



Biologics in atopic dermatitis

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Purpose of review

Until recently there have been limited options for systemic therapy in atopic dermatitis, which is unresponsive to topical treatments. However, the last few years have seen a rapid progression in this field. The purpose of this review is to summarise some of the recent literature and ongoing studies in the field of biologicals in atopic dermatitis.

Recent findings

Dupilumab has been shown to be effective in moderate to severe atopic dermatitis and is now licensed in the USA and Europe. Tralokinumab is currently under review by the Food and Drug Administration and the European Medicines agency. Phase 2 and 3 studies are taking place with other biological therapies. There is increasing evidence for the use of biologicals in children and for their role in multisystem disease.

Summary

The recent breakthroughs in treatment represent an opportunity to resolve an unmet need; the management of atopic dermatitis which is unresponsive to topical therapy.

Keywords

atopic dermatitis, biological therapy, dupilumab, eczema

INTRODUCTION

Atopic dermatitis is one of the most common skin diseases with a prevalence of 2–10% in adults and up to 20% in children. It can be associated with significant impairment of quality of life (QoL). Until recent years, our therapeutic options for atopic dermatitis have remained relatively limited when topical therapy failed. As a result of an understanding that atopic dermatitis is a consequence not only of skin barrier dysfunction, but also of the underlying immune pathways, there is an increasing appreciation that the relevant pathways can be targeted by biological therapies. This has led to the recent, rapid developments in atopic dermatitis treatment.

TEXT OF REVIEW

Helper T cell (Th2)

Atopic dermatitis is characterized by excessive helper T cell (Th2) cell activation, associated with consequent expression of type 2 cytokines, interleukin (IL)-4, IL-5, IL-13 and IL-31 and type 2 innate lymphoid cell activation. In addition, there exists a diverse clinical pattern of atopic dermatitis with, for example, age-related and ethnic variations. This is reflected in activation of different patterns of cytokines, such as IL-22, IL-17, IL-9 and interferon- γ

which may also be potential targets for biological therapy.

Anti-interleukin-4 and interleukin-13: dupilumab

The main type 2 pathway mediators, IL-4 and IL-13, have a number of roles in atopic dermatitis. They stimulate immunoglobulin E (IgE) and Th2 cell production, inflammation, epidermal barrier dysfunction and itch. Based on the understanding of the importance of these immunological pathways, dupilumab, which targets the alpha subunit of the IL-4 receptor thereby blocking both IL-4 and IL-13 pathways, was an off-the-shelf drug used in the pivotal LIBERTY atopic dermatitis (AD) SOLO 1 and 2 studies [1^{••}].

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KEY POINTS

- Dupilumab has been shown to be effective in moderate-severe atopic dermatitis and is the first systemic therapy to be approved for patients with atopic dermatitis for some time.
- Ongoing work has identified other promising candidates which are in rapid development.
- Early treatment of atopic dermatitis may restore the skin barrier, prevent allergen sensitisation and potentially halt the atopic march and the development of atopic disease, such as food allergies, asthma and allergic rhinitis.
- Dupilumab has also shown that a single therapeutic agent may have multisystem effects where different atopic conditions already co-exist.

These were 2 identical randomised, placebo-controlled phase 3 studies of nearly 1400 adult patients with moderate to severe atopic dermatitis, uncontrolled by topical treatment. For 16 weeks, they received weekly or two-weekly dupilumab or placebo. Pooled analysis of the data demonstrated significant improvements in primary clinical atopic dermatitis severity outcomes in the dupilumab group compared to placebo [2]. The Investigator Global Assessment (IGA) score improvement to 0 or 1, with at least a two-point reduction, was seen in 36.8% of participants receiving weekly dupilumab and 37.0% of participants receiving 2 weekly treatment, compared to 9.3% in the placebo group ($P < 0.0001$). The eczema area and severity index (EASI)-75 (75% or more reduction in EASI score) was achieved in 50.2% of participants receiving weekly dupilumab and in 47.7% receiving 2 weekly treatment, compared to 13.3% receiving placebo ($P < 0.0001$). There were also significant improvements in other clinical signs, including peak pruritis numerical rating scale (NRS), body surface area (BSA), global individual signs score, SCORing Atopic Dermatitis (SCORAD), itch, QoL and mental health. Further data show sustained benefits when treatment was continued for 52 weeks [3]. Dupilumab had an acceptable safety profile. There was an increased incidence of conjunctivitis, the cause of which is unclear, which was also observed across other dupilumab studies in atopic dermatitis. This was mostly of mild to moderate intensity, with the majority of cases resolving with continued treatment.

The Food and Drug Administration (FDA) in the USA approved the use of dupilumab for adult atopic dermatitis in March 2017. In the European Union,

the European Medicines Agency approved the use of dupilumab in adults in September 2017.

