

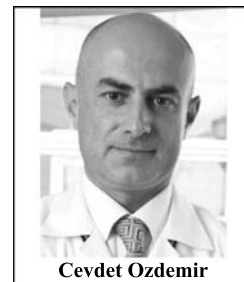
Monoclonal Antibodies in Allergy; Updated Applications and Promising Trials

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Abstract: Allergic disorders, as asthma, allergic rhinitis/rhinoconjunctivitis, atopic dermatitis, food allergies and anaphylaxis have an increasing burden in the general population and a growing body of evidence has shown that an increased interest has aroused to seek for more effective treatment strategies. Conventional pharmacotherapy by antihistamines, anti-leukotrienes, corticosteroids and bronchodilators can routinely control most of the cases, in addition to allergen avoidance which saves the date. Furthermore, allergen specific immunotherapy stands as the only curative method to treat the underlying cause of allergic immune response by induction of immune tolerance. However, response to pharmacotherapies can show diversity depending on the genotype and phenotype of the allergic disorders, which are known to be under the influence of multifactorial triggers. Thus, understanding the mechanisms of development of allergic disorders, in addition to selective description of the phenotypes can provide access to development of more specific therapies in order to control the disease progression. Monoclonal antibodies can be the major actors in this targeting process. Concerns about the safety, efficacy and long-term tolerability of these molecules always stand as a question for them, in order to gain indications for the treatment of allergic disorders. This review includes most recent developments and patents on usage of monoclonal antibodies for the treatment of allergic disorders.



Keywords: Allergy, asthma, atopic dermatitis, atopy, food allergy, monoclonal antibody.

INTRODUCTION

This review article further extends my previous publication [1] on the usage of monoclonal antibodies in the treatment of allergic disorders.

Monoclonal antibodies (mAb), produced by cell lines or clones obtained from animals that have been immunized with the respective antigen, are in-service of medicine for the diagnosis and treatment of diseases since their first description in 1975 by Köhler and Milstein [2]. Fusion of B cells harvested from the immunized animals with myeloma cells produces hybridomas [2], which provide a line of immortal mAb-producing cells that can divide *in vitro* to generate daughter cells and, therefore, produce more antibodies [3]. However, development of human anti-mouse antibodies has possessed significant risks to the patient and reduced the affectivity of treatment with these pioneering mAbs. Generation of chimeric mAbs with the constant human domain and rodent variable domains has opened a new trend in the mAb field [4-6], which has been then similarly limited due to generation of human anti-chimeric antibodies [7, 8]. Humanization of mAbs by Greg Winter *et al.* in 1988 [8] has resolved

these problems mostly. This has been followed by the usage of transgenic mice, in which murine immunoglobulin genes have been disrupted and replaced with human immunoglobulin gene clusters with diversity of the human immunoglobulin complement retains, which has allowed the generation of 'fully human' antibodies [6, 9], Table 1.

Inhibition of interactions of specific effector molecules with their unique receptors or blocking a functional receptor is the general leading principle of antibody centered treatment modalities [3]. Understanding the real-life mechanistic of immune responses is essential before prescribing a monoclonal antibody regimen, as the possible risk of mAb treatment can range from mild-to-moderate flu-like reactions to severe cytokine release syndromes, the development of opportunistic infections, generation of neutralizing antibodies and anaphylaxis [10, 11].

ALLERGIC IMMUNE RESPONSE

The allergic immune response directed to inhalant allergens, foods or insect venoms is presented clinically as allergic rhinitis, asthma, food allergy, allergic skin inflammation, ocular allergy, insect venom allergy and/or anaphylaxis. Primarily, this response can be defined as an antibody-mediated event, where a dysregulation of intense allergen specific immunoglobulin E (IgE) generation is tracked by the

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Table 1. Monoclonal Antibodies of Interest: Their Targets and Modes.

