Evidence Report	**EuroGuiDerm** Centre for Guideline Development

EUROGUIDERM GUIDELINE ON ATOPIC ECZEMA– EVIDENCE REPORT

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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><td 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?</td></tr>
<tr><td>Population:</td><td>Children and adults with atopic eczema</td></tr>
<tr><td>Intervention:</td><td>Systemic therapies
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<tr><th>Conventional immunosuppressants</th><th>TH2-blockers</th><th>Anti-IL 31</th><th>Small molecules</th><th>Other</th></tr>
<tr><td>Azathioprine</td><td>Dupilumab</td><td>Nemolizumab</td><td>Apremilast</td><td>Alitretinoin</td></tr>
<tr><td>Ciclosporin</td><td>Tralokinumab</td><td></td><td>Abrocitinib</td><td>Adriforant</td></tr>
<tr><td>Methotrexate</td><td>Lebrikizumab</td><td></td><td>Baricitinib</td><td>Corticosteroids (oral, IV, IM)</td></tr>
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</table>

Pink: commonly used drugs,
Baricitinib, tralokinumab and upadacitinib are also approved by the EMA for the treatment of AE (the latter two were licensed during the guideline development process). Abrocitinib is approved by the MHRA in the UK.
</td></tr>
<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);
– Overall disease severity as measured by the composite score SCORing of Atopic Dermatitis (SCORAD) index;
– Patient-reported symptoms: Patient-Oriented Eczema Measure (POEM);
– Quality of life: Dermatology Life Quality Index (DLQI), Children’s Dermatology Life Quality Index (CDLQI), Infant's Dermatitis Quality of Life Index (IDQOL);</td></tr>
</table>

	– Objective SCORAD (o-SCORAD); – Patient-oriented SCORAD (PO-SCORAD); – Investigator's Global Assessment (IGA); – Visual analogue scale itch (VAS-itch); – 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. – Several guidelines for the treatment of atopic eczema exist, but recommendations vary[1] and evidence-based recommendations for novel treatments are needed. – 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]. – There is also a lack of clear guidance on switching patients from one systemic therapy to another and combined systemic therapy.
Conflict **of interests:**	Less than 50% of the guideline development committee declared to have personal-financial (PF) interests. The EuroGuiDerm Team has declared no PF interest.

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, baricitinib, upadacitinib and tralokinumab 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.

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.

Patients and parents needs/preferences:

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 39 RCTs with 6360 patients evaluating 20 systemic AE medications. An excerpt of effectiveness outcomes of approved drugs against placebo in adult patients receiving 8 to 16 weeks of treatment is presented below (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*) Ranking** SUCRA	Certainty of evidence (GRADE)	Standardized mean difference in O-SCORAD, SASSAD and other scales for signs (95% CrI)*** Ranking SUCRA	Certainty of evidence (GRADE)	Mean difference in POEM score (95% CrI) Ranking SUCRA	Certainty of evidence (GRADE)	Mean difference in itch-VAS score (95% CrI) Ranking SUCRA	Certainty of evidence (GRADE)	Mean difference in DLQI score (95% CrI) Ranking SUCRA	Certainty of evidence (GRADE)
Azathioprine TPMT adjusted			–0.4 (–0.8 to –0.1) Azathioprine no dose given Rank 5 SUCRA 0.43	⊕⊕◯◯ Low [1,2,3]			–1.4 (–5.6 to 2.8) Rank 5 SUCRA 0.60	⊕⊕◯◯ Low [1,2,3]	–3.4 (–7.1 to 0.2) Rank 7 SUCRA 0.72	⊕⊕◯◯ Low [1,2,3]
Baricitinib, 2 mg/d	–5.6 (–10.9 to –0.4) Rank 11 SUCRA 0.59	⊕⊕⊕◯ Moderate[1,2]							–0.6 (–3.6 to 2.4) Rank 16 SUCRA 0.38	⊕⊕⊕◯ Moderate[1,2]
Baricitinib, 4 mg/d	–5.2 (–10.4 to –0.1) Rank 14 SUCRA 0.56	⊕⊕⊕◯ Moderate[1,2]							–1.7 (–4.7 to 1.3) Rank 9 SUCRA 0.53	⊕⊕⊕◯ Moderate[1,2]

