Biological therapies for atopic dermatitis: An update (Review)

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Abstract. Severe atopic dermatitis, which affects both adults and children, is a debilitating disorder with a significant decline of patients' quality of life. Although aetiopathogenic factors are currently a topic of study and interpretation, the main features of atopic eczema are skin barrier disturbance and immune dysregulation. Severe refractory disease that fails to improve with conventional therapy may benefit from biologic therapy. Progress in understanding immunopathology of atopic dermatitis have allowed identification of therapeutic molecular targets in the field of biological therapy. We reviewed the different biological treatments with a focus on novel targeted agents: Systemic immunotherapy (Omalizumab, Dupilumab, Lebrikizumab, Tralokinumab, Nemolizumab, Ustekinumab, Fezakinumab, Tezepelumab, Apremilast, allergen specific immunotherapy), and topical agents (Tofacitinib, Crisaborole).

Contents

1. Introduction

Atopic dermatitis (AD), also known as atopic eczema is a common chronic or recurrent inflammatory skin disorder with a significant social and economic impact worldwide, affecting 2.1-4.9% of adult population, and 15-20% of children (1,2). An increasing prevalence of AD has been reported, especially in low-income countries (3). Furthermore, the past decades brought a 2-3-fold increase in prevalence in industrialized countries (3). Generally AD onset is in early childhood, as one of the first steps of the 'atopic march', which describes the natural history of atopic manifestations, and it is characterized by xerotic skin and acute flare-ups of intensely pruritic eczematous lesions (4). Recent studies recognize a predilection of AD for persistence in adulthood, with a lifetime prevalence accounting for 34.1% (5). Early onset, allergic rhinitis and hand eczema in childhood are high-risk factors for persistent AD (5). AD is a debilitating skin disorder in both children and adults, and severe refractory cases pose a difficult challenge for clinicians and patients alike. Approximately 20% of patients with AD have moderate to severe forms of the disease and treatment options approved by the Food and Drug Administration (FDA) are of limited or zero efficacy (5).

The aetiology of AD remains a topic of study and interpretation. Initially regarded as an allergic skin disorder, AD is currently interpreted in the context of the complex interplay between genetic predisposition to dysfunctional epidermal barrier and/or lipid composition and exposure to harmful environmental factors. Therefore, allergy is presumably an epiphenomenon of the impaired cutaneous barrier function in atopic individuals. Allergen sensitization may be involved in disease exacerbation and persistent pattern (6,7).

Recent years brought significant improvement in elucidating the complex interactions between skin barrier, genetic and environmental factors. The better understanding of pathologic pathways is a stepping-stone to improved management for AD patients.

The aim of this review is to summarize the topic of severe refractory atopic dermatitis from the perspective of novel therapeutic immunomodulatory methods. We have conducted a review on the different biotherapeutic strategies for AD with focus on novel treatments. PubMed database has been consulted for the following keywords: Atopic dermatitis or atopic eczema and biologics or biological treatment or antibody treatment. We selected articles that were published within the last five years, in English language and approaching the topic of biological therapies for AD. Based on their mechanism of action, these are classified into: IgE directed therapy (Omalizumab), anti IL-4 (Dupilumab) and anti IL-4/IL-13 agents (Lebrikizumab, Tralokinumab), IL-31 directed therapy (Nemolizumab), anti IL-12/23 (Ustekinumab), IL-22 blockade (Fezakinumab), thymic stromal lymphopoietin

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directed therapy (Tezepelumab), phosphodiesterase inhibitors (Apremilast, Crisaborole), and JAK inhibitors (Tofacitinib).

2. Systemic immunotherapy in AD

T-helper 1 (Th1)/Th2 imbalance and their associated cytokines are one facet of the pathological processes of AD. Several experimental agents have been investigated for their potential beneficial effects in the treatment of AD, by modulating Th1/Th2 homeostasis.

