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Current State of Monoclonal Antibody Therapy for Allergic Diseases

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ABSTRACT

Allergic disease is one of the most common chronic diseases, which can affect both children and adults, be often caused by allergen-induced unfavorable immune responses, and initiate various symptoms in different organs, including up-/low-airways and skin, such as asthma, atopic dermatitis, and rhinosinusitis. With increasing prevalence of allergic disease worldwide and their impact on the quality of life, new biological therapeutic approaches for these disorders become hot areas of intensive research. Multiple factors are involved and play important role in the pathogenesis of allergic disease, which can promote or trigger T helper 2 (Th2)-type immune responses, leading to production of the type 2 cytokines and immunoglobulin E (IgE), the two critical events in the allergic diseases. Using monoclonal antibodies to target these molecules, therefore, might provide possible benefits for the patients suffered from these diseases. Apart of those having approved biologics for allergic diseases, some potential targets such as epithelial-derived alarmins thymic stromal lymphopoietin (TSLP) and interleukin 33 (IL-33) have been also described and proposed to develop monoclonal antibodies against either these cytokines, their receptors, or both. These new and potential targets have substantially enriched the therapeutic opportunities in the field of allergic diseases. The present review aims to briefly outline the role of monoclonal antibodies targeting the cytokines and immunoglobulin involved in the development of allergic diseases, and to discuss the clinical effects of these antibodies.

1. Introduction

Allergic diseases are chronic inflammatory disorders that represent a significant global health burden; furthermore, the global prevalence of such diseases is increasing [1]. Normally, most symptoms of allergic diseases can be effectively relieved with various available drugs; however, in some patients, the disease itself remains uncontrolled after the use of currently recommended therapies. Therefore, more effective and well-tolerated therapies are required that target the etiologic mechanisms of allergic diseases rather than simply providing symptom relief.

The allergic diseases addressed in this article comprise a group of disorders correlated with dysregulated immune responses to allergens. Allergic diseases usually occur in different organs such as the skin, respiratory tract, conjunctiva, and gastrointestinal tract, which are directly exposed to the external environment, causing atopic dermatitis (AD), asthma, rhinosinusitis, allergic conjunctivitis, food allergies, and so on. Although the target organs and clinical manifestations are different, allergic diseases often coexist; for example, asthma is commonly associated with rhinitis and AD. Furthermore, most allergies are driven by type 2 immune responses and the secretion of immunoglobulin E (IgE) [2,3]. Based on this common mechanism, biologic therapies have been developed that target the key molecules driving the T helper 2 (Th2) cell response. In particular, humanized therapeutic antibodies have been developed that specifically act against key mediators contributing to the pathogenesis of atopic allergic diseases, including essential cytokines, cytokine receptors, and soluble or membrane-bound IgE (summarized in Table 1 and Table S1 in Appendix A). Starting from this basis, this article discusses monoclonal antibodies for the treatment of allergic diseases that have been approved for marketing and are being clinically validated.

2. Anti-IgE antibodies

IgE is the least abundant immunoglobulin in human serum, but its levels are usually elevated in patients suffering from atopic allergic disorders. Once a specific IgE is produced—which occurs when sensitized individuals encounter specific allergens—it

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Table 1
Monoclonal antibodies potential used for allergic disease treatment.

Target molecule	Monoclonal antibody	Approved by US Food and Drug Administration	Applied in these allergic diseases
Anti-IgE	Omalizumab	Approved for asthma on 20 June 2003	Asthma, chronic urticaria, food allergies
	Ligelizumab (QGE031)	Not yet approved	Asthma
	Quilizumab (MEMP1972A/RG7449)	Not yet approved	Asthma, allergic rhinitis, chronic spontaneous urticaria
	MEDI4212	Not approved	—
Anti-IL-4	Pascolizumab	Not approved	—
Anti-IL-4R	Pitrakinra	Not yet approved	Asthma, atopic eczema
	Dupilumab	Approved for atopic dermatitis on 28 March 2017	Atopic dermatitis, asthma, allergic rhinitis, chronic rhinosinusitis with nasal polyposis
Anti-IL-13	Lebrikizumab	Not yet approved	Atopic dermatitis
	Tralokinumab	Not yet approved	Asthma, atopic dermatitis
Anti-IL-5	Mepolizumab	Approved for asthma on 4 November 2015	Asthma, eosinophilic nasal polyposis
	Reslizumab	Approved for asthma on 25 March 2016	Asthma
Anti-IL-5Rα	Benralizumab	Approved for asthma on 16 November 2017	Asthma
Anti-TSLP	Tezepelumab (AMG 157/MEDI9929)	Not yet approved	Asthma
Anti-IL-33	Etokimab (ANB020)	Not yet approved	Asthma, peanut allergy, atopic dermatitis, chronic rhinosinusitis with nasal polyps
IL-33R(ST2)	AMG 282/RG 6149	Not yet approved	Asthma, chronic rhinosinusitis with nasal polyps
	GSK3772847	Not yet approved	Asthma