Cyclosporine–lower dose			-0.7 (–1.3 to –0.1) Rank 3 SUCRA 0.64	⊕⊕◯◯ Low[2,3]			–2.2 (–6.6 to 2) Rank 3 SUCRA 0.71 Dose: 5mg/kg daily	⊕⊕◯◯ Low [1,2,3]		
Cyclosporine–higher dose			–1.1 (–1.7 to –0.5) Rank 1 SUCRA 0.94	⊕⊕◯◯ Low[4]						
Dupilumab, 600 mg for 1 dose, then 300 mg every 2 wk	–11.3 (–13.1 to –9.7) Rank 4 SUCRA 0.88	⊕⊕⊕⊕ High	–0.9 (–1.0 to –0.8) Rank 2 SUCRA 0.80	⊕⊕⊕⊕ High	–7.5 (–8.5 to –6.4) Rank 7 SUCRA 0.59	⊕⊕⊕⊕ High			–4.8 (–5.8 to –3.7) Rank 2 SUCRA 0.88	⊕⊕⊕⊕ High
Methotrexate			–0.6 (–1.1 to 0.0) Rank 4 SUCRA 0.51	⊕⊕◯◯ Low[4]						
Tralokinumab, 300 mg every 2 wk	–4.9 (–9.3 to –0.4) Rank 15 SUCRA 0.55	⊕⊕⊕◯ Moderate[1,2]							–1.8 (–4.9 to 1.3) Rank 8 SUCRA 0.54	⊕⊕⊕◯ Moderate[1,2]
Upadacitinib, 15 mg/d					–7.0 (–11.4 to –2.6) Rank 9 SUCRA 0.58	⊕⊕◯◯ Low [2,3]				
Upadacitinib, 30 mg/d					–10.7 (–15.1 to –6.3) Rank 2 SUCRA 0.88	⊕⊕◯◯ Low [1,2,3]				

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]

***Only medications currently in use.

† Results for fevipiprant are only available from clinical trial registries and standard errors given in EASI are very small and maybe in error.

Explanatory footnotes

1. NMA estimates imprecise and would suggest different conclusions at either end of the 95% Credible Intervals.
2. Number of participants included in analysis below optimal information size.
3. Significant issues related to risk of bias from included trials.
4. Very serious imprecision (lowered 2 levels) for very imprecise NMA estimate.

Drucker et al report:

"EASI score

Dupilumab 300 mg every 2 weeks (the approved dosage for adults) was superior to placebo (mean difference, 11.3-point reduction; 95% CrI, 9.7-13.1 [GRADE assessment: high certainty[1]]). Several investigational medications demonstrated reduction in EASI score compared with placebo, including baricitinib, 2 mg daily (mean difference, 5.6-point reduction; 95% CrI, 0.4-10.9 [GRADE assessment: moderate certainty]) and 4 mg daily (mean difference, 5.2-point reduction; 95% CrI, 0.1 10.4 [GRADE assessment: moderate certainty]), and tralokinumab, 150mg every 2 weeks (mean difference, 4.3-point reduction; 95% CrI, –0.2 to 8.9 [GRADE assessment: moderate certainty]) and 300 mg every 2 weeks (mean difference, 4.9-point reduction; 95% CrI, 0.4-9.3 [GRADE assessment: moderate certainty])".

Clinical signs

Azathioprine, lower dose cyclosporine, higher-dose cyclosporine, methotrexate, and dupilumab had moderate or large benefits relative to placebo. Higher-dose cyclosporine (SMD, −1.1; 95% CrI, −1.7 to−0.5 [low certainty]) and dupilumab (SMD, −0.9; 95% CrI, −1.0 to −0.8 [high certainty]) were similarly effective vs placebo in clearing clinical signs of AD and may be superior to methotrexate (SMD, −0.6; 95% CrI, −1.1 to 0.0 [low certainty]) and azathioprine (SMD, −0.4; 95% CrI, −0.8 to −0.1 [low certainty]). Higher-dose cyclosporine may be associate with improvement in clinical signs compared with azathioprine (SMD, −0.6; 95% CrI, −1.2 to 0.0 [low certainty]) and methotrexate (SMD, −0.5; 95%CrI, −1.1 to 0.0 [low certainty]), with similar improvement to dupilumab (SMD, −0.2; 95%CrI, −0.8 to 0.4 [low certainty]).