Anti-interleukin-13: tralokinumab

Anti-IL-13 on its own has also proved to be useful in the treatment of atopic dermatitis. The phase 3 ECZTRA studies in adults from 18 years of age, with moderate to severe atopic dermatitis, comprised ECZTRA 1 ($n=802$) and 2 ($n=794$) studies with tralokinumab monotherapy and ECZTRA 3 ($n=380$) with tralokinumab in combination with topical corticosteroids (TCS).

In ECZTRA 1 and 2, treatment was commenced at 300 mg 2 weekly (following a 600 mg loading dose) or placebo [4]. Participants receiving tralokinumab, who achieved their primary endpoint by week 16 (IGA score of 0/1 or EASI-75), were re-randomised to 36 weeks of continued treatment with 2-weekly tralokinumab, had their dose frequency reduced to 4-weekly tralokinumab, or were assigned to placebo and re-assessed at 52 weeks.

At 16 weeks, there were improvements in the primary outcomes of atopic dermatitis severity. A total of 15.8% and 22.2% of participants receiving tralokinumab in ECZTRA 1 and 2, respectively, achieved an IGA score of 0 or 1, compared to 7.1% and 10.9% of participants on placebo, a difference of 8.6 (4.1–13.1) ($P < 0.002$) and 11.1 (5.8–16.4) ($P < 0.001$) compared to placebo, respectively. The data for EASI-75 were 25.0% and 33.2% in the treatment arms, compared to 12.7% and 11.4% in the placebo arms, with differences of 12.1 (6.5–17.7) ($P < 0.001$) and 21.6 (15.8–27.3) ($P < 0.001$), respectively. There were also significant improvements in the secondary endpoints of worst daily pruritis NRS, SCORAD and Dermatology Life Quality Index (DLQI).

In the second phase of the study, following re-randomisation, 51% of participants in the treatment arm maintained an IGA score of 0/1, compared to 47% in the placebo arm in ECZTRA 1; 59% of participants in the treatment arm and 25% of participants in the placebo arm maintained their response in ECZTRA 2. 60% maintained an EASI-75, compared to 33% in the placebo arm in ECZTRA 1, whereas 56% maintained this response compared to 21% of placebo-treated patients in ECZTRA 2. The authors speculated that the high level of response in the placebo arm may have been due to tralokinumab treatment inducing remission in a proportion of patients in the initial phase.

The ECZTRA 3 study had a similar design, but the use of TCS was permitted if required [5]. At 16 weeks, 38.9% of tralokinumab-treated participants, compared to 26.2% of participants on

placebo achieved an IGA of 0/1 [difference (95% confidence interval, CI): 12.4% (2.9–21.9); $P=0.015$] while 56.0% on tralokinumab and 35.7% on placebo [difference of 20.2% (9.8–30.6); $P<0.001$] achieved EASI-75. There were significant improvements reported in worst daily pruritus NRS, SCORAD and DLQI scores in the treatment arm. The cumulative amount of topical steroid use at week 15–16 was 134.9 ± 11.7 g in the tralokinumab arm and 193.5 ± 16.7 g in the placebo arm, a difference of -58.6 (-98.7 to -18.5 ; $P=0.004$) in favour of the tralokinumab arm.

Participants were then re-randomised at 16 weeks and reassessed at 32 weeks. At 32 weeks, 89.6% of those that responded to tralokinumab at 16 weeks, maintained their IGA score and 92.5% maintained their EASI-75 response. This was not associated with increased TCS use.

Tralokinumab was well tolerated although more cases of conjunctivitis were seen in tralokinumab-treated participants.

Studies in adolescents (ECZTRA6; NCT03526861), Japanese subjects (ECZTRA 8; NCT04587453) and long-term extension studies (ECZTEND; NCT03587805) are ongoing.

The biologics license application for tralokinumab for adult atopic dermatitis has been accepted by the FDA, with a decision scheduled for the second quarter of 2021. A marketing authorisation is also currently being reviewed by the European Medicines Agency.

Anti-interleukin-13: lebrikizumab

A phase 2b study of lebrikizumab for adults with moderate to severe atopic dermatitis has reported statistically significant improvement in the primary end point, which was dose dependent [6]. At 16 weeks, they reported results for: 125 mg every 4 weeks [EASI least squares mean percentage change, -62.3% (37.3%), $P=0.02$], 250 mg every 4 weeks [-69.2% (38.3%), $P=0.002$], and 250 mg every 2 weeks [-72.1% (37.2%), $P<0.001$], relative to placebo [-41.1% (56.5%)].

