

What progress have we made in the treatment of atopic eczema? Putting the new biological therapies into a wider context

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Atopic eczema, also known as atopic dermatitis or eczema,¹ is a common chronic inflammatory skin disease that has a significant impact on the quality of life of affected patients, as well as their close family members. Despite this considerable burden of disease, treatment options are limited, and many patients and healthcare practitioners have expressed uncertainty in the appropriate use of established forms of therapy.²

Atopic eczema is a complex trait arising from the interaction of multiple genetic and environmental effects. Genetic studies have identified mechanisms contributing to the pathogenesis of eczema, including both immune factors and skin barrier dysfunction.^{3,4} In light of these findings from basic research, it seems likely that treatment strategies will require a dual approach, to reduce inflammation and to repair the skin barrier.

Eczema can often be managed effectively using a combination of allergen and irritant avoidance, regular use of emollients, and topical anti-inflammatory treatments. However, there remains a substantial minority of adult and paediatric patients for whom phototherapy or systemic treatments are required.⁵ Narrow-band UVB and UVA1 are the most effective forms of phototherapy for atopic eczema and may be used in adults or older children.^{6,7} Ciclosporin is currently the only systemic immunosuppressant approved for the treatment of atopic eczema by the European Medicines Agency, but only for adult patients and for only up to 8 weeks' duration because of the risk of irreversible renal toxicity.⁸ The efficacy of methotrexate and azathioprine in moderate-to-severe atopic eczema has been demonstrated in randomized controlled trials;^{9,10} these systemic immunomodulatory therapies are widely used by dermatologists in Europe^{11,12} and North America.¹³ Methotrexate, azathioprine and ciclosporin appear to have roughly comparable efficacy,^{9,14} although no studies have been specifically designed, or adequately powered, to demonstrate equivalence in efficacy between these three drugs.

Some patients and caregivers express a preference for nonpharmacological interventions, which may be used in parallel or independently from other topical or systemic treatments. Educational and psychological support are valuable interventions, but their optimal use is dependent on the available time, resources and healthcare setting. Epidemiological studies have provided evidence of an association between water hardness and the incidence of atopic eczema,^{15,16} but a randomized controlled trial of water softeners showed no efficacy in the treatment of atopic eczema in

children.¹⁷ Silk clothing is an attractive option for some patients, with the aim of reducing the troublesome symptoms of itching and scratching. However, a recent trial showed no difference in efficacy vs. standard care, and it was deemed unlikely to be cost-effective.^{17,18}

Crisaborole, a phosphodiesterase-4 inhibitor with anti-inflammatory effect, can be used topically and has recently been licensed in the U.S.A. following phase III clinical trials for mild-to-moderate atopic eczema in children and adults. In one double-blind vehicle-controlled study, crisaborole ointment applied twice daily for 28 days had a significantly greater efficacy than vehicle as assessed by Investigator's Static Global Assessment.¹⁹ However, further clinical trials comparing crisaborole with topical treatments of established efficacy, including corticosteroids and calcineurin inhibitors, will be required to define its place within our current therapeutic options.

A minority of paediatric and adult patients with severe atopic eczema remain resistant to all current treatments. Eczema has lagged behind psoriasis in the development of biological drugs despite progress in understanding the complex immunological mechanisms in atopic skin. Recent clinical trials have generated substantial interest, as several biologics have been developed to target pathways of importance in atopic inflammation. Among them is dupilumab, a human monoclonal antibody that binds to the alpha-chain of the interleukin (IL)-4 receptor, inhibiting both the IL-4 and IL-13 pathways.²⁰ In a phase II study, published in 2014, 85% of patients given subcutaneous dupilumab injections as monotherapy for 12 weeks had a 50% reduction in Eczema Area and Severity Index (EASI) score, compared with 35% of those in the placebo group ($P < 0.001$).²⁰ More recently, in two phase III trials of identical design, including 671 and 708 adult patients with moderate-to-severe atopic eczema, 37–38% were considered 'clear' or 'almost clear' of eczema according to Investigator's Global Assessment, compared with 9–10% in the placebo group, while weekly and fortnightly administration of dupilumab showed no difference in efficacy.²¹ The latest phase III randomized double-blind trial compared dupilumab plus topical corticosteroids; 39–40% of patients were clear or almost clear of eczema (by Investigator Global Assessment) at 16 and 52 weeks.²² In the patients treated for 52 weeks there were no significant dupilumab-induced biochemical or haematological abnormalities, but an increase in the prevalence of conjunctivitis was noted (19% in dupilumab-treated patients vs. 8% in placebo-treated patients).²² Dupilumab therefore appears to be well tolerated, but the

long-term safety remains unknown beyond 52 weeks, and the results of ongoing paediatric trials are awaited.

