

What is the most effective systemic treatment for atopic dermatitis?

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Funding information

This research did not receive any specific grant from funding agencies in the public, commercial or non-profit sectors.

Eczema/atopic dermatitis (AD) is a chronic inflammatory skin condition with a remitting and relapsing course diagnosed clinically with the onset, often in early childhood, of pruritic, erythematous skin lesions, which are excoriated, sometimes exudative in the acute phase, turning into lichenified in the long-term.¹ The worldwide prevalence of eczema is up to 20% of children and 3% of adults.²

Systemic treatments may be used for AD if topical treatments fail to achieve control or are poorly tolerated.³ The comparative safety and effectiveness of different systemic immunosuppressive treatments for AD are not clear, and multiple new treatments are in use or in development.⁴

This Cochrane review used network meta-analysis (NMA) to compare the efficacy and safety of systemic immunosuppressive agents for treating AD. NMA is used so that indirect comparisons can be made between treatments that have been tested against a common comparator such as placebo, and this information can be combined with data from direct head-to-head comparisons. NMA is often useful because pharmaceutical trials often compare immunosuppressive treatments with a placebo but not with an alternative immunosuppressive agent.

**1 | COCHRANE ABSTRACT:
SYSTEMIC TREATMENTS FOR ECZEMA:
A NETWORK META-ANALYSIS BY
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1.1 | Disclaimer

This is an abstract of a Cochrane review published in the Cochrane Database of Systematic Reviews 2020, Issue 9. (see www.cochranelibrary.com for information). Cochrane reviews are regularly updated as new evidence emerges and in response to feedback, and the Cochrane Library should be consulted for the most recent version of the review.

1.2 | Background

Eczema is a common and chronic, relapsing, inflammatory skin disorder. It seriously impacts quality of life and economic outcomes,

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especially for those with moderate-to-severe eczema. Various treatments allow sustained control of the disease; however, their relative benefit remains unclear due to the limited number of trials directly comparing treatments.

1.3 | Objectives

To assess the comparative efficacy and safety of different types of systemic immunosuppressive treatments for moderate-to-severe eczema using NMA and to generate rankings of available systemic immunosuppressive treatments for eczema according to their efficacy and safety.

1.4 | Search methods

We searched the following databases up to August 2019: the Cochrane Skin Specialised Register, CENTRAL, MEDLINE and Embase.

1.5 | Selection criteria

All randomized controlled trials (RCTs) of systemic immunosuppressive agents for moderate-to-severe atopic eczema when compared to placebo or any other eligible eczema treatment.

1.6 | Data collection and analysis

We synthesized data using pair-wise analysis and NMA to compare treatments and rank them according to their effectiveness.

Effectiveness was assessed primarily by determining the proportion of participants who achieved at least 75% improvement in the Eczema Area and Severity Index (EASI75) and improvement in the Patient-Oriented Eczema Measure (POEM). Safety was evaluated primarily by considering the proportion of participants with serious adverse events (SAEs) and infection.

We deemed a short-term follow-up as ≤ 16 weeks and a long-term follow-up as > 16 weeks.

We assessed the certainty of the body of evidence from NMA for these primary outcomes using six domains of CiNEMA grading.

1.7 | Main results

We included a total of 74 studies, with 8177 randomized participants. Approximately 55% of participants were male, with average age of 32 years (range 2–84 years), although age and gender were unreported for 419 and 902 participants, respectively. Most of the included trials were placebo-controlled (65%), 34% were head-to-head studies (15% assessed the effects of different doses of the

Key Messages

- In the short-term, dupilumab was the most effective biologic for moderate-to-severe eczema.
- Long-term data regarding the effectiveness and safety of new biologics are lacking.
- There is a need for data comparing the new biologics with the conventional systemic therapies for eczema.

same drug), and 1% were multi-armed studies with both an active comparator and a placebo.

