Chapter

Biologicals in Atopic Dermatitis

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Abstract

Atopic dermatitis (AD) is a debilitating condition, and its management in both children and adults can be challenging for clinicians and patients alike. The current treatment options approved by the Food and Drug Administration (FDA) have variable efficacies, and long-term adverse effects, which further complicate the plan of management. There has been considerable progress towards the use of targeted medicines like biologicals and small molecular agents for atopic dermatitis. Various molecules targeting the TH2 pathway, JAK/STAT pathway, cAMP, IL-22, Il-12/IL-23 and IgE, have been developed, and are being studied extensively in both adults and pediatric patients of atopic dermatitis. Currently, only Dupilumab is approved by the FDA for the treatment of moderate to severe refractory atopic dermatitis. The other biological agents are currently in phase 2 or phase 3 trials. There is a paucity of multicentric, large-scale studies on the above drugs, along with a lack of comparative studies with the existing modalities of treatment. Therefore, more studies with a larger sample size and longer follow up periods are needed to determine their efficacy and long-term safety profiles. Overall, these agents are likely to be a part of the therapeutic armamentarium for atopic dermatitis in the near future.

Keywords: atopic dermatitis, biologicals, Dupilumab, Th2 pathway, JAK/STAT pathway

1. Introduction

Atopic dermatitis (AD) is a debilitating condition, and its management in both children and adults can be challenging for clinicians and patients alike. About 20% of patients with AD manifest with moderate to severe forms of the disease, which are refractory to conventional treatment. The current treatment options approved by the Food and Drug Administration (FDA) have variable efficacies, and long-term adverse effects, which further complicate the plan of management [1].

There has been considerable progress towards the use of targeted medicines like biologicals and small molecular agents to block specific cytokines, their receptors, or transcription factors. The indications for these agents are also rapidly expanding, from adults to the pediatric population. Their formulations range from injections to oral tablets, and topical creams and ointments [2].

Advances in understanding the various immunopathological changes occurring in atopic dermatitis have allowed the identification of various therapeutic molecular targets and synthesis of various biological agents [1].

2. Classification of biological agents (based on their mechanism of action)

1. IgE directed therapy-Omalizumab
2. Th2 inhibitors:
   - Anti IL-4-Dupilumab
   - Anti IL-4/IL-13 agents-Lebrikizumab, Tralokinumab
   - IL-31 directed therapy-Nemolizumab
3. Anti IL-12/23 agents-Ustekinumab
4. IL-22 blockade-Fezakinumab
5. Thymic stromal lymphopoietin directed therapy-Tezepelumab
6. JAK inhibitors-Tofacitinib, Abrocitinib, Delgocitinib, Upadacitinib, Ruxolitinib, Baricitinib
7. Miscellaneous agents

2.1 IgE directed therapy-Omalizumab

Omalizumab is a recombinant humanized monoclonal IgG1 antibody, which has been approved by the FDA for the treatment of moderate to severe persistent asthma and chronic spontaneous urticaria. It has also been shown to be beneficial in chronic inducible urticaria, allergic rhinitis, eosinophilic esophagitis, food allergy, anaphylaxis, as premedication in allergen specific immunotherapy, Churg-Strauss disease, eosinophilic otitis media, allergic bronchopulmonary aspergillosis, chronic rhinosinusitis, bullous pemphigoid, contact dermatitis and atopic dermatitis [1].

Mechanism of action

It is composed of 5% murine and 95% human sequence. Omalizumab combines with the free, soluble IgE, blocking its binding to its receptors, and subsequently preventing allergen-induced mediator release.

It dramatically reduces the serum levels of free IgE (by 99% in the first two hours after administration), which then downregulates the expression of IgE high-affinity receptors on immune cells. It also decreases the expression of several cytokines (such as IL-5, 8, 13) and inhibits the recruitment of immune cells (T-cells, eosinophils, and macrophages) to the affected sites. Therefore, it inhibits both the immediate and the late inflammatory phases. It is also involved in apoptosis of mast cells and eosinophils.