IL: interleukin; IL-4R: IL-4 receptor; IL-5Rα: α subunit of the IL-5R; TSLP: thymic stromal lymphopoietin; IL-33R: IL-33 receptor; ST2: suppression of tumorigenicity 2.

promotes degranulation of mast cells and basophils, which contain active mediators that lead to the inducing and recruitment of Th2 cells. This causes allergic symptoms such as smooth muscle convulsion, increased vascular permeability, and mucus production. Due to its crucial role, IgE is an ideal target for the treatment of allergic diseases [4].

Omalizumab is a humanized anti-IgE monoclonal antibody that was the first therapeutic antibody approved by the US Food and Drug Administration (FDA) for the treatment of moderate/severe persistent allergic asthma, in 2003 [5]. By binding to serum-free IgE, omalizumab inhibits the binding of IgE to high-affinity IgE receptors (FcεRI) on effector cells, and thereby prevents the degranulation of mast cells and basophils from releasing pro-inflammatory mediators and cytokines (interleukin (IL)-4, IL-5, IL-13, etc.) [6]. In addition to its effect on mild/moderate asthma patients, clinical trials have shown that omalizumab therapy is effective for patients with severe refractory allergic asthma [7]. Since omalizumab administration is followed by a decrease in free IgE levels, subsequent downregulation of FcεRI expression in inflammatory cells can occur. In addition, it has been demonstrated that omalizumab decreases asthma exacerbation by downregulating the expression of FcεRI on dendritic cells (DCs) [8]. It is thought that binding IgE to the FcεRI expressed on myeloid DC could inhibit influenza-induced plasmacytoid DC (pDC) interferon (IFN)-α production in patients with allergic asthma [8]. Furthermore, treatment with omalizumab prevents autumn asthma exacerbation caused by virus infection in inner-city children, adolescents, and young adults, and reduces the need for other medications to control asthma [9,10].

Omalizumab is also being tested against a wide range of allergic conditions. Some studies have shown that this antibody might benefit diseases other than allergic asthma, such as seasonal allergic rhinitis, chronic urticaria [11], and food allergies [12]. Omalizumab treatment for patients with chronic spontaneous urticaria resulted in clinical benefits, as it decreased levels of FcεRI and IgE expression on peripheral blood basophils. However, the IgE produced in chronic spontaneous urticaria might not be induced by allergens but by auto allergens [13,14]

In addition to omalizumab, other monoclonal antibodies against IgE are still under validation in clinical trials. Ligelizumab (QGE031), which acts on circulating IgE by binding the Cε3 domain, has greater efficacy than omalizumab on inhaled and skin allergen responses in patients with mild allergic asthma [15]. Quilizumab (MEMP1972A/RG7449), which binds to the M1-prime segment present on membrane IgE, has an acceptable safety profile and can decrease the concentration of serum IgE. However, quilizumab treatment did not have a clinically significant impact on exacerbation rate, lung function, or quality of life in a phase 2 trial on allergic asthma [16], although its efficacy for allergic rhinitis and chronic spontaneous urticaria is still under testing [17]. Aside from the above mentioned antibodies, MEDI4212, another kind of monoclonal antibody that acts against IgE, can also bind to IgE with high affinity, and rapidly reduces the level of free serum IgE; however, its effect on patients with allergic disease is unclear [18].

