What’s new in atopic eczema? An analysis of systematic reviews published in 2018. Part 2: systemic therapies

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Summary

This review forms part of an annual update series on atopic eczema (AE), where systematic reviews (SRs) are gathered and appraised to provide a summary of key recent research findings. The focus of this article is systemic therapies used in AE, while a review on prevention and topical therapies is provided in Part 1. In total, 17 SRs on various systemic treatments used in AE were first published or indexed in 2018. There is a lack of evidence to support vitamin D supplementation, montelukast and naltrexone in AE treatment. The adverse effects of systemic corticosteroids are the main barrier to their use, and there is also a lack of data to determine the optimal delivery and duration of treatment with them. Of other immunosuppressants, ciclosporin has the most robust evidence of efficacy. Biologic therapies in AE treatment are being increasingly investigated, and to date, the greatest quantity of data and evidence of efficacy relates to dupilumab. The most commonly reported adverse effects are injection-site reactions and conjunctivitis. Other biologics showing some evidence of efficacy include nemolizumab, lebrizumab and tralokinumab, although further data are needed. There are currently insufficient data on oral small molecules, including Janus kinase inhibitors, in the treatment of AE. A Cochrane review on probiotics showed no significant benefit, and SRs and meta-analyses on complementary and alternative medicines, including probiotics, in paediatric AE demonstrated significant heterogeneity, thereby limiting their interpretation. This summary of recent SRs provides up-to-date evidence for clinicians on systemic therapies in AE.

Background

The aim of this two-part evidence update is to present key findings from systematic reviews (SRs) published in 2018 summarizing systemic therapies for atopic eczema (AE). Part 1 covered prevention and topical treatment of AE. The details of the search methods can be found at: https://www.nottingham.ac.uk/research/groups/cebd/documents/methodological-resources/ebu-protocol.pdf

The quality of all SRs was appraised using the AMSTAR2 checklist,1 and details of each of the SRs, including assessments of quality, can be found in Table S1. Where SRs have included meta-analyses, the results are summarized in Table S2.

Vitamin D supplementation

An SR investigating the effect of vitamin D supplementation on AE severity in children2 included 4
randomized controlled trials (RCTs) and 2 cohort studies (277 participants). Four studies suggested that vitamin D supplementation improved AE while two did not, and a meta-analysis was not conducted. The authors concluded that there was weak evidence to support this treatment; however, as the SR did not fulfil any of the AMSTAR2 critical domains, it raises questions about the methodological quality of the review.

Montelukast

Two SRs assessed the effect of montelukast in AE treatment.3,4 A Cochrane review on leucotriene antagonists4 evaluated 5 RCTs (202 participants), and found no evidence of a difference between montelukast and placebo in terms of disease severity, pruritus and topical corticosteroid use. A second montelukast review3 evaluated 11 RCTs (385 participants); 6 of these studies were excluded from the Cochrane review as they were crossover trials. This SR found conflicting results, and the authors concluded that there was limited evidence to support the use of montelukast in AE. Although the Cochrane review4 methodologically scored highly using AMSTAR2, the other review3 did not adequately address four critical domains, thereby indicating ‘critically low’1 confidence in the results of the SR.

Naltrexone

In a review assessing the dermatological use of naltrexone for pruritic skin conditions,5 2 RCTs (54 participants) evaluated oral naltrexone in AE. The authors concluded that high-dose naltrexone caused a significant reduction in pruritus. However, no statistical analysis was given, a meta-analysis was not carried out and this review did not fulfil most of the items in the AMSTAR2 checklist.

Systemic corticosteroids

An SR assessing the safety and efficacy of systemic corticosteroids6 evaluated 64 articles. The authors concluded that the evidence was not sufficiently strong to determine the optimal treatment delivery or duration. The safety profile was of particular concern, and was the main barrier to this treatment. The reported adverse effects included growth suppression in children, hypertension, diabetes, weight gain, cataracts, behavioural changes and rebound flaring.