Type	Target	Mode
Omalizumab	IgE	Humanized
Ligelizumab	IgE	Humanized
MEDI-4212	IgE	Humanized
Dupilumab	IL-4	Human
Mepolizumab	IL-5	Humanized
Reslizumab	IL-5	Humanized
Benralizumab	IL-5R	Humanized
Enokizumab	IL-9	Humanized
Anrukinzumab	IL-13	Humanized
IMA-026	IL-13	Humanized
Tralokinumab	IL-13	Human
Lebrikizumab	IL-13	Humanized
Brodalumab	IL-17RA	Human
Secukinumab	IL-17A	Human
Ustekinumab	p40 subunit of IL-12 and IL-23	Human
Infliximab	TNF- α receptor	Chimeric
Adalimumab	TNF- α receptor	Human
Golimumab	TNF- α receptor	Human
Etanercept	TNF- α receptor	Receptor fusion protein
Daclizumab	CD25	Humanized
Bertilimumab	Eotaxin-1	Human
Canakinumab	IL-1 β	Human

allergen-allergen specific IgE interaction, which triggers the activation of effector cells that is causing signs and symptoms of the disease [12]. Antigen-presenting cells, T cells, B cells, mast cells, basophils, eosinophils, epithelial cells are key cellular players that exert particularly specific roles. Additionally, several cytokines, chemokines and signaling pathways also have undeniable roles in this sophisticated immune response. It is inevitable that understanding the mechanisms of allergic immune response is crucial to develop novel monoclonal antibody treatment strategies to cure allergic diseases, Fig. (1).

In allergic immune response, dendritic cells (DCs), which reside as sentinels in entry sites such as skin and mucosa, capture and process allergens into peptide fragments coupled to major histocompatibility complex (MHC)-II molecules. These peptide fragments are presented on the surface of DCs to T cells in association with concomitant co-stimulatory signals [13-15]. Two principal stimuli (signal 1 and signal 2) are essential for T cell activation. Interaction of MHC-II-

coupled peptides with TCR represented as signal 1 [16]. However, this signal itself is not sufficient for the entire activation. Signaling through the TCR must be accompanied by co-stimulatory signals; otherwise T cell anergy occurs in the absence of this co-stimulation [17]. Signal 2, mediated by triggering of CD28 by CD80 (B7.1) and CD86 (B7.2) that are expressed by DCs after ligation of pattern recognition receptors (PRRs), is essential for T cell activation and induces interleukin (IL)-2 productions that act as the T cell growth factor [17-19]. CD40 ligands on T cells are also up-regulated and bind to CD40 on the DCs. Besides, CD28 co-stimulation up-regulates inducible co-stimulator (ICOS) for a co-stimulation by DC expressed ICOS ligand [20]. Contrarily, cytotoxic lymphocyte antigen-4 (CTLA-4) diminishes T cell responses in an inhibitory manner [21].

After DC-T cell interaction, atopic individuals exert T helper (Th)-2 type immune response, which leads to Th2 type cytokine production (mainly IL-4, IL-5, IL-9 and IL-13) [14, 22]. IL-4 induces differentiation of CD4⁺ naïve T