Omalizumab. Blocking the consequences of mast cells and basophil activation during the allergic inflammatory cascade has been a major therapeutic goal, and the use of Omalizumab has inaugurated a new era in the treatment of atopic disease. Initially, Omalizumab was approved by the FDA for the treatment of moderate to severe persistent asthma that is uncontrolled with a combination of a medium to high-dose inhaled corticosteroid and a long-acting β2-agonist, in adults and patients of 6 years and older who are sensitized to perennial aeroallergens (8,9). In 2014, FDA also approved Omalizumab for the treatment of chronic spontaneous urticaria in adults and children over 12 years of age who exhibit severe symptoms, inadequately controlled by high doses of H1 antihistamines (10). In addition, Omalizumab was proven to bring favourable results in patients with different subtypes of chronic inducible urticaria, allergic rhinitis, eosinophilic esophagitis, food allergy and anaphylaxis, as well as premedication in allergen specific immunotherapy, Churg-Strauss disease, eosinophilic otitis media, allergic bronchopulmonary aspergillosis, chronic rhinosinusitis, bullous pemphigoid, contact dermatitis and atopic dermatitis (11-15).

Mechanism of action. Omalizumab is a recombinant humanized monoclonal IgG1 antibody composed of 5% murine and 95% human sequence. It prevents the interaction of IgE with its receptors by recognizing and binding to the Fc portion (the CH3 domain) of free serum or membrane-bound on B cells immunoglobulin E molecule, but not IgE bound to its high (FcεRI) or low (CD23) affinity receptors (16). The CH3 domain serves as the site by which IgE binds to its receptors (17).

Binding of Omalizumab to free, soluble IgE blocks the binding of IgE to its receptors, and subsequently blunts allergen-induced mediator release. Once Omalizumab is administered, it results in the formation of soluble immune complexes with free IgE, typically trimers, which are cleared by the reticuloendothelial system (17,18). Administration of Omalizumab dramatically reduces the serum levels of free IgE (by 99% in the first two hours after administration), which subsequently downregulates the expression of IgE high-affinity receptors on immune cells (18). Expression of FcεRI facilitates antigen presentation by DCs. The latter cells appear to be crucial in the phenotypic development of Th1/Th2 cells and have a documented overexpression of FcεRI on the surface of DCs in allergic individuals (19,20). Moreover, IgE neutralization therapy decreases the serum expression of several cytokines (such as IL-5, -8, -13) and negatively regulates the recruitment of immune cells (T-cells, eosinophils, and macrophages) to inflammatory sites (21). Thus, Omalizumab decreases both the immediate and the late phase allergic inflammation. Another mechanism of action involves mast cells and eosinophils' apoptosis in allergic patients treated with Omalizumab compared to controls (22,23).

Omalizumab in AD. Anti-IgE therapy in AD brought 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 (24-33). The response variation to treatment helped to pinpoint patients that are most likely to respond to anti-IgE therapy. Lack of filaggrin mutations and lower elevations of total serum IgE are factors associated with a likely favourable response to Omalizumab (34,35). All of the studies noted the safety profile in both adult and paediatric population treated with Omalizumab. However, the wide variability of response to treatment remains largely obscure, while lack of standardized protocols regarding dosing is currently an unanswered task. Another notable conclusion of placebo-controlled studies showed that the improvement in clinical outcome of patients treated with Omalizumab was similar to improvements in control groups (27,36).

In the authors' experience, in a case series of three patients with severe refractory atopic dermatitis with atopic diathesis (sensitization to house dust mites, and moderate serum levels of total IgE in all three cases, co-existing asthma and rhinitis in one patient), Omalizumab, 300 mg monthly, brought a significant disease improvement, which occurred within the first three months of treatment.

Dupilumab. In 2017, the FDA approved Dupilumab for the treatment of adult patients with moderate to severe atopic refractory dermatitis, clinical studies proving concomitant efficacy in other atopic disorders, such as asthma and nasal polyposis (37). In addition, Dupilumab efficacy is under investigation for eosinophilic esophagitis and atopic dermatitis in paediatric patients (37).

Mechanism of action. Dupilumab is a fully human monoclonal antibody directed against interleukin-4 (IL-4) receptor-α (IL-4Rα) that blocks the synergistic effects of IL-4 and IL-13 on allergic inflammation. Atopy is the inappropriate secretion of immunoglobulin of E isotype in response to allergen exposure. IL-4 and IL-13 are key drivers of the Th2 allergic inflammation and of consecutive production of IgE. Both IL-4 and IL-13 signal through a common receptor, IL-4Rα, to activate the signalling proteins [signal transducer and activator of transcription 6 (STAT6) and Janus kinase-1 (JAK1)] (38). IL-4 is a crucial positive regulator of allergic inflammation. It induces the immunoglobulin isotype class switch to IgE, promotes the Th2 phenotype, prevents T-cell apoptosis, renders the refractory status of T-cells to corticosteroids, and induces the expression of VCAM-1 on endothelial cells, subsequently promoting the recruitment of cells characteristic to the allergic inflammation (T-cells, eosinophils, basophils and monocytes) (39-41). Gene polymorphisms in IL-4, -13 and IL-4Rα have been associated with AD in certain populations (42-45).

