA | 1.4 (0.5, 3.9) | 2.7 (1, 7.4) | not in NMA | not in NMA | 1.7 (0.7, 4) | not in NMA | 1.7 (1, 3.2) | 1.6 (0.7, 3.9) | **Upadacitinib 15 mg daily** | 1 (0.5, 2) |
| 1 (0.5, 2.3) | 1 (0.4, 2.2) | not in NMA | 1.1 (0.4, 3.1) | 2.1 (0.8, 5.7) | not in NMA | not in NMA | 1.3 (0.6, 3.1) | not in NMA | 1.4 (0.8, 2.5) | 1.2 (0.5, 3) | 0.8 (0.4, 1.5) | **Upadacitinib 30 mg daily** |

An effect estimate less than 1 in a given cell favors the column-defining treatment.dark red = ⊕◯◯◯ very low certainty of evidence
dark red = ⊕◯◯◯ very low certainty evidence

red = ⨁⨁◯◯ low certainty evidence
yellow = ⨁⨁⨁◯ moderate certainty evidence
white = no further data available
*Dose of dupilumab and tralokinumab is 600 mg then 300 mg every 2 weeks

**A complete overview of all analyses performed as part of the living systematic review can be found here:**
https://eczematherapies.com/research/ (last accessed 14 June 2022)

## Recommendations

| **Recommendation** | **Adults; short term (8-16 weeks) vs placebo**<br>Bold = statistically significant difference |
|---|---|
| Azathioprine | ⊕⊕⊕◯ MODERATE for standardized mean difference **change in signs**<br>⊕⊕◯◯ LOW for standardized mean difference QoL, itch |
| Ciclosporin | ⊕⊕⊕◯ MODERATE for standardized mean difference **change in signs**<br>⊕⊕⊕◯ MODERATE - ⊕⊕◯◯ LOW for standardized mean difference QoL<br>⊕⊕◯◯ LOW for standardized mean difference itch |
| Methotrexate | ⊕⊕◯◯ LOW for standardized mean difference change in signs, Qol, itch |
| Dupilumab | ⊕⊕⊕⊕ HIGH for mean difference/ standardized mean difference **EASI, change in signs, POEM, peak pruritus NRS, DLQI, QoL, itch**<br>⊕⊕⊕◯ MODERATE - ⊕⊕◯◯ LOW for undesirable effects |
| Tralokinumab | ⊕⊕⊕⊕ HIGH for mean difference/ standardized mean difference **EASI, change in signs, POEM, peak pruritus NRS, DLQI, QoL, itch**<br>⊕⊕◯◯ LOW for undesirable effects |
| Abrocitinib | ⊕⊕⊕⊕ HIGH for mean difference/ standardized mean difference **EASI, change in signs, POEM, peak pruritus NRS, DLQI, QoL, itch**<br>⊕⊕◯◯ LOW - ⊕◯◯◯ VERY LOW for undesirable effects |
| Baricitinib | ⊕⊕⊕⊕ HIGH for mean difference/ standardized mean difference **EASI, change in signs, POEM, peak pruritus NRS, DLQI, QoL, itch**<br>⊕⊕◯◯ LOW - ⊕◯◯◯ VERY LOW for undesirable effects |
| Upadacitinib | ⊕⊕⊕⊕ HIGH for mean difference/ standardized mean difference **EASI, change in signs, POEM, peak pruritus NRS, itch**<br>⊕⊕⊕◯ MODERATE - ⊕⊕◯◯ LOW for undesirable effects |

Bold = statistically significant difference
AE = atopic eczema; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; NMA = network meta analysis; OR = Odds ratio; POEM = Patient-Oriented Eczema Measure; PPNRS = Peak Pruritus Numerical Rating Scale; RoB = Risk of Bias; VAS = visual analog scale

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