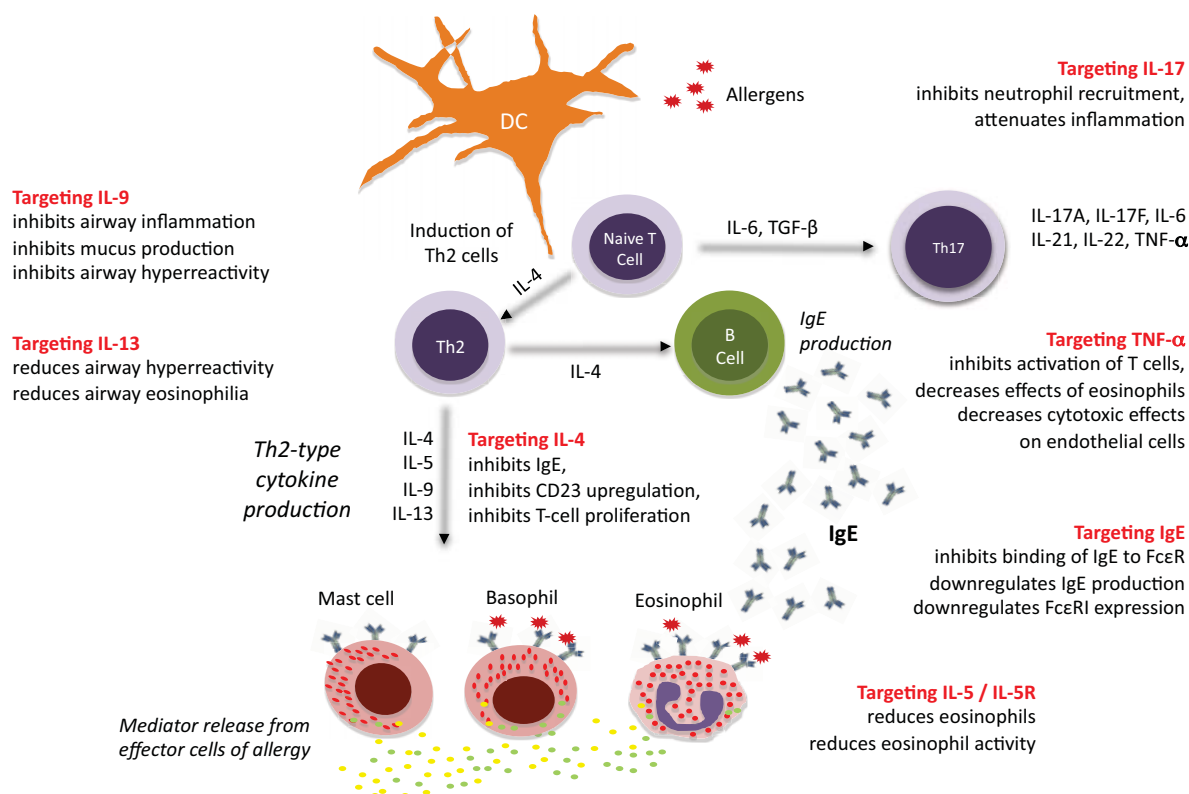


Fig. (1). Schematic presentation of allergic immune response and possible targeting steps.

cells into Th2 profile and stimulates activated B and T cell proliferations, additionally up-regulates MHC-II expression. Allergen specific IgE production in class switched B cells is the anticipated step in this phase of sensitization by IL-4 [13]. Allergen specific IgE antibodies bind to Fc ϵ -receptors on mast cells, basophils and eosinophils, which are the effector cells of allergic inflammation. Encounter of allergen with its specific IgE antibody triggers Fc ϵ -receptors on mast cells and basophils, which is then followed by receptor-triggered release of preformed and also synthesis of mediators like histamine, leukotrienes, prostaglandins and proteases. While, cytokines released from these effector cells affect vascular permeability, angiogenesis and fibrosis that are responsible for the allergic inflammation, consequent infiltration by eosinophils, neutrophils, basophils, macrophages and T cells perpetuate chronic inflammatory responses exaggerated by further synthesis and release of cytokines and mediators [14, 23-25]. IL-13 has similar properties as IL-4 and exerts its functions through α chain of the IL-4 receptor (IL-4R α) and shares common signaling pathways [26]. IL-13 is important for epithelial cell maturation and mucus production, generation of extracellular matrix proteins, and enhances contractility of airway smooth muscle cells [27]. IL-5 has key roles on eosinophils, which activates and prolongs survival of them in addition to stimulatory effects on B cell growth [28]. Although, TNF- α is not a specific cytokine for Th2 responses, it can activate T cells, increases the cytotoxic effects of eosinophils and endothelial cells [29-31]. TNF- α is

a chemo-attractant for neutrophils and eosinophils and increases expression of adhesion molecules [32, 33].

Nowadays, individualized and target specific treatment strategies are promising for the treatment of chronic disorders including allergic ones. A detailed characterization of the mechanisms of allergic immune response in addition to advances in developmental area of monoclonal antibodies and engineering are encouraging. The aim of this updated article is to review most recent data about monoclonal antibodies trialed for the management of allergic disorders [1]. Studies that appeared in PubMed and ClinicalTrials.gov are mostly mentioned.