POEM score

Dupilumab,300mg every 2weeks (mean difference, –7.5; 95% CrI, –8.5 to –6.4 [high certainty]), and investigational drugs abrocitinib, 100mg daily (mean difference, –7.6; 95%CrI, –11.6 to –3.6 [low certainty]) and 200 mg daily (mean difference, –11.3; 95%CrI, –15.0 to –7.5 [low certainty]), and upadacitinib, 15mg daily (mean difference, –7.0; 95%CrI, –11.4 to –2.6 [low certainty]) and 30mg daily (mean difference, –10.7; 95% CrI, –15.1 to –6.3 [low certainty]) were associated with clinically relevant improvements in the POEM score compared with placebo".

Itch VAS

Nemolizumab 2.0 mg/kg every 4 weeks (mean difference, –3.2; 95%CrI, –7.3 to 0.8 [low certainty]), nemolizumab 0.5 mg/kg every 4 weeks (mean difference, –3; 95%CrI, –7.3 to 1.1 [low certainty]) and cyclosporine 5mg/kg (mean difference, –2.2; 95%CrI, –6.6 to 2 [low certainty]) were associated with clinically relevant improvement in the itch VAS score compared with placebo, however evidence is imprecise and rated as low certainty.

DLQI score

Dupilumab, 300 mg every 2weeks (mean difference, –4.8; 95%CrI, –5.8 to –3.7 [high certainty]), and abrocitinib, 100mg daily (mean difference, –5.2; 95% CrI, –9.3 to –1.1 [low certainty]) and 200 mg daily (mean difference, –4.9; 95% CrI, –8.8 to –1.0 [low certainty]), were associated with clinically important differences in the DLQI score compared with placebo. Azathioprine dosed according to thiopurine methyltransferase levels was associated with clinically meaningful improvement in the DLQI score compared with placebo, but this improvement was based on low certainty evidence owing to imprecision (mean difference, −3.4; 95% CrI, −7.1 to 0.2)".

(Taken from Drucker et al.; results section, page 664 [15])

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

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 39 RCTs with 6360 patients evaluating 20 systemic AE medications. An excerpt of safety outcomes of approved drugs against placebo in adult patients receiving 8 to 16 weeks of treatment is presented below (modified from Drucker et al. [15]).

Medication and dose (all versus placebo)	Odds ratios (95% CrI)* for serious adverse events** Ranking*** SUCRA	Certainty of evidence (GRADE)	Odds ratios (95% CrI) for serious adverse events only medications currently use**	Odds ratios (95% CrI) for withdrawal due to adverse events	Certainty of evidence (GRADE)	Odds ratios (95% CrI) for withdrawal due to adverse events only medications currently use**