Omalizumab in AD

Anti-IgE therapy in AD has shown conflicting results. Although most data from small randomized trials, case series and case reports documented clinical benefit and resolution of eczema, a small number of studies showed no improvement of disease with Omalizumab. Filaggrin mutations and raised serum IgE levels were associated with a poorer response to Omalizumab [3]. All of the studies noted the safety profile in both adult and pediatric population treated with Omalizumab. However, the variable response to treatment and lack of standardized dosing

protocols remain major drawbacks. Another notable conclusion of placebo-controlled studies showed no significant improvement with Omalizumab compared to the control groups [1].

2.2 TH2 inhibitors

2.2.1 Anti IL-4 (Dupilumab)

Dupilumab was approved by the FDA in 2017 for the treatment of adults with moderate to severe refractory atopic dermatitis [1]. It was further approved in 2020 for children aged 6 to 11 years with moderate-to-severe atopic dermatitis [4]. Currently, it is the only biological approved for the treatment of AD.

Dose—It is available as prefilled syringes containing 300 mg 0r 200 mg of the drug

- Adults and children (6–11 years weighing >60 kgs): Loading dose of 600 mg subcutaneously followed by 300 mg every 2 weeks
- Pediatric patients (weight > 30-<60 kgs)-400 mg s/c loading dose followed by 200 mg every 2 weeks
- Pediatric patients (weight > 15-<30 kgs)-Loading dose of 600 mg subcutaneously followed by 300 mg every 4 weeks

Mechanism of action

Both IL-4 and IL-13 are key drivers of the Th2-mediated allergic inflammation. They synergistically act via a common receptor, IL-4Rα, to activate the signaling proteins [signal transducer and activator of transcription 6 (STAT6) and Janus kinase-1 (JAK1)]. IL-4 induces the immunoglobulin isotype class switch to IgE, promotes the Th2 phenotype, prevents T-cell apoptosis, renders the T-cells refractory to corticosteroids, and induces the expression of VCAM-1 on endothelial cells, subsequently promoting the recruitment of T-cells, eosinophils, basophils and monocytes. Gene polymorphisms in IL-4, IL − 13 and IL-4Rα have been associated with AD in certain populations.[1] In the presence of IL-4 and IL-13, keratinocytes exhibit significantly less FLG gene expression, leading to epidermal barrier dysfunction. Dupilumab is a fully humanized monoclonal antibody against interleukin-4 (IL-4) receptor-α (IL-4Rα) [5].

Dupilumab in AD

Dupilumab has been a major addition to the therapeutic armamentarium of moderate to severe refractory AD.

Administration of dupilumab leads to the following molecular changes:

1. downregulation of markers of epidermal proliferation
2. downregulation of inflammatory mediators
3. upregulation of structural proteins
4. upregulation of lipid metabolism proteins
5. upregulation of epidermal barrier proteins resulting in normalization of skin.

6. Reduction in genes activating T cells

7. reduction in serum levels of CCL17 (or thymus and activation-regulated chemokine), a key regulator of Th2-mediated immunity and a specific biomarker of AD disease activity [6].

Mono-therapy or combined therapy with Dupilumab has shown to be beneficial in the effective control of disease, improvement in skin lesions, significant reduction in pruritus and an improved quality of life of affected patients. Studies have shown that the transcriptome of skin lesions of AD resembled that of the non-lesional skin after only 4 weeks of treatment with Dupilumab. Many clinical trials investigating the efficacy and safety of Dupilumab in AD have shown a rapid and marked improvement of disease activity, and a safe profile of administration [1].

A phase 3 trial [7] conducted in 251 adolescents showed statistically significant improvement in the signs, symptoms, and quality of life after 16 weeks of Dupilumab injection, with the 2-weekly regimen showing a better response.

In pediatric patients, a multi-centre review [8] done on 111 children showed ≥2 point improvement in the Investigator Global Assessment (IGA) score in 64.3% patients after 9 weeks.

The mean dosage used in children was 8.7 mg/kg loading dose followed by 5.1 mg/kg maintenance dose every other week.