TARGETING IgE; OMALIZUMAB

Omalizumab is a humanized monoclonal antibody directed against IgE and is the first approved mAb for the treatment of moderate to severe allergic asthma in the US and for severe allergic asthma in Europe in adolescents (aged 12 and above) and adults. The main target of omalizumab is to inhibit the function of IgE [34-36]. Omalizumab binds to the receptor-binding portion of IgE, which inhibits the ability of IgE to bind to high-affinity Fc ϵ R1 receptors on mast cells and basophils [37, 38]. Omalizumab neutralizes and inhibits free IgE, and downregulates IgE production by B cells [34-36]. Reduction in free IgE after treatment with omalizumab has been reported compared to treatment with placebo [39]. Although, omalizumab can bind to IgE that is in circulation, it is not able to crosslink IgE molecules that are already

bound to the cell surfaces [40]. The conformational change in the IgE molecule after IgE-Fcε receptor interaction perpetuates the second heavy chain unavailable to omalizumab [40]. The binding of the FcεRI to one CH₃ domain of one heavy chain inhibits or prevents the binding of omalizumab to the CH₃ region of the other heavy chain [40]. Omalizumab also indirectly downregulates FcεRI on basophils [41], and inhibits histamine release from basophils even under very favorable conditions [35]. It has been reported that omalizumab has significantly reduced circulating basophil numbers in asthmatic children [42]. Furthermore, omalizumab has also negatively regulated FcεRI expression in patients with severe nonatopic asthma, as it does in severe atopic asthma [43]. Omalizumab attenuates airway inflammation and IL-5 production by mononuclear cells in patients with severe allergic asthma [44]. Several clinical trials have pointed out the efficacy of omalizumab in allergic asthma, rhinitis, food allergy and atopic dermatitis (AD) [45-57]. It has also been reported that add-on therapy with omalizumab has significantly reduced the symptoms and increased health-related quality of life in patients with chronic spontaneous urticaria and persistent symptoms despite treatment with antihistamines [58, 59]. Omalizumab is also recommended as a third line drug in the treatment of chronic urticaria [60].

Until today four Cochrane analyses have been performed regarding omalizumab usage [39, 61-63]. In these analyses omalizumab has been shown to be effective in reducing asthma exacerbations and hospitalizations as an adjunctive therapy to inhaled corticosteroids compared with placebo. It has also been reported that omalizumab has been significantly more effective than placebo in increasing the numbers of participants who have been able to reduce or withdraw their inhaled steroids [39, 61-63]. In a recent systematic review and meta-analysis of randomized clinical trials, omalizumab treatment has been found to be statistically significantly associated with symptom relief, decreased rescue medication use, and improvement of quality of life in patients with inadequately controlled allergic rhinosinusitis [64]. Omalizumab has also been successfully used for the prevention of recurrent anaphylaxis and larynx angioedema cases [65, 66]. Besides, omalizumab exerts a potential to be an additional treatment option in patients with cystic fibrosis and allergic bronchopulmonary aspergillosis [67, 68].

As an adjuvant to allergen specific immunotherapy (SIT) omalizumab has provided some hopeful results. Use of omalizumab has enabled more symptomatic asthmatics to achieve the target immunotherapy maintenance dose with fewer systemic allergic reactions [69]. It has been reported that combination of omalizumab with grass pollen specific immunotherapy has reduced the symptom load in a statistically significant and clinically meaningful manner for treatment of patients with seasonal allergic rhinitis and asthma during the first pollen season [70]. Pretreatment with omalizumab has enhanced the safety of rush immunotherapy, which delivers higher doses of allergen rapidly to patients [71]. Recently, Phase I data has demonstrated that rush oral immunotherapy

to multiple foods with omalizumab has allowed for a fast desensitization in subjects with multiple food allergies [72]. Omalizumab has also facilitated rapid oral desensitization in high-risk peanut allergic children [73].

Omalizumab has been generally well tolerated, and the most common side effect is injection-site reactions [39, 61-63]. It has been reported that omalizumab has exhibited a good safety and tolerability profile with a proven efficacy [74]. *In vitro* studies have shown that omalizumab forms complexes of limited size with IgE [75], which are stable cyclic hexamers [76]. The Omalizumab Joint Task Force formed by the American Academy of Allergy, Asthma & Immunology and the American College of Allergy, Asthma and Immunology Executive Committees announced an anaphylaxis-reporting rate of 0.09% and provided recommendations for physicians who use this mAb [75, 77]. The epidemiologic study evaluating clinical effectiveness and long-term safety of omalizumab in patients with moderate-to-severe asthma (EXCELS) has assessed the long-term safety in a clinical practice setting as part of a Phase IV study and has suggested that omalizumab therapy has not been associated with an increased risk of malignancy [78]. Recently, two cases of good outcomes in omalizumab treated pregnant severe asthmatic women have been reported from Poland, [79]. It is a query whether there is a threshold level of baseline serum IgE for optimum efficacy of omalizumab. Cost of the drug is a limiting concern, which in future needs identification of possible biomarkers that will predict efficacy of the drug [63].