Additionally, IL-4 and -13 regulate expression of genes encoding proteins involved in skin susceptibility to skin pathogens (46-48). IL-4 receptors that function to stimulate the IgE

receptors expression and cysteinyl leukotriene synthesis are also expressed on mast cells (49).

Dupilumab in AD. Targeting Th2 polarization with Dupilumab brought unprecedented advances in the treatment of moderate to severe refractory AD. Dupilumab mono-therapy or combined therapy is associated with effective control of disease, improvement in skin lesions, significant reduction in pruritus and a substantial contribution to the reduced quality of life of affected patients (50). Dupilumab proved to reduce the expression of Th2 biomarker levels and of genes associated with the activation of T-cells, and to favour a genetic profile involved in skin barrier function. Data regarding the molecular signature showed that after 4 weeks of treatment with Dupilumab, the transcriptome of skin lesions of AD resembled that of non-lesional skin (51). A collection of clinical trials that included large number of patients with moderate to severe AD vs. control groups investigated the efficacy and safety of Dupilumab in AD (50-57). With no exception, evidence proved a rapid and marked improvement of disease activity, to the placebo group, and a safe profile of administration.

Lebrikizumab and Tralokinumab are monoclonal antibodies that target IL-13. The latter plays a pathogenic role in AD. It is overexpressed in the skin lesions of AD patients and it appears to be involved in the impairment of the epidermal barrier by negatively regulating the expression of genes encoding crucial structural proteins (loricrin, involucrin) (48). Blocking of IL-13 biological pathways with Lebrikizumab and Tralokinumab induced significant clinical improvement in moderate to severe AD in a small number of studies (58-60). 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.

Nemolizumab is a humanized monoclonal antibody against the receptor A of IL-31. IL-31, a cytokine expressed predominantly by Th2 lymphocytes, functions to target keratinocytes, epithelial cells, eosinophils, basophils and monocytes. IL-31 is overexpressed in skin AD lesions and stimulation of IL-31 in murine models induces inflammatory pruritic skin disease (61,62). A phase 2 randomized, placebo-controlled clinical trial noted a significant clinical improvement profile in adult patients with refractory moderate to severe AD, as compared to the placebo group (63). The length of the study (only 12 weeks) limited the results. Further studies are needed to confirm long-term efficacy and safety profile.

Ustekinumab, approved for treating moderate to severe psoriasis, appears to emerge as a potential efficacious treatment option in AD (64). Ustekinumab is a human immunoglobulin G1κ monoclonal antibody that targets the common p40-subunit shared by IL-12 and -23. IL-23 is required for Th17 cell development, key effectors in inflammation and tissue damage involved in several diseases (65). In addition, IL-23 induces atopic dermatitis-like inflammation in experimental murine models and serum IL-23 level positively correlates with the severity of disease among children with AD (66,67). 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 (68-73). The multifactorial aetiopathology of AD variability may explain the response to treatment with Ustekinumab. Recently, Noda *et al* showed a predominant Th17 immune pattern in Asian AD patients (74). Such data is valuable for identifying individuals who are most likely to benefit from therapy. Further studies are needed to address the applicability of Ustekinumab in the treatment of AD.

IL-22 promotes epidermal hyperplasia and skin barrier dysfunction in AD. Fezakinumab, an anti IL-22 antibody showed progressive and sustained clinical improvement of moderate-to-severe AD (7).

Clinical trials performed and completed for Tezepelumab, a human monoclonal antibody that prevents the interaction of thymic stromal lymphopoietin (TSLP) with its receptor. TSLP is a pivotal pro-inflammatory cytokine in both acute and chronic skin lesions of AD. However, information is not yet available (7).