Azathioprine TPMT adjusted	15.7 (0.8 to 1255.9) Rank 38 SUCRA 0.11	⊕⊕◯◯ Low [2,3]	13.2 (0.7 to 1077.8) Rank 4 SUCRA 0.33 (Azathioprine no dose given)	4.7 (0.2 to 301.6)	⊕⊕◯◯ Low [1,2,3]	7 (1.2 to 9.0) Rank 6 SUCRA 0.32 (Azahtioprine no dose given)
Baricitinib, 2 mg/d	0.3 (0 to 2) Rank 10 SUCRA 0.68	⊕⊕⊕◯ Moderate[2]		0.2 (0 to 5)	⊕⊕◯◯ Low [2,4]	
Baricitinib, 4 mg/d	1.4 (0.3 to 6) Rank 25 SUCRA 0.39	⊕⊕◯◯ Low [2,4]		1.3 (0.1 to 27)	⊕⊕⊕◯ Moderate[1,2]	
Cyclosporine–lower dose						0.4 (0 to 92.2) Rank 1 SUCRA 0.81
Cyclosporine–higher dose						7 (0.2 to 679) Rank 5 SUCRA 0.38
Dupilumab, 600 mg for 1 dose, then 300 mg every 2 wk	0.5 (0.3 to 1.1) Rank 14 SUCRA 0.62	⊕⊕⊕◯ Moderate[1]	0.5 (0.3 to 1.1) Rank 1 SUCRA 0.92	1.1 (0.2 to 5.4)	⊕⊕⊕◯ Moderate[1,2]	1.1 (0.4 to 2.6) Rank 3 SUCRA 0.73
Methotrexate			3.3 (0 to 1218.2) Rank 3 SUCRA 0.59			3.3 (0.1 to 97.7) Rank 4 SUCRA 0.51
Tralokinumab, 300 mg every 2 wk	0.1 (0 to 2.3) Rank 5 SUCRA 0.80	⊕⊕◯◯ Low [2,4]				
Upadacitinib, 15 mg/d	0.8 (0 to 10.2) Rank 18 SUCRA 0.52	⊕◯◯◯ Very Low[2,3,4]				
Upadacitinib, 30 mg/d	0.1 (0 to 2.6) Rank 6	⊕◯◯◯ Very Low[2,3,4]				

	SUCRA 0.79			

Table definitions
*Crl: 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
1. NMA estimates imprecise and would suggest different conclusions at either end of the 95% Credible Intervals.
2. Number of participants included in analysis below optimal information size.
3. Significant issues related to risk of bias from included trials.
4. Very serious imprecision (lowered 2 levels) for very imprecise NMA estimate.
5. Very serious risk of bias issues (lowered 2 levels) from included trials.

"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." (Taken from Drucker et al.; result section, page 664 [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).

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]

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].

Indirect evidence on patient´s preference:

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).

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

Drucker et al report:
"This network meta-analysis is based on 39 RCTs including 6360 patients taking 20 systemic AD medications. In analyses of outcomes in adult patients receiving between 8 and 16 weeks of treatment, dupilumab was efficacious based on high certainty evidence with regards to improving clinical signs, including clinically important differences in EASI scores. Dupilumab and the investigational Janus kinase inhibitors upadacitinib and abrocitinib provided clinically meaningful improvement in POEM scores and dupilumab and abrocitinib were associated with clinically meaningful improvements in the DLQI score compared with placebo.

[…] the SMD scale permitted comparisons of dupilumab with older systemic AD medications, for which no head-to-head trials exist, to our knowledge. Dupilumab and higher-dose cyclosporine appear to have better effectiveness during the first 4 months of therapy in improving clinical signs, itch, and quality of life relative to methotrexate and azathioprine. 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".

[…] Our safety analyses were uninformative and future updates including studies with larger sample sizes and longer duration may improve our ability to detect differences in safety and tolerability."
(Taken from Drucker et al.; discussion section, page 664 [15])

Table 1: Effectiveness and safety of currently used drugs for AE (Data taken from Drucker et al.; Supplementary Appendix for Baseline Review – Published online April 22, 2020). Lower left hand triangle: standardized mean difference clinical signs / upper right hand triangle odds ratios of withdrawal due to adverse events, credibility intervals.

Azathioprine	0.9 (0, 134.8)	0 (0, 17)	0.1 (0,1.1)	0.5 (0, 4.7)	0.1 (0, 0.8)
0.6 (0,1.2)	**Ciclosporin higher dose**	0.1 (0,1)	0.2 (0, 6)	0.5 (0, 62.2)	0.1 (0, 5.2)
0.3 (-0.3, 0.9)	-0.4 (-0.7, 0)	**Ciclosporin lower dose**	2.9 (0, 837.4)	9.3 (0, 5451.3)	2.7 (0, 751.1)
0.4 (0, 0.8)	-0.2 (-0.8, 0.4)	0.2 (-0.4, 0.8)	**Dupilumab 600 mg 1x then 300 mg Q2W**	3.2 (0.1, 103.6)	1 (0.4, 2.4)
0.1 (-0.4, 0.6)	-0.5 (-1.1, 0)	-0.2 (-0.6, 0.3)	-0.3 (-0.9, 0.3)	**Methotrexate**	0.3 (0, 8.2)
-0.4 (-0.8, -0.1)	-1.1 (-1.7, -0.5)	-0.7 (-1.3, -0.1)	-0.9 (-1, -0.8)	-0.6 (-1.1, 0)	**Placebo**