OTHER NOVEL PROMISING ANTI-IgE MABS

Ligelizumab (QGE031) is a novel high-affinity humanized monoclonal anti-IgE antibody. Preclinical assessments and two randomized, placebo-controlled, double-blind clinical trials have demonstrated increased suppression of free IgE compared to omalizumab. It has been reported that QGE031 has translated superior pharmacodynamic effects in atopic subjects, including those with high IgE levels [80]. MEDI-4212 is another novel, high affinity antibody that binds specifically to IgE and prevents IgE binding to its receptors. MEDI-4212 has inhibited responses potentially through FcεRI and also prevented the binding of IgE to CD23. Phage display technology has been used to generate MEDI-4212 [81]. Phase 1 dose escalation safety study has been completed in allergic subjects [82].

TARGETING IL-4; DUPILUMAB

IL-4 induces differentiation of naïve T helper cells into Th2 cells and stimulates activation of B cells. IL-4 induces class switching on B-cells, which causes synthesis of allergen-specific IgE [13]. MHC-II expression is also upregulated by IL-4 [83]. In murine asthma models, anti-IL-4 mAb therapy has been shown to inhibit IgE production, but not affected airway eosinophilia or hyper-responsiveness in the absence of anti-IL5 mAbs [84].

Dupilumab is a fully human mAb that binds to the α subunit of the interleukin-4 receptor (IL-4R α). Dupilumab inhibits the biological activity of both the IL-4 and IL-13. As compared with placebo, dupilumab has reduced asthma exacerbations and levels of Th2 associated inflammatory markers such as fractional exhaled nitric oxide and eotaxin in patients with persistent, moderate-to-severe asthma with elevated eosinophil levels, who have withdrawn long-acting beta agonists (LABAs) and inhaled glucocorticoid therapy. Significant improvements have been observed for most measures of lung function and asthma control in these patients, as well [85]. In another trial with dupilumab, adult patients with moderate-to-severe atopic dermatitis treated with this mAb have shown marked and rapid improvements in clinical indexes and biomarker levels [86].

TARGETING IL-5; MEPOLIZUMAB, RESLIZUMAB, BENRALIZUMAB

Targeting IL-5 is attractive as this cytokine is a key regulator of eosinophils and acts as a growth factor for terminal differentiation of the eosinophil precursors [28]. Blocking IL-5 in murine allergic asthma models has inhibited pulmonary eosinophilia and airway hyper-responsiveness [87]. Mepolizumab (SB-240563) is one of the most commonly studied mAb, which is humanized against IL-5 and is in clinical trials for the treatment of severe asthma, nasal polyposis, hypereosinophilic syndrome (HES), eosinophilic esophagitis and Churg-Strauss Syndrome [88]. It has been suggested that patients with eosinophilic inflammation have received significant therapeutic benefit with mepolizumab [89]. The meta-analysis of randomized placebo-controlled trials that has been conducted to evaluate the effect of mepolizumab on clinical outcomes of asthmatics, has revealed that mepolizumab has reduced the risk of exacerbations and improved quality of life in patients with eosinophilic asthma [90]. Recently, in a randomized, double-blind, double-dummy study, in which 576 asthmatic patients have been enrolled with recurrent exacerbations and evidence of eosinophilic inflammation despite high doses of inhaled glucocorticoids, mepolizumab has been shown to reduce asthma exacerbations and associated with improvements in markers of asthma control [91]. Oral glucocorticoid-sparing effect of mepolizumab has been studied in another randomized double-blind trial, in which 135 patients with severe eosinophilic asthma have been enrolled. Mepolizumab has shown a significant glucocorticoid-sparing effect, reduced exacerbations, and improved control of asthma symptoms compared to placebo [92]. Mepolizumab therapy has induced a marked decrease in blood eosinophilia, reduced eosinophil activation and circulating levels of IL-5 in hyper-eosinophilic disorders [1, 93]. It has been reported that mepolizumab can reduce the numbers of esophageal intraepithelial eosinophils both in children and adults with eosinophilic esophagitis [94, 95]. Mepolizumab has also shown a statistically significant reduction in nasal polyp size in 12 of 20 patients characterized by prominent eosinophilia [96]. Additionally, mepolizumab has reduced eosinophil counts and allowed for safe corticosteroid

