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Biologic drugs, a new therapeutic paradigm in moderate-severe atopic dermatitis

Carlo Alberto Vignoli[1,2]*, Riccardo G. Borroni[1,2]

[1]Department of Biomedical Sciences, Humanitas University, 20072 Pieve Emanuele, Italy
[2]Dermatology Unit, IRCCS Humanitas Research Hospital, 20089 Rozzano, Italy

***Correspondence:** Carlo Alberto Vignoli, Department of Biomedical Sciences, Humanitas University, Via Rita Levi Montalcini, 4, 20072 Pieve Emanuele, Italy. c.alberto.vignoli@gmail.com
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Abstract

Atopic dermatitis (AD), also referred to eczema, is a common inflammatory skin disease that usually presents during infancy or childhood but affects patients of all ages. It is a pruritic, chronic/relapsing condition that may significantly impact the patients' quality of life and can be associated with other atopic comorbidities including asthma and rhinoconjunctivitis. Inflammation in AD is mostly sustained by type 2 inflammation. Most patients are satisfactorily managed with a combination of emollients, avoidance of triggering factors, topical glucocorticoids, and/or topical calcineurin inhibitors. However, a proportion of patients with moderate or severe AD might require phototherapy or systemic immunosuppressants, which are limited in time due to possible safety concerns and progressive efficacy loss. In recent years, the availability of T helper 2 (Th2)-blocking agents dupilumab and tralokinumab has revolutionized the long-term treatment of moderate-to-severe AD. Here are discussed recent advances in the clinical development of biologic treatments for AD. The clinical implementation of these novel drugs has the potential not only to greatly improve the quality of life of patients with this chronic and disabling condition but also to clarify the biological processes underlying AD, in turn enabling further development of more effective, safer treatments. This research paper aims to provide an overview of biological therapies currently in use and under investigation in the setting of AD.

Keywords

Atopic dermatitis, eczema, biologic drugs

Introduction

Atopic dermatitis (AD), also referred to eczema, is one of the most common inflammatory diseases of the skin. It is a pruritic, chronic-relapsing condition with a multifactorial etiology, a variable clinical presentation, and a significant impact on the quality of life of patients and their caregivers. AD occurs in

2–10% of adults globally and is often associated with other atopic comorbidities such as asthma and oculorhinitis [1–5]. Although AD often presents in infancy or childhood and may spontaneously resolve after puberty, in approximately a quarter of the patients it persists in adulthood [5–8]. Interestingly, however, the proportion of patients who develop the first signs of the disease in adulthood is growing in developed countries [9]. This may, at times, make the diagnosis more challenging as adult-onset AD might lack clinical features that are typical in children, showing more heterogenous manifestations [10].

AD is primarily supported by type 2 inflammation, which includes the activation of innate lymphoid cells, T helper 2 (Th2) cells, T cytotoxic 2 (Tc2) cells, γ/δ T cells, B cells, eosinophils, and mast cells. The cytokines involved in type 2 inflammation, in AD in particular, include interleukin-4 (IL-4), IL-5, IL-9, IL-13, IL-25, IL-31, and IL-33 [11]. Among others, IL-4 and IL-13 represent the main drivers of atopic illnesses and particularly of AD, correlating also with disease activity [12–14]. AD is linked to an elevated risk of other atopic conditions, for example, allergic rhinoconjunctivitis, food allergies, asthma, and eosinophilic esophagitis. AD is also proven to be associated with an elevated risk of cardiovascular, infectious, and psychiatric conditions [15–18].

To assess the severity of AD in daily practice, and guide therapeutic decisions, clinicians make use of various scoring systems such as the Eczema Area and Severity Index (EASI), body surface area (BSA), and SCORing AD (SCORAD) [19, 20].

Most patients, both in the pediatric and adult age, have mild disease. They are satisfactorily managed with a combination of emollients, avoidance of triggering factors such as irritants and allergens, topical glucocorticoids, and/or topical calcineurin inhibitors. A proportion of patients with moderate or severe AD might require phototherapy or systemic immunosuppressants (mainly cyclosporin, in some cases methotrexate, azathioprine, and corticosteroids [21–24]). Patients with persistent or relapsing flares of moderate-severe AD might require protracted treatment; nevertheless, continuous therapy with "conventional" systemic immunosuppressants is limited in time due to possible safety concerns and progressive efficacy loss [12, 25]. This suggests that further improvements are needed in AD management. In the last few years, the systemic approach to AD has thrived, new molecules have been developed and are in the course of being licensed or marketed.

More recently, new molecules have been introduced into AD management, for instance, the Th2 blocking agents dupilumab and tralokinumab which have revolutionized AD therapy for long-term management offering an effective treatment with a high-security profile [26, 27]. Besides, the development of dupilumab, through studies of gene expression, offered the possibility to study new therapeutic targets and new drugs that will be further discussed in this paper.

This research paper aims to provide an overview of biological therapies currently in use and under investigation in the setting of AD.