Biologics

Biologics were evaluated in an SR including 23 studies (13 RCTs and 10 observational studies, 3773 participants).7 Meta-analyses of five RCTs comparing dupilumab 300 mg weekly or biweekly against placebo showed favourable outcomes in achieving 75% reduction in Eczema Area and Severity Index (EASI75) [relative risk (RR) 3.3, 95% CI 2.9–3.6] and Investigator’s Global Assessment (IGA) 0/1 responder rates (RR 3.7, 95% CI 3.2–4.3). Eight other treatments, including nemolizumab, lebrikizumab and tralokinumab, showed promise, although further data are needed. However, omalizumab, ustekinumab, infliximab, rituximab and antithymic stromal lymphopoietin receptor MK-8226-003 lacked adequate evidence of efficacy. The methodological quality of this SR was considered to be thorough and robust.

Dupilumab

Three SRs assessed the use of dupilumab for AE treatment. One review performed a meta-analysis of 6 RCTs (2447 participants),8 which showed significant improvements in EASI, body surface area involvement, pruritus, Dermatology Life Quality Index and IGA. The benefits conferred by dupilumab 300 mg weekly were comparable to an alternate weekly treatment regimen at the same dose. Another review assessed the adverse effects of dupilumab on adults with moderate–severe AE; meta-analyses demonstrated reduced risk of skin infection and exacerbation of AE compared with placebo, but slightly increased risk of headache and moderately increased risk of injection-site reactions and conjunctivitis.9 A further review analysed infection rates in these dupilumab trials, and pooled estimates showed that dupilumab was associated with a decreased risk of skin infections and eczema herpeticum; no significant difference was found between dupilumab and placebo for risk of overall herpesvirus infection or overall infection rates.10

Omalizumab

An SR of omalizumab reviewed eight studies involving children with moderate–severe AE.11 However, only one study was an RCT; the rest were cohort studies, case series and case reports, and the number of participants in each study was no greater than 11. Although the authors concluded that omalizumab ‘decreases SCORAD [SCORing Atopic Dermatitis] in all of severe AE’, this assertion was based on small,
uncontrolled and underpowered studies. The SR had multiple quality concerns when assessed using AMSTAR2.

**Ustekinumab**

The benefit of ustekinumab was evaluated in an SR that evaluated two RCTs and eight case studies. While neither RCT showed that treatment yielded a significant improvement in EASI, it should be kept in mind that the review did not fulfil any of the AMSTAR2 critical domains.

**Other immunosuppressants**

An SR evaluating systemic treatments for adults and children with AE included 41 RCTs (4938 participants), and encompassed 17 different medications. Meta-analyses were not carried out, and the authors concluded that, at present, the strongest evidence is for dupilumab and ciclosporin in improving disease severity. However, the SR did not report on the quality of the individual studies, although it did highlight nonuniform reporting of outcome data as a barrier in the comparison of studies.

**Small molecules**

The use of Janus kinase (JAK) inhibitors in multiple dermatological conditions was evaluated by one SR. The only AE study involved was a case series (six participants) treated with oral tofacitinib; all had improvements in SCORAD. Another SR of oral small molecules in AE included the aforementioned case series of six patients treated with tofacitinib, as well as data on another oral JAK inhibitor, baricitinib. A single phase II RCT of baricitinib (124 participants) demonstrated that when combined with standard care (topical corticosteroids), significantly more patients achieved EASI50 using baricitinib 2 and 4 mg daily for 16 weeks compared with placebo. Data on oral apremilast were derived from two cohort studies, a small case series and case report (total of 32 participants). The results were so varied that it is not possible to draw firm conclusions. A phase IIa RCT on a histamine-4 receptor antagonist (NJ-39758979) was also included; this showed no evidence of efficacy and there were multiple adverse effects. Risk of bias assessments of the individual included studies that were not carried out.

**Complementary and alternative medicine, including probiotics**

Complementary and alternative medicine (CAM) for children with AE under the age of 14 was evaluated by an SR. The interventions included probiotics, diet, biofilm, borage oil and swimming. A preregistered protocol was used and 24 RCTs were included (2233 participants). Meta-analysis demonstrated a superior effect of treatment with probiotics compared with placebo for SCORAD, with a mean difference of 9.01 (95% CI 7.12–10.90). Combining CAM interventions, meta-analysis demonstrated lower relapse rates and global improvement in symptoms and signs when combined with usual care, compared with usual care alone. These conclusions were limited by significant clinical and statistical heterogeneity.

Two other SRs studied treatment of AE with probiotics. A Cochrane review to assess the effects of probiotics for AE treatment included 39 RCTs (2599 participants). Significant heterogeneity was noted, and it was concluded that probiotics made little to no difference in improving patient-rated eczema symptoms, quality of life or investigator-rated eczema severity score.