reduction in all 7 treated subjects with Churg-Strauss syndrome in an open-label pilot study [97]. Reslizumab (CTx55700) is a humanized anti-IL-5 monoclonal antibody. Safety and pharmacokinetic study with reslizumab has revealed a reduction in the size of nasal polyps in half of the study population in a double blind, placebo-controlled manner [98]. The safety and efficacy of reslizumab have been trialed and Phase III studies have been completed for eosinophilic esophagitis and asthma [99, 100]. Children and adolescents with eosinophilic esophagitis receiving reslizumab have shown significantly reduced intraepithelial esophageal eosinophil counts [101]. Also, reslizumab significantly has reduced sputum eosinophils and improved airway function and let a trend toward greater asthma control than those receiving placebo [102]. Benralizumab (MEDI-563) is a humanized mAb directed against IL-5R α (CD125). Benralizumab targets eosinophils by inducing apoptosis through antibody-dependent cell-mediated cytotoxicity [103]. Phase I safety, pharmacokinetic and biologic activity study with this mAb in mild asthmatics has revealed an acceptable safety profile and resulted in marked reduction of peripheral blood eosinophil counts within 24 hours after dosing [104]. Benralizumab has reduced eosinophil counts in airway mucosa/submucosa and sputum, and suppressed eosinophil counts in bone marrow and peripheral blood in a double-blind, placebo-controlled Phase I study [105]. A Phase III efficacy and safety study of benralizumab is currently recruiting patients in inadequately controlled asthmatic adults and adolescents [106].

TARGETING IL-9; ENOKIZUMAB

Preclinical studies suggest that IL-9 may be a central mediator in the development and maintenance of airway inflammation in asthma as this cytokine regulates the development of airway inflammation, mucus production, airway hyper responsiveness, and airway fibrosis largely by increasing mast cell numbers and activity in the airways [107]. Enokizumab (MEDI-528) is a humanized monoclonal antibody against IL-9. Safety profile and clinical activity of MEDI-528 have been studied in two randomized Phase 2a studies in subjects with asthma. In MEDI-528 treated groups, a decrease in asthma exacerbations and a trend of reduction in mean of post-exercise maximum decrease in FEV1 compared to placebo have been observed with an acceptable safety profile with suggestive clinical activity [108]. In a prospective double-blind, multicenter, parallel-group study the addition of MEDI-528 to existing asthma controller medications has not been associated with any improvement in Asthma Control Questionnaire-6 scores, asthma exacerbation rates, or FEV1 values, nor associated with any major safety concerns [109].

TARGETING IL-13; ANRUKINZUMAB, IMA-026, TRALOKINUMAB, LEBRIKIZUMAB

IL-13 plays a central role in asthma pathogenesis by contributing to airway hyper-reactivity, mucus hypersecretion, inflammation, and fibrosis. Neutralization of IL-13 has inhibited airway hyper-reactivity and prevented development

of subepithelial fibrosis and progression of inflammation in a chronic murine model of asthma [110]. Preclinical safety and pharmacology studies of an anti-human IL-13 mAb in normal macaques and in macaques with allergic asthma have shown well tolerance in both study groups and that serum eotaxin concentrations may be a useful early *in vivo* marker for evaluating IL-13 inhibition in patients with asthma [111].