All trials included participants with moderate-to-severe eczema, but 62% of studies did not separate data by severity; 38% of studies assessed only severe eczema. The total duration of included trials ranged from 2 weeks to 60 months, whereas treatment duration varied from a single dose (CIM331, KPL-716) to 60 months (methotrexate (MTX)).

Seventy studies were available for quantitative synthesis; this review assessed 29 immunosuppressive agents from three classes of interventions. These included (a) conventional treatments, with ciclosporin assessed most commonly; (b) small-molecule treatments, including phosphodiesterase (PDE)-4 inhibitors, tyrosine kinase inhibitors and Janus kinase (JAK) inhibitors; and (c) biological treatments, including anti-CD31 receptors, anti-interleukin (IL)-22, anti-IL-31, anti-IL-13, anti-IL-12/23p40, anti-OX40, anti-TSLP, anti-CRTH2 and anti-immunoglobulin E (IgE) monoclonal antibodies, but most commonly dupilumab.

Most trials (73) assessed outcomes at a short-term duration ranging from 2 to 16 weeks, whereas 33 trials assessed long-term outcomes, with duration ranging from 5 to 60 months. All participants were from a hospital setting. Fifty-two studies declared a source of funding, and of these, pharmaceutical companies funded 88%. We rated 37 studies as high risk; 21, unclear risk; and 16, low risk of bias, with studies most commonly at high risk of attrition bias.

Network meta-analysis suggests that dupilumab ranks first for effectiveness when compared with other biological treatments. Dupilumab is more effective than placebo in achieving EASI75 (risk ratio (RR) 3.04, 95% confidence interval (CI) 2.51–3.69) and improvement in POEM score (mean difference 7.30, 95% CI 6.61–8.00) at short-term follow-up (high-certainty evidence).

Very low-certainty evidence means we are uncertain of the effects of dupilumab when compared with placebo, in terms of the proportion of participants who achieve EASI75 (RR 2.59, 95% CI 1.87–3.60) at long-term follow-up.

Low-certainty evidence indicates that tralokinumab may be more effective than placebo in achieving short-term EASI75 (RR 2.54, 95% CI 1.21–5.34), but there was no evidence for tralokinumab to allow us to assess short-term follow-up of POEM or long-term follow-up of EASI75.

We are uncertain of the effect of ustekinumab compared with placebo in achieving EASI75 (long-term follow-up: RR 1.17, 95% CI

0.40–3.45; short-term follow-up: RR 0.91, 95% CI 0.28–2.97; both very low certainty). We found no evidence on ustekinumab for the POEM outcome.

We are uncertain whether other immunosuppressive agents that targeted our key outcomes influence the achievement of short-term EASI75 compared with placebo due to low- or very low-certainty evidence.

Dupilumab and ustekinumab were the only immunosuppressive agents evaluated for long-term EASI75. Dupilumab was the only agent evaluated for improvement in POEM during short-term follow-up.

Low- to moderate-certainty evidence indicates a lower proportion of participants with SAEs after treatment with QAW039 and dupilumab compared with placebo during short-term follow-up, but low- to very low-certainty evidence suggests no difference in SAEs during short-term follow-up of other immunosuppressive agents compared with placebo.

Evidence for effects of immunosuppressive agents on the risk of any infection during short-term follow-up and SAEs during long-term follow-up compared with placebo was of low or very low certainty but did not indicate a difference.

We did not identify differences in other adverse events (AEs), but dupilumab is associated with specific AEs, including eye inflammation and eosinophilia.

1.8 | Authors' conclusions

Our findings indicate that dupilumab is the most effective biological treatment for eczema. Compared with placebo, dupilumab reduces eczema signs and symptoms in the short-term for people with moderate-to-severe atopic eczema. Short-term safety outcomes from clinical trials did not reveal new safety concerns with dupilumab. Overall, evidence for the efficacy of most other immunosuppressive treatments for moderate-to-severe atopic eczema is of low or very low certainty.

Given the lack of data comparing conventional with newer biological treatments for the primary outcomes, there remains high uncertainty for ranking the efficacy and safety of conventional treatments such as ciclosporin and biological treatments such as dupilumab.