Lower triangle: 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
Upper triangle: An effect estimate less than 1 in a given cell favors the column-defining treatment.
red = ⊕⊕◯◯ low certainty evidence

green = ⊕⊕⊕⊕ high certainty evidence

Table 2: Quality of life and itch, currently used drugs for AE (Data taken from Ducker et al.; Supplementary Appendix for Baseline Review – Published online April 22, 2020). Lower left hand triangle: standardized mean difference quality of life, upper right hand triangle standardized mean difference change in itch)

Azathioprine	-0.5 (-1.9, 0.8)	no ciclosporine lower dose in this NMA	-0.6 (-1.5, 0.3)	0 (-0.8, 0.9)	0.3 (-0.6, 1.1)
0.5 (-0.3; 1.3)	**Ciclosporin higher dose**	no ciclosporin lower dose in this NMA	0 (-1.2, 1)	0.6 (-1.1, 2.2)	0.8 (-0.3, 1.8)
0.2 (-0.5, 1)	-0.3 (-0.8, 0.3)	**Ciclosporin lower dose**	no ciclosporin lower dose in this NMA	no ciclosporin lower dose in this NMA	no ciclosporin lower dose in this NMA
0.7 (0, 1.3)	0.1 (-0.6, 0.9)	0.4 (-0.4, 1.2)	**Dupilumab 600 mg 1x then 300 mg Q2W**	0.6 (-0.6, 1.9)	**0.8 (0.5, 1.2)**
0.1 (-0.6, 0.7)	-0.5 (-1.2, 0.3)	-0.2 (-0.7, 0.4)	-0.6 (-1.4, 0.2)	**Methotrexate**	0.2 (-1, 1.4)
-0.1 (-0.8, 0.5)	-0.7 (-1.4, 0)	-0.4 (-1.1, 0.4)	-0.8 (-1, -0.6)	-0.2 (-1, 0.5)	**Placebo**

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
dark red = ⊕◯◯◯very low certainty of evidence
red = ⊕⊕◯◯ low certainty evidence
green = ⊕⊕⊕⊕high certainty evidence
white = no further data available

A complete overview of all analyses performed as part of the living systematic review can be found here:
https://eczematherapies.com/research/ (last accessed 5 July 2021)

Recommendations

Recommendation	Short term (8-16 weeks) vs placebo (NMA main analysis) Bold = statistically significant difference
We suggest using azathioprine in AE patients who are candidates for systemic treatment.	⊕⊕◯◯ LOW for mean difference / standardized mean difference **change in signs**, DLQI, Itch VAS; OR undesirable effects
We recommend using ciclosporin to achieve disease control in AE patients who are candidates for systemic treatment.	⊕⊕◯◯ LOW for mean difference / standardized mean difference **change in signs**, Itch VAS
We suggest using methotrexate in AE patients who are candidates for systemic treatment.	⊕⊕◯◯ LOW for standardized mean difference **change in signs**
We recommend dupilumab in AE patients who are candidates for systemic treatment.	⊕⊕⊕⊕ HIGH for mean difference/ standardized mean difference **EASI**, **change in signs**, **POEM**, **DLQI** ⊕⊕⊕◯ MODERATE for undesirable effects Long term (52 weeks) vs placebo RoB low for change in **EASI**, POEM, DLQI, undesirable effects
We recommend baricitinib in AE patients who are candidates for systemic treatment.	⊕⊕⊕◯ MODERATE for mean difference **EASI**, DLQI ⊕⊕⊕◯ MODERATE - ⊕⊕◯◯ LOW for undesirable effects
We recommend tralokinumab in AE patients, who are candidates for systemic treatment.	⊕⊕⊕◯ MODERATE for mean difference **EASI**, DLQI ⊕⊕◯◯ LOW for undesirable effects
We recommend upadacitinib in AE patients who are candidates for systemic treatment	⊕⊕◯◯ LOW for mean difference **POEM** ⊕◯◯◯ VERY LOW for undesirable effects

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

Subgroup considerations - children and adolescents

Subgroup considerations – children and adolescents

Three studies of children were identified, due to scarcity of studies no pooling of studies was done.