Anrakinzumab (IMA-638) and IMA-026 are fully humanized IgG1 antibodies that bind to different epitopes and neutralize bioactivity of IL-13 [112]. While anrakinzumab allows IL-13 interaction with IL-13R α 1 or IL-13R α 2 and blocks recruitment of IL-4R α to the IL-13/IL-13R α 1 complex, IMA-026 competes with IL-13 interaction with IL-13R α 1 and IL-13R α 2 [113]. It has been reported that IL-13R α 2 has acted as a scavenger for IL-13. Cells with high IL-13R α 2 expression rapidly and efficiently deplete extracellular IL-13, which persists in the presence of anrakinzumab, but not IMA-026. This proposal has been supported in a randomized double blind trial in mild asthmatics by comparing the effects on late phase asthmatic responses of anrakinzumab and IMA-026 with placebo. No significant effect has been detected on allergen-induced airway hyper-responsiveness or sputum eosinophils with both antibodies, while anrakinzumab has attenuated allergen provoked late phase reactions [112]. It has been suggested that these findings have important implications for the design and characterization of future IL-13 antagonists [113]. Anrakinzumab has inhibited antigen-induced late responses and airway hyper-responsiveness in a dose dependent manner in a sheep model of asthma, as well [114]. Also, IL-13 blockade with anrakinzumab has reduced lung inflammation after challenge in cynomolgus monkeys [115]. Phase-I/II trials have been completed for anrakinzumab [116]. Tralokinumab (CAT-354) is another human anti-IL-13 mAb. It has been reported that *in vitro* CAT-354 has functionally inhibited IL-13-induced eotaxin production, CD23 upregulation and IgE production. CAT-354 has inhibited airway hyper-responsiveness and bronchoalveolar lavage eosinophilia in *in vivo* mouse and cynomolgus monkey antigen challenge models [117]. Also, pretreatment with CAT-354 has significantly reduced airway hyper-reactivity, airway eosinophilia and esophageal eosinophilia in a murine model of respiratory and esophageal inflammation induced by intratracheal human IL-13 [118]. Phase-I and II clinical trials have been completed comparing the pharmacokinetics, safety and tolerability of CAT-354 [119-121] and a Phase III trial is recruiting patients to evaluate the efficacy and safety of tralokinumab in adults and adolescents with uncontrolled asthma [122]. Lebrikizumab is a humanized mAb against IL-13. Lebrikizumab has significantly improved prebronchodilator forced expiratory volume in 1 s (FEV₁) in a subset of subjects with asthma [123]. Lebrikizumab has also reduced the late asthmatic responses in mild asthmatics. Additionally, serum IgE, CCL-13, and CCL-17 chemokines, which are considered to be systemic biomarkers of Th2 inflammation, have also been

reduced approximately 25% after lebrikizumab treatment [124]. Phase III trials are ongoing with this mAb [125, 126].

TARGETING IL-17; BRODALUMAB, SECUKINUMAB, USTEKINUMAB

IL-17A, IL-17F, IL-21, and IL-22 are Th17 cytokines, among which IL-17A and IL-17F play pivotal roles in the pathogenesis of asthma and share a common receptor subunit, IL-17 receptor A (IL-17RA), and IL-17 receptor C (IL-17RC) [127]. IL-17 is a pro-inflammatory cytokine and is important for the induction of neutrophil recruitment and migration at sites of inflammation. In severe asthmatics IL-17 levels are increased and both eosinophils and neutrophils infiltrate the airways. Especially, Th17 cells have key roles in inflammation during late stages of chronic asthma. It has been suggested that targeting IL-17A attenuates inflammation but not host defense, while IL-17F has exerted a potential to compensate for immuno-compromised conditions [128].

Brodalumab (AMG 827) is a human mAb directed against IL-17RA. It binds to the IL-17 receptor and prevents IL-17 from activating the receptor. No treatment difference for the overall study population with brodalumab has been reported in moderate to severe asthmatics in a randomized, double-blind, placebo-controlled study [129]. A Phase II study is currently recruiting patients to evaluate whether brodalumab is safe and effective compared to placebo in inadequately controlled asthmatic patients [130, 131]. Secukinumab (AIN457) is a human mAb, which targets IL17A. It is developed for uveitis, rheumatoid arthritis and psoriasis [132]. A Phase II safety, tolerability and efficacy study of secukinumab is recruiting patients with asthma who are not adequately controlled with inhaled corticosteroids and long acting beta-agonists [133]. Ixekizumab (LY2439821) is another humanized anti-IL17 mAb, which binds to IL-17 itself, is under trial for psoriasis [134]. On the other hand, ustekinumab is a human mAb against p40 subunit of IL-12 and IL-23, which are important cytokines in Th1 and Th17 driven inflammatory immune responses. A case report of concurrent treatment of chronic psoriasis and asthma with ustekinumab has been recently reported [135]. Also, several different groups have reported their treatment experience with ustekinumab in severe refractory atopic dermatitis cases [136-138]. A Phase II pilot study of ustekinumab for subjects with atopic dermatitis is currently recruiting patients [139].