Adverse effects reported include worsening of alcohol flushing; new regional dermatitis in face, conjunctivitis and eosinophilia have been reported with Dupilumab [9, 10].

2.2.2 Anti Il-4/Il-13 agents: Lebrikizumab and Tralokinumab

IL-13 is overexpressed in the skin lesions of AD patients and appears to negatively regulate the expression of genes encoding crucial structural proteins (such as loricrin, involucrin), leading to be the impairment of the epidermal barrier. Lebrikizumab and Tralokinumab selectively target IL-13 and prevent the formation of the IL-13Rα1/IL-4Rα heterodimer receptor signaling complex [11]. Significant clinical improvement has been seen in moderate to severe AD in a small number of Phase 2 studies, with a good safety profile. However, concomitant topical corticosteroid therapy in enrolled patients limits data regarding their efficacy. Therefore, further studies are needed to confirm their beneficial effects in AD [1]. It is currently in Phase 3 trials. It is given subcutaneously every 4 weeks, but its effective dose is yet to be determined [12].

2.2.3 IL-31 directed therapy: Nemolizumab

It is a humanized monoclonal antibody against IL-31 receptor A. IL-31 is expressed predominantly by Th2 lymphocytes, functions to target keratinocytes, epithelial cells, eosinophils, basophils and monocytes. It is overexpressed in AD skin lesions [13]. A phase 3 randomized, double blind, placebo-controlled clinical trial [14] noted a significant clinical improvement profile in adult patients with refractory moderate to severe AD, as compared to the placebo group. However, the duration of the study was only for 16 weeks. Further studies are needed to confirm long-term efficacy and safety profile. The maximum efficacy has been seen with 60 mg subcutaneous injections given every 4 weeks.

2.3 Anti IL-12/IL-23 agent: Ustekinumab

Ustekinumab is a human immunoglobulin G1κ monoclonal antibody against the common p40-subunit shared by IL-12 and – 23. IL-23 is responsible for Th17 cell development, and is associated with tissue damage in several inflammatory conditions. IL-23 levels positively correlates with the severity of atopic dermatitis among children. Results regarding the utility of Ustekinumab in the treatment of AD brought inconclusive results. While several case reports have suggested the efficacy of Ustekinumab in severe AD, some others show a moderate effect or a lack of it. This may be due to the multifactorial aetiopathology of the disease. Recently, Noda et al. [1] showed a predominant Th17 immune pattern in Asian AD patients. Such data is valuable for identifying individuals who are most likely to benefit from therapy. Further studies are needed to determine its efficacy and safety and the treatment of AD.

2.4 IL-22 blocker: Fezakinumab

IL-22 promotes epidermal hyperplasia and skin barrier dysfunction in AD. Fezankinumab is an anti IL-22 antibody. Phase 2 placebo-controlled studies have shown progressive and sustained clinical improvement of moderate-to-severe AD after 12 weeks of treatment. It is given intravenously with a loading dose of 600 mg followed by 300 mg every 2 weeks [1, 15].

2.5 Thymic stromal lymphopoietin directed therapy

TSLP is a pivotal pro-inflammatory cytokine in both acute and chronic skin lesions of AD. Tezepelumab is a human monoclonal antibody that prevents the interaction of thymic stromal lymphopoietin (TSLP) with its receptor [1]. Phase 2a trials [16] using 280 mg subcutaneous injections every 2 weeks showed an insignificant improvement in the EASI and SCORAD values after 12 weeks of treatment. Therefore, it is unlikely to be a major treatment option in the near future.

2.6 JAK inhibitors

Targeting of the Janus kinase (JAK) and spleen tyrosine kinase (SYK) pathways attenuates signaling via multiple immune pathways (Th1, Th2, Th17 and Th22) and enhances keratinocyte differentiation [17]. Although these drugs have emerged as promising treatment options for AD, their long-term safety profiles are yet to be determined [4].

Tofacitinib shows specificity for JAK3, baricitinib mainly inhibits JAK1 and JAK2, upadacitinib, ruxolitinib and abrocitinib are selective for JAK1. Delgocitinib inhibits JAK1, JAK2 and JAK3. At present, baricitinib and upadacitinib are also at the final stages of clinical development for atopic dermatitis [18].