It is known that Th2 cytokines (IL-4, IL-13, IL-5, etc.) play a key role in the pathogenesis of allergic diseases, especially in asthma, AD, and allergic rhinitis. Thus, it is reasonable to pursue that intervention therapy targeting these cytokines with related monoclonal antibodies might be a beneficial therapeutic strategy against atopic allergic diseases.

3. Anti-IL-4/IL-13 and their receptor antibodies

IL-4 and IL-13 are pleiotropic Th2 cytokines produced by different cells, and are responsible for various biological activities and functions. IL-4 is critical for IgE production and mast cell activation, while IL-13 is essential for goblet cell hyperplasia, mucus production, and worm expulsion [19]. Recent clinical trials have shown that the IL-4/IL-13 pathways are targetable candidates for intervention treatment for the amelioration of allergic disease.

3.1. Anti-IL-4/IL-13

IL-4 blockage can be achieved either directly, by blocking IL-4 from binding to its receptor IL-4R, or indirectly, by blocking the IL-4R to prevent the binding of IL-4. Pascolizumab is the first humanized monoclonal antibody developed for use against IL-4. Preclinical studies have shown that this antibody reduces asthma-related Th2 cell activation and IgE production [20].

However, despite successful phase 1 studies, pascolizumab showed little effect on free IgE in subsequent clinical trials, so it has not been further developed.

Due to the role of IL-13 in the pathogenesis of atopic diseases, particularly in asthma, anti-IL-13 antibodies are also being validated at present in clinical trials targeting allergic diseases. Lebrikizumab, an IgG4 humanized monoclonal antibody that specifically neutralizes IL-13 and inhibits its function, resulted in significant improvement in prebronchodilator forced expiratory volume in 1 s (FEV1) in poorly controlled asthma [21]. However, inhibiting IL-13 alone was insufficient to significantly improve the FEV1 of patients who did not receive inhaled corticosteroids (ICSs) [22]. It is possible that this antibody is no longer under development due to a lack of convincing efficacy in clinical trials for asthma. On the other hand, in combination with topical corticosteroid (TCS), lebrikizumab 125 mg every four weeks treatment resulted in significant improvement in patients with moderate-to-severe AD who had a history of inadequate control by TCS in a phase 2 trial [23]. Tralokinumab, which blocks IL-13 by interacting with the IL-13Rs, showed an acceptable safety and tolerability profile in phase 2b and phase 3 clinical trials [24,25]. It was also reported that treatment with 300 mg of tralokinumab resulted in improvements in the severity scoring of atopic dermatitis (SCORAD), Dermatology Life Quality Index, and the Pruritus Numerical Rating Scale (7-day mean) scores versus a placebo in AD patients. Taken together, these studies suggest that targeting IL-13 might be beneficial for patients with AD [26].

3.2. Anti-IL-4R/IL-13R

It is commonly thought that IL-4 and IL-13 regulate cellular functions via cell surface receptors. Because the receptors for IL-4 and IL-13 both contain α subunit of the IL-4R (IL-4Rα) and signal through signal transducers and activators of transcription 6 (STAT6), it has been suggested that monoclonal antibodies working against both the IL-4 and IL-13 pathways would be more effective than monoclonal antibodies that are specific to just a single cytokine. In fact, pitrakinra, an IL-4Rα antibody that contains two targeted point mutations, blocks further binding of IL-4 and IL-13. Subcutaneous and inhaled administration of pitrakinra reduced airway inflammation in phases 1 and 2 clinical trials of patients with asthma [27]. Interestingly, symptoms of atopic eczema also appeared to improve as a result of pitrakinra treatment in a phase 2 clinical trial. Dupilumab, a fully human monoclonal antibody that binds to the IL-4Rα inhibits the signaling pathways of IL-4 and IL-13. In March 2017, the FDA approved this antibody for the treatment of adult patients with moderate-to-severe AD [28]; however, it has not yet been approved for the treatment of asthma. At present, phase 3 clinical trials show that dupilumab therapy improves lung function and the rate of severe asthma exacerbation in patients with uncontrolled asthma or glucocorticoid-dependent severe asthma [29,30]. Recently, the efficacy of dupilumab was explored against other allergic diseases, including allergic rhinitis and chronic rhinosinusitis with nasal polyposis, and promising results were obtained [31,32].