It was generally well tolerated and phase 3 studies in adolescents (ADore; NCT04250350), adolescents and adults (ADvocate 1 & 2; NCT04146363 & NCT04146363), and in combination with TCS (NCT04250337), are underway.

Anti-interleukin-31: nemolizumab

IL-31 is secreted by activated Th2 cells; it mediates pruritus and correlates with disease severity.

A phase 2b study of 226 participants with moderate to severe atopic dermatitis demonstrated improved EASI relative to baseline at 24 weeks, most

prominent in participants receiving 30 mg of treatment (-68.8% vs. -52.1% , least-square mean reduction for placebo; $P=0.016$), suggesting that this was not a dose-dependent response [7]. Nemolizumab improved IGA, and/or NRS-itch scores, with the 30-mg dose again being most effective. It was safe and well tolerated.

A phase 3 study assigned 143 Japanese atopic dermatitis participants from 13 years of age with moderate to severe pruritus, to receive 60 mg of nemolizumab or placebo for 16 weeks [8]. At week 16, the nemolizumab group showed a mean percentage change in the primary endpoint, the pruritus visual analogue scale score of -42.8% , and of -21.4% in the placebo group (difference, -21.5 percentage points; 95% CI, -30.2 to -12.7 ; $P<0.001$). Other outcomes included a mean percentage change in the EASI score of -45.9% with nemolizumab, compared with -33.2% in the placebo group. There were also greater improvements in DLQI and Insomnia Severity Index. The incidence of injection-related reactions was greater in the nemolizumab arm.

There are currently phase 3 studies underway, involving participants over 12 years old (NCT 03989206, NCT03985943, NCT03989349)

TSLP-OX40 axis

The thymic stromal lymphopoietin (TSLP)-OX40 axis is thought to initiate the allergic response, leading to Th2 polarisation and maintenance of chronic inflammation. IL-33 amplifies the axis and downregulates filaggrin expression.

Anti-OX40

GBR 830 improved EASI scores compared to placebo up to day 71 of treatment in a phase 2a study [9]. IGA and SCORAD also improved, with associated immunological changes and an acceptable safety profile. A phase 2b study is currently underway (NCT03568162).

Anti-TSLP

In a phase 2a study tezepelumab numerically improved EASI-50 and other outcomes compared to placebo, but failed to achieve statistical significance [10]. The authors speculated that the results may have been confounded by concomitant TCS use. A phase 2b adult study is currently underway (NCT03809663).

A phase 1b study with intravenous MK-8226 was terminated for business reasons (NCT01732510).

Anti-interleukin-33

A proof-of-concept phase 2a study of etokimab (ANB020) demonstrated that 29 days after a single dose, 83% of the 12 participants achieved EASI-50 and 33% achieved EASI-75 [11]. There were also improvements in other atopic dermatitis severity scores, QoL and itch. It was well tolerated. A phase 2 study to assess the efficacy, safety and pharmacokinetics is underway (ATLAS; NCT03533751).

A phase 1 study of another anti-IL33 candidate, PF-06817024, is also in progress (NCT02743871).

Other pathways

Fezakinumab (ILV-094), an anti-IL-22, in a phase 2b study of moderate–severe adult atopic dermatitis, resulted in a nonsignificant improvement in SCORAD in the treatment arm [12]. However in the subgroup of patients with severe atopic dermatitis, with a SCORAD over 50, there was a significant improvement in SCORAD at 12 weeks compared to placebo. No ongoing studies are taking place with fezakinumab.

IL-12 and IL-23 are overexpressed in atopic dermatitis and IL-23 plays a role in Th17 differentiation. However ustekinumab, a monoclonal anti-IL-12/IL-23p40 antibody, has yielded disappointing results in studies of atopic dermatitis. A phase II trial with concomitant TCS showed nonsignificant improvement over placebo [13]. Risankizumab, which targets the p19 subunit of IL-23, is undergoing phase 2 studies in adults and adolescents (NCT03706040). Although a significant role for Th17 pathway activation has been demonstrated amongst Asian patients with atopic dermatitis, a 16-week phase 2 trial in Japanese patients with severe atopic dermatitis, showed no increase in efficacy compared to placebo [14].

Paediatrics

Dupilumab

A phase 3 study (LIBERTY atopic dermatitis ADOL) in 251 adolescent patients aged 12–18 years, with moderate to severe atopic dermatitis, showed significant improvements in primary clinical endpoints [15]. In participants treated with dupilumab, EASI-75 at week 16 was achieved by 41.5% of participants receiving treatment 2-weekly and in 38.1% of those on 4-weekly treatment, compared to 8.2% of participants on placebo ($P < 0.001$). 24.4% of participants on 2-weekly treatment and 17.9% of those receiving 4-weekly treatment achieved an IGA 0 or 1 at week 16, compared to 2.4% receiving placebo

($P < 0.001$). Participants also showed significant improvements in Peak Pruritus NRS, EASI-50, EASI-90 and SCORAD, compared to placebo. There is evidence that these effects persist with more prolonged treatment up to 52 weeks [16]. Adverse events were consistent with adult studies.

