What’s new in atopic eczema? An analysis of systematic reviews published in 2019. Part 2: Treatment

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Summary

This review forms part of a series of annual evidence updates on atopic eczema (AE), and provides a summary of key findings from systematic reviews (SRs) published or indexed in 2019 related to AE treatment. Several SRs assessed the efficacy of topical corticosteroids (TCSs), topical calcineurin inhibitors, topical phosphodiesterase 4 inhibitors and topical JAK/STAT pathway inhibitors. However, there is a lack of good quality trials comparing topical treatment agents to TCSs, which remain the standard of care for patients with AE. Most included trials lack meaningful comparisons as they use vehicle as a comparator. There is also lack of harmonisation of outcome measures for AE across studies. Large, well-designed RCTs are needed to further determine whether any specific emollients offer superior benefit. There is evidence highlighting limited benefit of oral H1 antihistamines as ‘add-on’ therapy to topical treatment of eczema. Mycophenolate mofetil may have a role in patients with refractory AE. Among biologic therapies, most efficacy data relate to dupilumab. Furthermore, there is growing evidence for efficacy and safety of systemic JAK/STAT pathway inhibitors, but existing data are of low quality.

Background

The annual eczema evidence updates aim to summarise and appraise recent systematic reviews (SRs). This article is the second of a two-part series and highlights key findings on the treatment of atopic eczema (AE) from SRs published in 2019. Risk factors and prevention are covered in part 1 of this update.

The AMSTAR2 checklist was used to appraise the quality of the examined SRs. The characteristics and quality of individual SRs are summarised in Table S1. Table S2 details the results of meta-analyses, where conducted.

Topical therapies

Topical corticosteroids

A well-conducted SR and meta-analysis that included 12 randomised controlled trials (RCTs) and 2224 participants assessed the safety and efficacy of topical corticosteroids (TCS) versus vehicle/moisturiser in children under 2 years of age. TCS appeared more effective than, and as safe as, vehicle/moisturiser; however, included studies were poorly designed and included children...
older than 2 years of age. Authors also recognised the lack of harmonisation of outcome measures for AE across studies as an important limitation for interpretability of the findings.

Another SR\(^3\) investigated the risk of adrenal insufficiency with short-term use of low to moderate potency TCS in children with AE, concluding that there was a low prevalence of biochemical adrenal insufficiency and no evidence of clinical adrenal insufficiency with short-term use. However, this review did not meet any critical domains of AMSTAR2, and combined with the short-term follow-up in the included studies, raises uncertainty on the generalisability of the findings.

**Topical calcineurin inhibitors**

A SR and meta-analysis\(^4\) compared the efficacy and safety of different topical calcineurin inhibitors (TCI) with TCS for the treatment of moderate-severe AE, and included 14 RCTs and 7376 children and adults. The authors reported that TCI therapy may be marginally more effective than TCS, however TCI were associated with more adverse effects, including skin burning and pruritus. Analyses was limited by the variability of follow-up durations, and statistical significance for the main outcome was only reached when the authors compared TCI to TCS, irrespective of the TCS potency.

**Topical phosphodiesterase 4 inhibitors**

Two SRs reviewed the efficacy and safety of topical phosphodiesterase 4 inhibitors (PDE4) in the management of mild-moderate AE. One SR reported on studies of crisaborole exclusively\(^5\) and included eight RCTs and open label studies from drug development stages. Authors concluded that crisaborole was a safe and efficacious second-line option for the treatment of mild-moderate AE in patients over the age of 2 years, though this SR did not meet all AMSTAR2 critical domains. The other SR, which included a meta-analysis, examined seven RCTs (1869 participants) on crisaborole and other PDE4 inhibitors\(^6\). The meta-analysis supported the efficacy and safety of topical PDE4 inhibitors for the treatment of mild-moderate AE, however, included studies had heterogeneous outcome measures.

**Emollients and bath additives**
One SR\textsuperscript{7} examined adverse events associated with the use of emollients in AE across 17 RCTs, five non-randomised studies on interventions (NRSIs), one cohort and one case-control study (total 1887 participants). The emollients examined appear to be safe to use but the authors recognised poor and incomplete reporting across the available studies and acknowledged the need for further and better-designed studies before any conclusive recommendations can be made. This SR, however, did not meet most domains on the AMSTAR2 checklist.

Ridd \textit{et al.} further highlight the evidence gap on emollient use in AE by examining emollient efficacy and acceptability in paediatric AE\textsuperscript{8}. The authors supplemented a previous Cochrane review published in 2017 by an updated search and concluded that the evidence on whether some emollients were superior to others was inconclusive as most studies were of poor quality.

Another SR\textsuperscript{9} reviewed the therapeutic effect of several commonly-used bath additives in AE across ten RCTs and NRSIs. The authors suggested that bathing additives had the potential to provide added therapeutic benefit for AE when used in combination with mainstay treatments and called for further well-designed large RCTs to assess individual bath additives, however, this SR scored low using AMSTAR2.