In one study (n=14) a greater reduction in mean SCORAD for ciclosporin 4 mg/kg when compared for IVIG was shown. In another small study (n=20) no significant difference in final SCORAD between ciclosporin 2.5 mg/kg and MTX was found. And the third study (n=251) found that dupilumab was superior to placebo (EASI75; IGA0/1). The overall risk of bias was high, high and unclear, respectively.

Author year and country	Age	Arm (drug and dose)	Trial duration	Primary outcome	Results*	Overall risk of bias
Bemanian 2005 Iran	NR	Cyclosporine 4 mg/kg PO OD IVIG 2 g/kg x1	Active treatment: 12 wks; Total trial duration: 12 wks	Mean change in SCORAD from baseline to 12 weeks	"There was a significant difference in the clinical outcomes of these two groups with a marked reduction in SCORAD of day 90th in group 1 in comparison to group 2 (P-value = 0.005). No significant adverse drug reaction was seen in these two groups".	- High
El-Khalawany 2013 Egypt	8 – 14 yrs	Methotrexate 5mg PO X1 then 7.5mg PO qweek Cyclosporine 2.5mg/kg PO OD	Active treatment: 12 wks Total trial duration: 24 wks	Absolute reduction in SCORAD score at the end of treatment period	"In group A, the mean SCORAD score at the beginning of the study was 57.90 ± 3.21 that was reduced at the end of the treatment period to reach 29.35 ± 6.32 with a mean absolute reduction of 26.25 ± 7.03. In group B, the mean SCORAD score was 56.54 ± 4.82 at the start of treatment and was 31.35 ± 8.89 at the end of 12 weeks of treatment. The mean absolute reduction was 25.02 ± 8.21. There was no statistically significant difference in the reduction of SCORAD score between both groups (*P* ± 0.93). Mild and temporary adverse effects were reported in some patients in both groups".	- High
Paller 2019	12 – 17 yrs	Dupilumab 600 mg then 300 mg q4 weeks	Active treatment: 16 wks	Co-primary at week 16:	"The proportion of patients with EASI-75 improvement from baseline increased (every 2 weeks, 41.5%; every 4 weeks, 38.1%; placebo, 8.2%) with differences vs placebo of 33.2% (95% CI, 21.1%-45.4%) for every 2 weeks and 29.9% (95% CI,	?

USA		Dupilumab 600 mg then 300 mg q2 weeks OR 400 mg then 200 mg q2 weeks (weight-based) Placebo	Total trial duration: 28 wks	1) IGA 0 or 1 and reduction of at least 2 points 2) Proportion of patient with EASI-75	17.9%-41.8%) for every 4 weeks ($P < .001$). Efficacy of the every-2-week regimen was generally superior to the every-4-week regimen. Patients in the dupilumab arms had higher percentage values of conjunctivitis (every 2 weeks, 9.8%; every 4 weeks, 10.8%; placebo, 4.7%) and injection-site reactions (every 2 weeks, 8.5%; every 4 weeks, 6.0%; placebo, 3.5%), and lower nonherpetic skin infections (every 2 weeks, 9.8%; every 4 weeks, 9.6%; placebo, 18.8%)".	Unclear

*Results as reported in the studies abstracts.

QUESTION

What is the efficacy (improvement long-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?

Long term effects

Desirable Effects – long term

How substantial are the desirable anticipated effects ?

RESEARCH EVIDENCE

Four studies of **long term** systemic therapies were identified, due to scarcity of studies no pooling of studies was done. A brief summary of studies with systemic therapies relevant to the key question is presented below (data from Drucker et al. [15]).