Apremilast. Apremilast is an oral phosphodiesterase 4 (PDE4) inhibitor approved by the FDA for the treatment of obstructive pulmonary disease, plaque psoriasis, and psoriatic arthritis (75). Leukocytes from patients with AD display an elevated PDE activity, particularly that of PDE4 (76). Apremilast down-regulates pro-inflammatory cytokine transcription of several mediators (TNF-α, IL-12, IL-2, IFN-γ, IL-5 and -8) and other cellular responses (77). In addition, Apremilast increases the production of IL-10, a potent suppressor of inflammatory cytokines (78). Treatment with Apremilast proved effective and safe in both adults and children with severe AD. Recent clinical trials illustrated the potential for Apremilast as a treatment option for AD (79-81).

Additional immunomodulatory agents. Mepolizumab, a humanized monoclonal anti-IL-5 antibody, Rituximab, a chimeric monoclonal antibody against CD20, a pan marker of B lymphocytes, as well as inhibitors of tumour necrosis-α factor/receptor (TNF-α), such as Infliximab, Etanercept, and Adalimumab, brought moderate and intermittent improvement of AD (82-87). High-dose intravenous immunoglobulins (IVIGs) were investigated for their immunodulatory effects in moderate to severe AD, and failed to bring significant improvements (86-88). Earlier studies on recombinant human interferon-γ (rhIFN-γ) proved its efficacy in reducing clinical severity of AD (89-92). However, rhIFN-γ is not currently approved by the FDA for AD (86). T-cell modulating agents, such as Efalizumab and Alefacept failed to bring spectacular results in adult patients with moderate to severe AD (93,94). In addition, Efalizumab was voluntarily withdrawn from the market because of the risk of severe neurological adverse reactions caused by reactivation of the John Cunningham human polyoma virus (86).

Allergen-specific immunotherapy. There is still controversy regarding the use of allergen immunotherapy (AIT) in AD patients. Data suggests that AIT improves the clinical course of AD, pleading for its potential form of treatment. Case reports and small cohort studies showed effectiveness of AIT on AD (95,96). A multi-centre randomized study that enrolled

89 adult patients with AD and sensitization to house dust mites, of whom 51 completed the study, assessing the usefulness of AIT, observed the improvement of disease and a reduction in the need for topical corticosteroids (95). A meta-analysis of eight randomized trials that included 385 patients brought moderate-level evidence for the efficacy of AIT in AD (96). As shown by a prospective placebo-controlled study that included 168 patients with AD, AIT is beneficial only in severe AD, with a SCORAD score greater than 50 (97). A systematic review using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach reported improvement of clinical symptoms of AD. However, the study also noted the strength of recommendation for use of SIT in patients with AD as weak, pinpointing the need for high-quality evidence to support AIT in AD (98). Several studies on sublingual immunotherapy in AD patients bring arguments in favour of AIT as a safe and effective strategy (99-101). There are no contraindications for AIT in AD; AIT does not worsen AD (102).

3. Novel topical agents for AD

Tofacitinib. Initially approved for the treatment of rheumatoid arthritis, Tofacitinib, an oral small-molecule JAK inhibitor that acts by blocking several Th2 cytokine signalling (IL-4, -5 and -13), shows promise in AD (103). Many of the cytokines involved in AD use JAK biological pathways. The latter encompasses several tyrosine kinase proteins that interact with the common γ-chain of cytokine receptors to initiate cytokine mediated responses.

Crisaborole. A topical PDE inhibitor ointment, has been approved by the FDA in the topical treatment of AD patients of at least 2 years of age (104). It proved to reduce skin inflammation and pruritus, as compared to controls, with the disadvantage of being less effective than low potency topical corticosteroids (105). In contrast to topical corticosteroids, topical PDE inhibitors do not pose the risk for telangiectasia and skin atrophy (105).

4. Conclusion

Atopic dermatitis poses a challenge for clinicians and patients alike, particularly in severe forms of disease. Recent progresses in understanding the pathophysiology of atopic dermatitis underlie its multiple facets and allow the introduction of novel substances for the systemic and topical treatment of severe atopic dermatitis. New therapeutic strategies brought tremendous advances in the management of refractory to conventional treatment, severe atopic dermatitis. Robust evidence pleads for efficacy of Dupliumab, while other immunomodulatory agents, such as Nemolizumab, Lebrikizumab, Tralokinumab, Ustekinumab and Apremilast show promise, but further data are needed to confirm their usefulness and safety in atopic dermatitis. Allergen specific immunotherapy may be of use in selected cases of atopic dermatitis.

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Competing interests

The authors declare that they have no competing interests.

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