The use of a biological agent provides the opportunity to intervene powerfully in selected molecular mechanisms in atopic eczema, and the documented efficacy of dupilumab has been reported to 'emphasise IL-4 and IL-13 as key drivers'.²³ However, these study findings raise the question: if IL-4 and IL-13 are key drivers in the pathogenesis of atopic inflammation, why did < 50% of the patients respond in the three phase III trials? This absence of universal efficacy for a targeted therapy reflects the diversity of the disease phenotype, as well as the multiplicity of pathomechanisms within this complex trait, indicating the need for subclassification of atopic eczema. IL-4 and IL-13 are cytokines with both shared and diverse roles in atopic inflammation; the effect of IL-13 in maintaining skin barrier function may be a physiological rather than pathological effect, as recently proposed.²⁴ Dupilumab targets both IL-4 and IL-13; it remains to be tested whether suppression of one of these cytokines, as opposed to both, may be more effective in inhibiting the pathogenesis of eczema. Trials of the IL-13 inhibitor lebrikizumab are awaited with interest.²⁵

Nemolizumab is a humanized antibody that targets IL-31 receptor A. IL-31 is produced by T helper 2 cells and is reported to play a role in pruritus²⁶ via IL-31 receptor A on cutaneous neurons. A phase II randomized double-blind trial of nemolizumab in 264 adults with moderate-to-severe atopic eczema showed up to 63% reduction in pruritus, measured by visual analogue scale after 12 weeks of treatment, compared with 21% reduction in the placebo group.²⁷ As pruritus is a major contributor to the impairment in quality of life in patients with atopic eczema, this finding is very promising. However, as for dupilumab we must await larger, longer and more comprehensive studies – with the inclusion of paediatric patients and an established active therapy for comparison – to define the safety, efficacy and positioning of nemolizumab as a therapeutic option.

Atopic eczema has been described as 'the itch that rashes'. Both dupilumab and nemolizumab reduce pruritus and, while a direct comparison between the two drugs is not possible because of differences in trial design, it is interesting to consider whether the direct targeting of IL-31 sheds light on the role of pruritus in the development of atopic eczema. Both clinical trials used a visual or numerical scale for the patients to score itch intensity and the percentage change from baseline as an indicator of effect. Nemolizumab treatment at the highest dose tested (2.0 mg kg⁻¹ monthly) resulted in ~63% reduction in itch score with no significant change in eczema severity or extent.²⁷ This is in contrast to dupilumab dosed weekly, giving approximately 40–45% reduction in itch score after 12 weeks of treatment, in concert with approximately 70% reduction in the EASI score.²¹ These preliminary findings seem to indicate that treatment of pruritus can indeed be uncoupled from the treatment of other clinical signs of skin inflammation.

The prominent placebo response in these trials is noteworthy.^{20,22,23,27} The placebo response in clinical trials for atopic

eczema is well recognized and likely to be explained, at least in part, by the support and supervision provided during the trial, improving both adherence to emollients and allergen and irritant avoidance. In the context of moderate-to-severe disease a placebo response of up to 13% clear or almost clear in the phase III trials of dupilumab is striking, but this may reflect specific inclusion criteria in these studies.

This is an exciting time in eczema research, with ongoing trials targeting several other aspects of atopic inflammation. These include studies using tezepelumab, an inhibitor of thymic stromal lymphopoietin; fezakinumab targeting IL-22; ustekinumab, which is already used for psoriasis, targeting IL-12/23p40;^{28,29} and the Janus kinase inhibitor tofacitinib citrate, which has shown preliminary evidence of efficacy in atopic eczema.³⁰ Drugs targeting the Janus kinase–signal transducer and activator of transcription pathway topically or systemically may be beneficial in a broad range of skin conditions with an autoinflammatory component.³¹

In summary, insight gained from the rapid progress in therapeutics has highlighted the diversity of phenotypes within the disease known as atopic eczema. As the complexity of disease mechanisms becomes more apparent, it emphasizes the need for therapeutic stratification of new and established eczema treatments. Multiple approaches to treating both the inflammatory pathways and skin barrier dysfunction are likely to be necessary to control atopic skin inflammation fully in each individual patient.

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Conflicts of interest

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