2.6.1 Tofacitinib

The first JAK inhibitor to be studied in humans, has been developed in both topical and oral formulations, although only oral tofacitinib is commercially available [4]. A single phase 2a randomized, double-blind, vehicle-controlled study on 69 adults with mild-to-moderate AD showed significant improvement(−81.7% vs. −29.9%) in the EASI score after 4 weeks of applying 2% tofacitinb ointment [19, 20].

2.6.2 Delgocitinib

0.025% and 0.5% ointment has shown encouraging results in recent Phase 3 [21] studies in adult patients, and Phase 2a studies [22] in pediatric patients with moderate to severe AD up to 4 weeks and 28 weeks respectively, with no serious side effects

2.6.3 Oral Abrocitinib

Oral Abrocitinib was evaluated in a phase 3 double-blind placebo-controlled trial, [23] and was effective and well tolerated in adolescents and adults with moderate-to-severe atopic dermatitis. In this trial, 387 patients (aged ≥12 years; 43% women) with moderate-to-severe atopic dermatitis (60% with moderate disease; 40% with severe disease) were randomly assigned (2:2:1) to receive oral abrocitinib 100 mg, 200 mg, or placebo once a day. At week 12, 37 (24%) of 156 patients in the abrocitinib 100 mg group and 67 (44%) of 154 patients in the abrocitinib 200 mg group had achieved an Investigator Global Assessment response of clear or almost clear (score 0–1) compared with six (8%) of 77 patients in the placebo group, and 62 (40%) of 156 patients in the abrocitinib 100 mg group and 96 (62%) of 154 patients in the abrocitinib 200 mg group achieved a 75% improvement or more in Eczema Area and Severity Index (EASI) score from baseline, compared with nine (12%) of 77 patients in the placebo group. This seems to be a promising future option for AD.

2.6.4 Baricitinib

Phase 2 RCT [24] in 124 adults with 2 mg and 4 mg qd dose of Baricitinib showed significant reduction in pruritus and inflammation after 16 weeks. The common adverse effects noted were headache, increased creatine phosphokinase levels and nasopharyngitis.

2.6.5 Ruxolitinib

Phase 2 RCT was conducted in 252 adults with AD, to study the efficacy of 0.15% cream qd, 0.5% RUX cream qd, 1.5% RUX cream qd and 1.5% RUX cream bid. The study showed significant symptomatic improvement after 4 weeks of application, which was sustained for 12 weeks, with good tolerability and no major adverse effects [19, 25].

2.7 Miscellaneous

Studies with the following drugs have either failed to demonstrate a significant improvement or are currently under phase 2 trials:

- Mepolizumab-a humanized monoclonal anti-IL-5 antibody
- Rituximab - a chimeric monoclonal antibody against CD20
- Tumor necrosis-α factor/receptor (TNF-α) inhibitors such as Infliximab, Etanercept, and Adalimumab.
- High-dose intravenous immunoglobulins (IVIGs)
- Anti IL-17: Secukinumab

- Anti IL-6: Tocilizumab
- Recombinant human interferon-γ (rhIFN-γ)
- Natural AhR (therapeutic aryl hydrocarbon receptor) modulating agent: Tapinarof
- T-cell modulating agents (Efalizumab and Alefacept) [1]
- Anti IL-1α-Bermekimab [26].

3. Conclusion

Biologicals offer exciting prospects in the future management strategies for atopic dermatitis. However, the paucity of multicentric, large-scale, randomized trials, a high cost of treatment, along with a lack of comparative studies with the existing modalities of treatment are the major obstacles to their large scale use in clinical practice. Therefore, more studies with a larger sample size and longer follow up periods are needed to determine their efficacy and long-term safety profiles. Although Dupilumab is currently the only biological drug approved by the FDA for atopic dermatitis, other biologicals have also shown promising results and are expected to be a major part of the therapeutic armamentarium for atopic dermatitis in the near future.

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