Biologic drugs for AD: current options and recent development

In recent years, the availability of dupilumab for AD, an anti-IL-4 receptor alpha (anti-IL-4Rα) monoclonal antibody now approved also for asthma, chronic rhinosinusitis with nasal polyposis, moderate-to-severe prurigo nodularis, and eosinophilic oesophagitis, enabled not only more effective and long-term, safer treatment of patients with severe eczema but also contributed to better understanding of the pathophysiology of AD, paving the way for development of further, targeted treatments. Dupilumab binds IL-4Rα, a subunit shared by both type I (IL-4Rα/IL-2Rγ) and type II (IL-4Rα/IL-13Rα1) receptors of IL-4 and IL-13, thus inhibiting the downstream signaling pathways of both cytokines [28, 29]. Dupilumab efficacy in adult eczema has been confirmed in phase III trials and in "real-life" data from many countries; other pivotal trials led to its regulatory approval also for AD in children from 6 years of age both in the EU and the USA and in children from 6 months in the USA [30–33]. CBP-201, another IL-4Rα antagonist, showed promising results in a phase Ib trial. As early as week 4 of treatment, Investigator's Global Assessment (IGA) 0/1 was observed in up to 50% of patients compared to 13% in the placebo arm. From baseline, the mean reduction in EASI amounted to 74% compared to 33% in the placebo arm. Even though

the mechanism of action is analogous to that of dupilumab, CBP-201 seemed to demonstrate a faster onset of effect [34].

Since IL-13 is one of the key Th2 cytokines in eczema [35–37], it is not surprising that this target has been exploited in clinical drug development. Tralokinumab, a fully humanized antibody that prevents IL-13 from binding to both IL-13Rα1 and IL-13Rα2 receptor subunits, was recently given a marketing authorization from the European Medicines Agency (EMA/779068/2022) [38, 39]. In phase III trials, tralokinumab was superior to placebo with 16% ("ECZTRA 1" trial) and 22% ("ECZTRA 2" trial) of patients reaching IGA 0/1 at week 16 *versus* 7% and 11% in placebo groups, respectively. After further randomization at week 16 and longer maintenance treatment, the clinical manifestations kept improving, with 51% (ECZTRA 1) and 59% (ECZTRA 2) of the patients reaching IGA 0/1, respectively [40].

Lebrikizumab is another anti-IL-13 fully humanized antibody that acts by preventing the heterodimerization of IL-4Rα and IL-13Rα1, thus inhibiting IL-13 signal transduction [39, 41]. Moreover, lebrikizumab does not interfere with the binding of IL-13 to the IL-13Rα2 receptor subunit, the role of which in AD is still to be clarified [28]. In a phase IIb trial with lebrikizumab, a mean percentage change in EASI of 72% *versus* 41% in the placebo arm was observed. The improvement in EASI was also accompanied by a rapid decrease in itch as measured with the pruritus Numerical Rating Scale (NRS). Few cases of conjunctivitis were observed, and the treatment was well tolerated [42].

The potential usefulness of biologics targeting IL-13 in atopic conditions and, more precisely, in patients with AD not responding or showing only partial response to dupilumab is still to be evaluated. From later development stage trials and real-world data, significant new observations are expected on the roles of IL-4, IL-13, and their receptors in Th2 immunity and consequently in the modulation of inflammation in the skin.

Because eosinophils are found in the inflammatory infiltrate of different conditions characterized by type 2 inflammation, therapeutic strategies that target IL-5, the main cytokine for eosinophil activation, are currently under study. However, mepolizumab, an anti-IL-5 antibody, despite reducing eosinophilia, seemed to fail to reduce SCORAD and pruritus in AD patients compared to baseline in a phase II study [43].

In AD, keratinocyte-derived alarmins of innate immunity such as IL-33, IL-25, and thymic stromal lymphopoietin (TSLP) are thought to provide a favorable environment towards Th2-polarized inflammation [44]. Due to their pro-inflammatory properties, these molecules linking innate with adaptive immunity have also been investigated as therapeutic targets. Tezepelumab (AMG 157), an anti-TSLP monoclonal antibody, has shown achievement of EASI50 (i.e., 50% reduction of severity and extent of lesions from baseline) endpoint in 64.7% of AD patients, compared to 48.2% in the placebo group, in a phase IIa study [45].

Regarding the adaptive immune response, biologic therapies may interfere with antigen presentation and several other pathways, beyond type 2 inflammation where immunoglobulin E (IgE), IL-4, IL-5, and IL-13 and their receptors play important roles. In fact, despite advances in targeted treatments of AD inhibiting the IL-4/IL-13 pathway or the Janus kinase pathways, a substantial number of patients do not respond adequately or cannot tolerate treatment. In these specific subjects, other cytokines, including IL-22, IL-31, IL-17, IL-23, and IL-36 might be suitable candidates for drug development [46–50].