LIBERTY atopic dermatitis presumably Pediatrics but not formally documented explored the use of dupilumab in children with severe atopic dermatitis aged 6–11 years, with concomitant medium-potency TCS therapy [17]. This 16-week double-blind, phase 3 trial enrolled 367 patients who were treated with 300 mg dupilumab every 4 weeks, a 2-weekly weight-based dupilumab regimen, or placebo.

At week 16, participants demonstrated improvement in atopic dermatitis severity. 29.5% of participants receiving 2-weekly dupilumab and 32.8% receiving 4-weekly treatment achieved the primary endpoint of an IGA score of 0 or 1, compared to 11.4% of those receiving placebo ($P = 0.0004$). And 67.2% and 69.7% of those on the 2- and 4-weekly regimens respectively, achieved an EASI-75, compared to 26.8% of those in the placebo arm ($P < 0.0001$). There were also significant improvements in EASI-50, EASI-90, BSA, SCORAD, peak pruritus NRS, QoL and mental health scores in the dupilumab-treated groups. Adverse events were consistent with studies in the older age groups.

The FDA extended approvals for dupilumab for adolescents, and then most recently to children with atopic dermatitis on 26th May 2020. In the European Union, the European Medicines Agency extended the marketing authorisation to children 6 years and over on the 19th October 2020.

A phase 3 study to assess the safety and efficacy in children from 6 months to 6 years of age is currently underway (NCT03346434).

Anti-immunoglobulin E

A randomised double-blind placebo controlled study in children with severe atopic dermatitis demonstrated significant improvement in primary endpoint for the change in objective SCORAD between active and placebo groups (Atopic Dermatitis Anti-IgE Pediatric Trial) [18]. The SCORAD index improvement between groups at week 24 was -6.9 (95% CI, -12.2 to -1.5 ; $P = 0.01$) and changes in SCORAD and EASI exceeded the minimum clinically important difference only in the treatment group. Improvements were also seen in other measurements of atopic dermatitis severity and QoL. This was despite lower potent TCS use in the treatment arm. Two prior controlled studies were small, enrolling only four children in total and using much lower

doses of omalizumab in line with earlier manufacturer's dosing regimes. The authors speculated that the clinical response in seen in this study may have resulted from not only targeting children with severe disease, where IgE may be more relevant, but also the use of higher doses of omalizumab than in previous studies.

Other pathways

Studies involving adolescents, including those targeting IL13 (tralokinumab and lebrikizumab), IL31 (nemolizumab) and Th17 (risankizumab), are underway.

Comorbidities

At 16 weeks, a study of 123 adult patients with dupilumab-treated atopic dermatitis, reported significant improvements in comorbid perennial allergic rhinoconjunctivitis ($n=41$) disease control (measured using a Rhinitis Control Scoring System) and QoL (measured using the Rhinoconjunctivitis QoL Questionnaire scores) [19]. A total of 32 patients with comorbid perennial allergic asthma reported significantly improved control (assessed by the Asthma Control Test and five-item Asthma Control Questionnaire scores) and QoL (by Asthma QoL Questionnaire scores).

The LIBERTY atopic dermatitis ADOL study in adolescents not only reported improvements in atopic dermatitis, but improvements in comorbidities of asthma and rhinitis detected on the Juniper Asthma Control Questionnaire and Total Nasal Symptom Score [15].

CONCLUSION

There has been a rapid growth of studies for biological therapies in atopic dermatitis in recent years. This has led to the approval of dupilumab, the first systemic therapy for atopic dermatitis for some time, with the potential approval of tralokinumab pending. Ongoing work has unearthed promising candidates in anti-IL13, 31, 33, 23, OX-40, TSLP and IgE. Work with dupilumab and other biologicals in children and adolescents may also begin to resolve the unmet needs in paediatric atopic dermatitis.

In children, atopic dermatitis often heralds the onset of the atopic march and may potentiate sensitisation to allergens. If the skin barrier can be repaired in early life, potentially interfering with sensitisation, this could have more far-reaching impact on the development and progression of atopic disease, such as food allergies, asthma and allergic rhinitis.

Finally, dupilumab has also shown that a single therapeutic agent may have multisystem effects,

potentially paving the way for a single therapeutic agent for patients with multiple co-existing atopic diseases.

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Conflicts of interest

Novartis supplied active and placebo drug for the ADAP-Trial.

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- of special interest
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