\textbf{Systemic therapies}

\textit{Antihistamines}

The effect of oral H1 antihistamines as add-on therapy to topical treatment in adults with AE was evaluated in a Cochrane review\textsuperscript{10}, including 25 RCTs and 3285 participants. The authors reported that it was not possible to conduct a meta-analysis given the wide variation in comparisons across trials and concluded that uncertainty remained on the benefit of this intervention.

Another SR\textsuperscript{11} assessed the synergistic effect of H1 antihistamines with TCS on pruritus in AE. Although the qualitative analysis included seven studies, only two (one RCT and one non-randomised trial) were included in the meta-analysis. The authors concluded that antihistamine therapy may have beneficial effect on pruritus in AE, however, limitations of this SR include the small number and heterogeneity of studies included, and the absence of an assessment of publication bias.
**Immunosuppressive agents**

The efficacy and safety of the off-label use of mycophenolate mofetil (MMF) in refractory AE was assessed in a SR and meta-analysis\(^1\). Most studies included were NRSIs. Authors reported that although the evidence was of low quality, MMF appeared to be effective and safe in recalcitrant adult and paediatric AE. However, sources of heterogeneity in included studies was not explored and this SR did not meet all the critical domains of AMSTAR2.

Blake *et al.* examined nephrotoxicity with ciclosporin use in AE\(^3\), including 38 studies, (RCTs and cohort studies) in their SR. Limited evidence to support the assessment of ciclosporin trough levels in AE management was found, though its use in specific patient groups was suggested, for example, in renal/hepatic dysfunction, polypharmacy and non-responders to therapy. Meta-analyses were not performed due to significant heterogeneity between studies.

**Biologics**

Rodrigues *et al.* reviewed the clinical efficacy and safety of dupilumab in adult AE management\(^4\) across nine phase I, II and III trials. Dupilumab was reported to be highly effective and safe in moderate-severe AE. Adverse event rates occurred with similar frequencies between the treatment and placebo groups, though conjunctivitis was a dupilumab-specific side effect. However, the SR only partially met one critical domain of AMSTAR2 and authors did not report on sources of funding of included studies.

Omalizumab treatment was studied in one SR\(^5\) of mostly NRSIs and two small pilot RCTs. Authors concluded that although omalizumab is safe and well tolerated, evidence for its efficacy is limited by a lack of large, well-designed RCTs and that the cost of omalizumab in comparison to currently available treatments is a limitation for its use. Most domains on AMSTAR2, however, were not met by this SR.

**JAK/STAT pathway inhibitors**

Two SRs investigated JAK/STAT inhibitors for AE treatment. One SR assessed off-label tofacitinib treatment of various dermatological conditions, but AE data were not presented separately\(^6\). Another SR reviewed different JAK/STAT inhibitors in the treatment of AE, alopecia areata and vitiligo\(^7\), which included 20 AE studies (RCTs and NRSIs). Growing evidence for the
use of JAK/STAT inhibitors in AE was reported, however, evidence was mainly derived from observational studies.

**Effect of placebo response in atopic eczema RCTs**

Lee *et al.* explored predictors of placebo responses in 64 RCTs of AE\(^\text{18}\), concluding that placebo responses could be reduced by double- and triple-blinding, balancing the sex distribution of patients, disallowing concomitant prescription topical therapy use and having shorter study durations. Although meta-analyses were carried out, heterogeneity in outcome measures across trials was noted.

**Conclusions**

The field of therapeutics for AE is expanding as novel treatments, including small molecules, are increasingly investigated for both topical and systemic use. Overall, however, the quality of recent SRs assessing these treatments is low. There is evidence to support the safety and efficacy of dupilumab, topical PDE4 inhibitors and JAK/STAT inhibitors, though the data are yet to be consolidated in large well-designed RCTs.

**Learning Points**

1. The efficacy of topical calcineurin inhibitors for AE treatment is reasonably evidenced, however, limitations include the specific side effect profile and cost of this treatment.
2. There is growing evidence for efficacy and safety of new topical therapies for AE including phosphodiesterase 4 inhibitors and JAK/STAT pathway inhibitors, but the evidence remains of low quality.
3. There is insufficient evidence to support the use of a specific emollient or bathing additive in the management of AE.
4. High quality evidence demonstrated limited efficacy of oral H1 antihistamines as ‘add-on’ therapy to topical treatment for eczema.
5. Low quality evidence suggests the use of mycophenolate mofetil in the management of refractory AE.
6. Insufficient evidence is available to support a role for omalizumab in AE. However, there is growing strong evidence for efficacy and safety of dupilumab, although conjunctivitis remains a drug-specific side effect.
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