Antigen presentation plays a critical role in generating and maintaining the different functions of innate immunity, eventually leading to inflammation. OX40, a variant of the tumor necrosis factor (TNF) receptor and costimulatory agent, is exposed on T-cell membrane after activation promoting lymphocyte expansion and survival. Rocatinlimab (KHK4083) is an anti-OX40 antibody, which in a recent phase IIb trial showed good tolerability and achievement of EASI75 in 52–64% of patients at week 36, compared to the placebo group in which 11–21.5% of the patients achieved the same endpoint. In addition, rocatinlimab showed a unique durability of response among current AD therapies, suggesting possible disease modification [51]. Other studies with biologic drugs blocking OX40 or OX40 ligand (OX40L; GBR 830 and KY1005, respectively) have demonstrated encouraging results. GBR 830 dramatically improved the clinical signs of AD, reaching EASI50 in 78% of patients, as opposed to 38% in the placebo arm, in a phase IIa trial

[52]. Similarly, KHK4083 led to a decrease of 74% of the EASI score, with a third of the patients (35%) reaching the IGA 0/1 in a phase Ib study [53]. The anti-OX40L drug amlitelimab (KY1005) blocks the effector T lymphocytes and supports regulatory T lymphocyte activity. In a phase IIa trial, amlitelimab induced a reduction of EASI up to 80, 1% from baseline, compared to 49, 4% in the placebo arm, with 44% of patients treated with amlitelimab reaching IGA 0/1 compared with 8% of those receiving placebo. As the interaction between OX40 and OX40L is assumed to affect not only Th2 immunity but also other subsets of T cells, therapeutic approaches aimed at blocking this molecular interaction might offer an interesting perspective, particularly with respect to the immunological processes implicated in the individual course of AD. Nonetheless, as antigen presentation is a key stage in anti-tumor immunity, the comprehensive analysis of the safety profile of biologics interfering with the interaction between OX40 and OX40L will be paramount [54].

Besides the Th2 profile, a promising therapeutic target in AD is IL-22, a cytokine induced by staphylococcal toxins in many inflammatory cells, such as Th1 and Th17 cells [55–58]. Serum IL-22 levels seem to relate with the eczema severity and play a significant role in AD [59, 60] modulating keratinocyte proliferation and filaggrin expression. In a first trial with patients with moderate-to-severe AD, fezakinumab, an anti-IL-22 antibody, did not show significant differences in the change of SCORAD *versus* the baseline. However, encouraging results have been observed in patients presenting severe AD (SCORAD > 50), whose average decrease in SCORAD was higher than that of the placebo group. This study was limited by its modest sample size (n = 60) and a probably too premature endpoint to allow observation of a clinically meaningful outcome [61].

Itch, the main symptom of AD, is the main cause of its negative impact on patient's quality of life. The pathophysiology of pruritus involves many mediators that activate the peripheral sensory receptors [62–64]. Dupilumab, lebrikizumab, and tralokinumab already showed high efficacy in reducing itch, as receptors for IL-4 and IL-13 are expressed on sensory neuron terminations [35, 42, 65]. Moreover, IL-31 is an important pruritogenic cytokine expressed by Th2 cells, therefore along with its receptor, it represents a target for superior itch control [66–69]. In a phase IIa trial, nemolizumab, an anti-IL-31Rα antibody, showed an important reduction in pruritus, although it did not impact the overall skin inflammation as the BSA, IGA, and EASI scorings did not improve in a significant way [70]. In another phase II trial with nemolizumab, the decrease in pruritus NRS (69% *versus* 34%) reflected the improvement in itching. One-third of the patients reached IGA 0/1 *versus* 12% in the placebo arm at week 16 but not at subsequent time points, possibly due to the high background consumption of topical corticosteroids [71]. The efficacy in the reduction of pruritus in addition to the use of topical corticosteroids was also proven in a phase II trial with a decrease of pruritus NRS of 43% compared to 21% in the placebo arm at week 16 [72].

Conclusions

The time has come for more effective, targeted treatments that are safer in the long-term treatment of patients with moderate-to-severe AD. In recent years, more numerous biologics have undergone clinical development than all biologics for chronic plaque psoriasis since the first introduction of infliximab. This is particularly promising as different specific pathways involved in the pathogenesis of AD are being investigated, each one generating several potentially druggable targets.

Moreover, the use of biomarkers to identify patients who are more likely to benefit from specific biologics will help tailor treatment to the individual patient on the one hand, and to further promote the development of novel mediations on the other hand. This personalized approach to treatment will improve outcomes and reduce the burden of AD on patients.

Challenges still need to be addressed, including the impact of treating a large number of patients for healthcare providers and the potential for long-term adverse events. Further research is needed to fully clarify safety concerns and their management.

Overall, the future of biological treatment in AD is promising, and these novel drugs have the potential to greatly improve the quality of life of patients with this chronic and disabling condition.

Abbreviations

AD: atopic dermatitis

anti-IL-4Rα: anti-interleukin-4 receptor alpha

EASI: Eczema Area and Severity Index

IGA: Investigator's Global Assessment

IL-4: interleukin-4

NRS: Numerical Rating Scale

OX40L: OX40 ligand

SCORAD: SCORing atopic dermatitis

Th2: T helper 2

Declarations

Author contributions

CAV: Conceptualization, Investigation, Writing—original draft, Writing—review & editing. RGB: Conceptualization, Investigation, Writing—review & editing, Validation, Supervision. Both authors read and approved the submitted version.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Not applicable.

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