Another review conducted a meta-analysis of eight RCTs of 741 participants under the age of 36 months. The weighted mean difference in SCORAD was −5.71 (−8.37 to 3.04) in favour of probiotics vs. placebo. However, significant heterogeneity was observed ($I^2 = 97.4\%$, $P < 0.01$) and the change in SCORAD did not meet the minimum clinically important difference. Furthermore, using the AMSTAR2 tool, the quality of this SR was rated as ‘critically low’, including the lack of a preregistered protocol and a list of excluded studies, compared with the Cochrane review, where the quality was rated as ‘high’.

**Conclusions**

Systemic treatments for AE are being extensively investigated globally, and newer treatments, including biologics and small molecules, need ongoing rigorous testing in high-quality trials. Although some SRs assessed were carried out with good methodological considerations, many SRs that score ‘critically low’ using the AMSTAR2 checklist continue to be published. Particular areas of concern include the lack of a preregistered protocol, information about excluded studies and assessments of bias in individual studies.
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CONFLICT OF INTEREST
The authors declare that they have no conflicts of interest.

Learning points
- There is insufficient evidence to support vitamin D supplementation, montelukast and naltrexone for AE treatment.
- There is a lack of evidence to allow determination of the optimal duration and delivery of systemic corticosteroids, and they carry a significant adverse effect profile.
- Ciclosporin and dupilumab both have robust efficacy data supporting their use in AE treatment.
- The risk of cutaneous infections is reduced in patients treated with dupilumab compared with placebo.
- Other biologics, including nemolizumab, lebrikizumab and tralokinumab, and small molecules have been under development and initial phase trials in recent years.
- There is limited evidence supporting the benefit of probiotics in patients with AE, particularly in adults.
- Two SRs of studies including only paediatric populations showed some benefit; however, significant heterogeneity of the included studies limited the interpretation of these results.
- Studies of CAM were also limited by significant heterogeneity.

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CPD questions

Learning objective

To gain up-to-date knowledge on the latest evidence regarding treatments for atopic eczema.

Question 1

Which of the following statements regarding the evidence for probiotics in the treatment of atopic eczema (AE) is true?

(a) A Cochrane review showed that probiotics are effective in the treatment of AE.
(b) Studies on probiotics demonstrate significant heterogeneity.
(c) Probiotics cannot be given to children.
(d) There is strong evidence indicating improved quality of life measures with probiotics.
(e) Specific brands of probiotics consistently show increased efficacy when compared to others.

Question 2

Based on the available evidence, which of the following consistently demonstrates efficacy in the treatment of atopic eczema?

(a) Vitamin D supplementation.
(b) Omalizumab.
(c) Naltrexone.
(d) Ciclosporin.
(e) Montelukast.

Question 3

Which of the following outcome measures have shown significant improvements with dupilumab for the treatment of atopic eczema in meta-analyses?

(a) Dermatology Life Quality Index (DLQI).
(b) Patient Orientated Eczema Measure (POEM).
(c) Atopic Dermatitis Control Test (ADCT).
(d) Recap of Atopic Eczema (RECAP).
(e) Children’s Dermatology Life Quality Index (CDLQI).

Question 4

Which of the following adverse effects have been observed in patients with atopic eczema (AE) treated with dupilumab compared with placebo?

(a) Increased risk of eczema herpeticum.
(b) Increased risk of cutaneous infection.
(c) Increased risk of AE flare.
(d) Increased risk of visual disturbance.
(e) Increased risk of headache.

Question 5

Which of the following treatments acts by inhibiting Janus kinase (JAK)?

(a) Apremilast.
(b) Ustekinumab.
(c) Abatacept.
(d) Baricitinib.
(e) Tocilizumab.

Instructions for answering questions

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• Read the article in print or online, paying particular attention to the learning points and any author conflict of interest disclosures
• Reflect on the article
• Register or login online at http://www.wileyhealthlearning.com/ced and answer the CPD questions
• Complete the required evaluation component of the activity

Once the test is passed, you will receive a certificate and the learning activity can be added to your RCP CPD diary as a self-certified entry.

This activity will be available for CPD credit for 2 years following its publication date. At that time, it will be reviewed and potentially updated and extended for an additional period.
Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Details and assessment of quality of individual systematic reviews.
Table S2. Details of the RCT meta-analyses performed in the included systematic reviews.