Most studies were placebo-controlled and assessed only the short-term efficacy of immunosuppressive agents. Further adequately powered head-to-head RCTs should evaluate comparative long-term efficacy and safety of available treatments for moderate-to-severe eczema.

2 | COMMENTARY

There is a significant unmet need to improve overall management of AD in order that patients of all ages can gain control of their symptoms using safe and effective treatments.⁵ This NMA has

clarified the effectiveness and safety of newer treatments as well as established systemic treatments. The review included 74 studies with 8177 participants, mostly assessing short-term outcomes up to 16 weeks, for this long-term condition. Dupilumab was the most effective biologic agent for reducing short-term signs and symptoms of AD, with high certainty of effectiveness compared with placebo. However, the evidence of such effectiveness in the long-term is uncertain, due to very low-certainty evidence. The reported effects may change with new studies. The effectiveness of ustekinumab is uncertain. The effectiveness of tralokinumab, teplizumab, ASN002 and GBR830 on short-term outcomes is based on low-certainty evidence with no evidence in long-term follow-up. Lebrikizumab was the least effective treatment. Safety data were limited, and systematic reviews of trials may not be the best way to evaluate drug safety. Dupilumab was the safest treatment in the trials in the long-term, but with only low-certainty evidence, and this treatment has known adverse effects especially ocular symptoms. Older systemic treatments such as ciclosporin A, methotrexate and azathioprine have generally not been compared directly with the biologic agents, meaning that their comparative effectiveness with dupilumab is unclear. A non-Cochrane systematic review of this topic, which used different methods than the Cochrane review, found that ciclosporin and dupilumab were similarly effective for reducing clinical signs of AD, compared with placebo.⁶ Ciclosporin is one of the most commonly used older systemic treatments for AD, but can cause hirsutism, gingivitis and gastrointestinal symptoms.

Dupilumab is recommended by NICE for refractory adult AD, which has not responded to at least one other systemic treatment and should be stopped at 16 weeks if there is no improvement, as measured by the EASI 50/DLQ1.⁷ The UK cost for a 16-week course is £1264.89. The equivalent US cost varies by insurance provider and is approximately \$100 or more monthly to insured patients.⁸

The failure of pharmaceutical companies to compare newer to conventional treatments, by only comparing them to placebo, has created a significant problem in treating refractory AD. This knowledge gap will partly be addressed in an upcoming trial funded by the UK National Institute for Health Research called BEACON (Best systemic treatments for adults with atopic eczema over the long-term: A randomized, assessor-blind trial comparing ciclosporin, methotrexate and dupilumab). Children have the highest AD burden, and there is limited information to guide systemic treatment in this age group, with again a lack of head-to-head comparisons of systemic treatments. People with eczema and their carers also need information about long-term effectiveness and safety, and the use of core outcome measures in clinical trials will mean that outcomes from future trials are more comparable than historical trials. The new biologic treatments for eczema look promising, especially dupilumab, but it is important to recognize the limitations of the current data supporting their use. Their unknown level of effectiveness compared with older systemic treatments (or indeed, with topical treatments), the limited data in children, limited long-term outcome data

and unknown long-term safety are all issues that should be covered in conversations about systemic treatment options for eczema with patients and their careers.

ACKNOWLEDGEMENTS

The authors would like to thank Dr Robert Boyle for his guidance in preparing this manuscript.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interests to disclose in relation to this paper.

AUTHOR CONTRIBUTIONS

AG drafted the introduction and methods. NB drafted the commentary, interpreted the data and reviewed the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

ETHICAL STATEMENT

Not applicable.

DATA AVAILABILITY STATEMENT

Not applicable.

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How to cite this article: Banerjee N, Grewal A. What is the most effective systemic treatment for atopic dermatitis? *Clin Exp Allergy*. 2021;00:1–4. <https://doi.org/10.1111/cea.13980>