4. Anti-IL-5/IL-5R antibodies

Blood and tissue eosinophilia are characteristic features of allergic inflammation and asthma, while IL-5, which is mainly produced by Th2 lymphocytes and group 2 innate lymphoid cells (ILC2s), plays a critical role in eosinophil proliferation, differentiation, maturation, survival, and activation. It has been shown that IL-5 is significantly elevated in asthma patients, and is closely related to the severity of the disease [33]. By binding to its receptor IL-5R, which is expressed on eosinophils, IL-5 exhibits its biological functions. For the reasons of eosinophils in the pathogenesis of allergic diseases, IL-5 and IL-5R become attractive targets for therapy against allergic disease. Two humanized anti-IL-5 monoclonal antibodies (mepolizumab and reslizumab) were developed and approved by the FDA for the biological therapy of uncontrolled eosinophilic asthma in 2015 and 2016, respectively. Another one (benralizumab), which targets the IL-5Rα, was approved by the FDA in 2017 for asthma treatment [34].

Mepolizumab, a high-affinity humanized monoclonal antibody that specifically binds to IL-5 and blocks it from binding to the IL-5R expressed on the surface of eosinophils, prevents IL-5-driven eosinophil proliferation, differentiation, survival, and activation. Several clinical trials have shown that mepolizumab treatment significantly decreases the numerous eosinophils in peripheral blood and sputum, and reduces exacerbation while leading to modest improvements in symptoms, indicating its effectiveness and safety in the subgroup of severe asthma patients [35–37]. Other studies revealed that mepolizumab has a significant effect on patients with eosinophilic nasal polyposis [38,39], patients allergic to *Dermatophagoides*, and those affected by chronic rhinosinusitis with nasal polyps [40]. However, it is not effective in patients with AD [41]. Reslizumab is another blocking antibody that targets IL-5. In comparison with mepolizumab, it has shown similar therapeutic effects in reducing asthma exacerbation and improving lung function, but has a higher affinity for binding human IL-5 *in vitro* [42,43]. Unlike the two antibodies described above, benralizumab (MEDI-563) selectively binds to the amino acid residue of human IL-5Rα and nearly completes the depletion of eosinophils by enhancing antibody-dependent cell-mediated cytotoxicity [44]. Clinical trials have shown that benralizumab treatment reduces the acute exacerbation of eosinophilic asthma and has similar clinical outcomes to anti-IL-5 antibodies [45].

Overall, anti-IL-5 or anti-IL-5R therapy could improve the symptoms of certain subgroups of patients suffering from eosinophil-associated diseases, especially those with eosinophilic asthma.

5. Anti-TSLP/IL-33 antibodies

Although the monoclonal antibody therapies discussed above are effective in different phenotypes of allergic patients, they are not a panacea for uncontrolled allergic diseases, probably because these biologics are directed against targets that are downstream in the inflammatory cascade that occurs in the pathogenesis of these diseases. Extensive studies currently report that blocking upstream cytokines, such as thymic stromal lymphopoietin (TSLP) and IL-33, which have been described as epithelial-derived alarmins, seems to result in broader downstream effects than the currently available biologics. This finding suggests that targeting these molecules might provide additional benefits in improving patient outcome. Interestingly, these alarmins might also contribute to the initiation of IgE production by inducing Th2 cytokine production by ILC2. In turn, anti-IgE treatment could decrease the expression of these alarmin molecules in the airways of atopic asthmatics [46], although the details of these mechanisms still need to be clarified.

5.1. Anti-TSLP

TSLP is a cytokine belonging to the IL-7 family that binds to its receptor (TSLP-R) in order to exert its biological activities. It has been clearly demonstrated that TSLP contributes to the initiation and development of Th2 responses by promoting the expression

of Oxford 40 ligand (OX40L) by DCs. It has been reported that TSLP is involved in the development of AD, as well as asthmatic and chronic rhinosinusitis [47,48]. Therefore, therapy targeting TSLP is a potential strategy for these allergic diseases.