Study	Arm (drug and dose	Timepoint long term	Sample size	Signs EASI scale	Symptoms POEM	Quality of life DLQI	Overall risk of bias
Blauvelt 2017 **USA**	Dupilumab 600 mg x1 then 300 mg every week	52 weeks	270	% change from baseline: -80.3 ± 2.64 SE	Mean change from baseline: -12.7 ± 0.45 SE	Mean change from baseline: -10.7 ± 0.36 SE	+ Low risk
	Dupilumab 600 mg x1 then 300 mg every 2 weeks		89	% change from baseline: -78.3 ± 4.44 SE	Mean change from baseline: -13.7 ± 0.75 SE	Mean change from baseline: -10.9 ± 0.59 SE	
	Placebo		264	% change from baseline: -45.8 ± 2.7 SE	Mean change from baseline: -5.3 ± 0.46 SE	Mean change from baseline: -5.6 ± 0.36 SE	
Goujon 2017 **France**	Methotrexate 15 mg q week[a]	24 weeks	23	Follow up mean: 5 ± 3.5 SD		Follow up mean: 5 ± 4.6 SD	- High risk
	Cyclosporine 2.5 mg/kg OD		31	Follow up mean: 5.4 ± 5 SD		Follow up mean: 3.3 ± 4.4 SD	
Simpson 2018 **USA**	Apremilast 30 mg BID[b]	24 weeks	50	% change from baseline: -49.6 ± 33.1 SD			? Unclear risk

	Apremilast 40 mg BID[b]		46	% change from baseline: -51.1 ± 42.2 SD		
Silverberg 2019 **USA**	Nemolizumab 20 mg 1x then 10 mg every 4 weeks	24 weeks	40	% change from baseline: -72.2 ± 25.96 SD		Unclear risk
	Nemolizumab 60 mg 1x then 30 mg every 4 weeks		44	% change from baseline: -73.4 ± 26.96 SD		
	Nemolizumab 90 mg 1x then 90 mg every 4 weeks		40	% change from baseline: -69.2 ± 31.06 SD		
	Placebo		38	% change from baseline: -58.4 ± 31.99 SD		

a Dose was increased to 25mg every week

b Patients could have started taking apremilast at week 0 or 12.

Undesirable Effects – long term

How substantial are the undesirable anticipated effects?

RESEARCH EVIDENCE

Four studies of long term systemic therapies were identified, due to scarcity of studies no pooling of studies was done. A brief summary of systemic therapies relevant to the key question is presented below (data from Drucker et al. [15]).

Study	Arm (drug and dose	Included in analysis	Serious adverse event	Included in analysis	Withdrew due to adverse event	Overall risk of bias
Blauvelt 2017 USA	Dupilumab 600 mg x1 then 300 mg qweek	315	9	315	9	 Low risk
	Dupilumab 600 mg x1 then 300 mg every 2weeks	110	4	110	2	
	Placebo	315	16	315	24	
Goujon 2017 France	Methotrexate 15 mg every week[a]	50	0	50	6	 High risk
	Cyclosporine 2.5 mg/kg OD	47	1	47	1	
Simpson 2018†	Apremilast 30 mg BID[b]	82	1	3	82	

USA	Apremilast 40 mg BID[b]	86	1	9	86	Unclear risk
Silverberg 2019 **USA**	Nemolizumab 20 mg 1x then 10 mg every 4 weeks	55	3	55	3	? Unclear risk
	Nemolizumab 60 mg 1x then 30 mg every 4 weeks	57	2	57	2	
	Nemolizumab 90 mg 1x then 90 mg every 4 weeks	57	2	57	3	
	Placebo	56	1	56	0	

a Dose was increased to 25mg q week
b Patients could have started taking apremilast at week 0 or 12.

Balance of effects – long term

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

RESEARCH EVIDENCE

Blauvelt et al. showed improvement in signs and symptoms and adequate safety with dupilumab against placebo (RoB low). No significant difference was found between nemolizumab 30 mg and placebo at 24 weeks (RoB unclear).[23] Simpson et al. reported more frequent adverse events with apremilast 40mg than apremilast 30mg and had to be discontinued during the trial. Goujon et al. found significant improvement at 20 weeks with methotrexate 25mg every week when compared with ciclosporin 2.5mg/kg daily (RoB high).
More studies of good methodological quality and longer duration are needed to detect differences in effectiveness and safety outcomes.

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