Tezepelumab (AMG 157/MEDI9929) is a human IgG2 monoclonal antibody that acts against TSLP, preventing its interaction with the TSLP-R complex. A proof-of-concept study involving patients with mild atopic asthma showed that tezepelumab effectively treats asthma by suppressing the biomarkers of type 2 inflammation after an inhaled allergen challenge [49]. Furthermore, a randomized, double-blind, placebo-controlled phase 2 clinical trial revealed that tezepelumab is the most promising biologic for the treatment of persistent uncontrolled asthma [50]. Based on its broad upstream blocking effect of TSLP and its role in AD, Simpson et al. [51] carried out a randomized phase 2a clinical trial of tezepelumab in moderate-to-severe AD. Unfortunately, the results showed that treatment with tezepelumab and TCS did not result in statistically significant improvements in these patients versus placebo controls in combination with TCS alone at week 12. Although Parnes et al. [52] evaluated the safety of tezepelumab in humans, its pharmacokinetic profiles, and its preliminary clinical activity in AD, additional clinical studies are clearly required to validate the findings in AD treatment. Recently, Venkataramani et al. [53] developed two bispecific antibodies (Zweimab and Doppelmab) that are utilized for targeting both TSLP and IL-13. Due to the significant overlap of the downstream signaling effects of these two cytokines in severe asthma, it is reasonable to assume that these two antibodies may provide better therapeutic effects in future in the treatment of asthma.

5.2. Anti-IL-33

IL-33, a tissue-derived nuclear alarmin, is a member of the IL-1 cytokine family and plays important roles in type 2 immunity via the activation of eosinophils, basophils, mast cells, macrophages, and ILC2 through suppression of tumorigenicity 2 (ST2). The binding of IL-33 to its receptor activates nuclear factor (NF)-κB and mitogen-activated protein kinase, induces the expression of Th2 cytokines, and aggravates the pathological damage of mucosal tissues. Upregulation of IL-33 expression has been observed in the nasal, pulmonary, or skin epithelium of patients with allergic rhinitis, allergic asthma, or AD [54,55].

Considering the multiple functions of IL-33, several clinical trials have attempted to explore the effects on these diseases of intervening in the IL-33/ST2 axis. Thus far, promising data have been obtained from a series of clinical trials in which IL-33 (etokimab/ANB020) or the IL-33R(ST2) (AMG 282/RG 6149 and GSK3772847) were targeted for the treatment of asthma. Etokimab showed some effects in adult patients with severe eosinophilic asthma (NCT03469934)[†] and peanut allergy (NCT02920021)[‡] in two phase clinical trials; its efficacy will also be investigated in phase 2 clinical trials on patients with AD (NCT03533751)[††] and patients with chronic rhinosinusitis with nasal polyps (CRSwNP) (NCT03614923)[‡‡]. The safety and tolerability profile of AMG 282 has been evaluated in phase 1 clinical trials of patients with asthma (NCT01928368)[†††] and patients with CRSwNP (NCT02170337)[‡‡‡]. In addition, GSK3772847 has undergone a phase 2a study in patients with moderately severe asthma (NCT03207243)[††††]. These clinical trials indicate that anti-IL-33 or anti-ST2 antibodies might provide an alternative therapeutic choice for the treatments of atopic allergic disorders.

6. Conclusions

In this review, we attempted to provide a general overview of the treatment of allergic diseases using monoclonal antibodies (anti-IgE or anti-cytokines). Whether they have been approved by the FDA or are still being applied in clinical trials, monoclonal antibodies have been shown to inhibit most early- and late-stage type 2 immune responses, and show promise in improving patient outcomes. Nevertheless, there is currently a lack of clinical trials comparing the efficacies of different monoclonal antibodies in the treatment of allergic patients with the same phenotypes. Without such trials, it is very difficult to objectively validate which treatment is better for what situation, however, this information is very difficult to obtain from clinic trials. Aside from the individual effects of these antibodies, the combined treatment of some antibodies is supported by a few studies in the literature, such as the reported effectiveness and sustainability of omalizumab–mepolizumab in severe asthma [56]. Clearly, more comparative studies on these biological agents are needed in future. Furthermore, it is important to define good responders and design therapeutic biomarkers based on the mechanisms of allergic diseases in future.

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Compliance with ethics guidelines

Yan Chen, Wei Wang, Huihui Yuan, Yan Li, Zhe Lv, Ye Cui, Jie Liu, and Sun Ying declare that they have no conflict of interest or financial conflicts to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eng.2020.06.029.

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