TARGETING TNF- α ; ADALIMUMAB, ETANERCEPT, GOLIMUMAB, INFlixIMAB

Tumor necrosis factor (TNF)- α has key roles in chronic inflammatory disorders by activating T cells, chemoattracting neutrophils and eosinophils, and increasing expression of adhesion molecules [29-33]. Monoclonal antibodies targeting TNF- α are mostly approved for selected autoimmune inflammatory disorders [140-142]. It has been suggested that TNF- α may play a role in the pathogenesis of asthma [143,

144]. Targeting TNF- α is promising, especially in the treatment of difficult-to-treat asthma. It has been reported that human lung mast cells and pulmonary macrophages can produce TNF- α after IgE receptor triggering [145]. Elevated levels of TNF- α have been detected in the bronchoalveolar lavage fluid samples of asthmatics patients [146]. It is reasonable to target TNF- α in severe chronic disorders including allergic diseases [147]. Role of this pro-inflammatory cytokine in difficult-to-treat asthma has been already described [148].

Infliximab is a chimeric and adalimumab and golimumab (CNTO-148) are human mAbs. They block the binding of TNF- α to its receptor on the cells, whereas etanercept is a soluble TNF receptor fusion protein. Patients with refractory asthma have had increased expression of TNF- α , whereas etanercept has been associated with improvement in airway hyper-reactivity and asthma-related quality-of-life scores [149]. However, in 132 moderate-to-severe persistent asthmatics, who have received etanercept in a randomized, double-blind, placebo-controlled manner, no significant difference has been observed between etanercept and placebo for any of the efficacy end-points at the end of the trial [150]. Besides, it has been previously reported that golimumab cannot demonstrate a favorable risk-benefit profile in patients with severe persistent asthma at the end of a multicentric, double blind, placebo-controlled, dose-ranging study based on pre-bronchodilator percent-predicted FEV1 and asthma exacerbations [151]. On the other hand, it has been reported that infliximab alleviates inflammation and airway hyper-reactivity in asthmatic rats [152]. Infliximab has been well tolerated and caused a decrease in the number of patients with exacerbations in symptomatic moderate asthma in a double-blind, placebo-controlled study [153]. In a case series in which patients with refractory asthma who have received infliximab has shown a favorable risk-benefit profile for most, considering asthma severity, occurrence of life-threatening exacerbations and complications of long-term oral steroids [154]. It has been recently reported that adalimumab has reduced airway inflammation and ameliorates lung histology in a murine model of acute asthma [155].

It must be kept in mind that warnings appearing in the product labeling of anti-TNF- α drugs instructing to screen and monitor patients more carefully especially for tuberculosis, invasive fungal infections and other opportunistic infections shall not be disregarded. Although, there are variable responsiveness and promising trials are ongoing in asthmatic patients with the therapies directed against TNF- α , the need for larger multicenter, placebo-controlled, randomized trials to enlighten the therapeutic efficacy and safety profile of anti-TNF- α drugs in patients with severe chronic asthma is essential [144].

OTHER POTENTIAL TARGETS

Daclizumab is a humanized IgG1 monoclonal antibody against CD25 (the α chain of IL-2R), which is approved for prophylaxis of acute organ rejection in patients receiving renal transplants in combination with other immunosuppres-

sive agents [140]. Daclizumab inhibits the pro-inflammatory cytokine generation by IL-2R blockade in T cells. In a randomized, double-blinded, placebo-controlled study, improvements in pulmonary function and asthma control have been reported in patients with moderate to severe chronic asthma who have been inadequately controlled on inhaled corticosteroids [156]. Also, it has been reported that daclizumab has been successfully used as an additional therapy to tacrolimus in an atopic keratoconjunctivitis case in which topical corticosteroids and antihistamines had failed to control signs and symptoms [157]. Bertilimumab is a human mAb that binds to eotaxin-1 (CCL11), which is a potent and selective eosinophil chemoattractant that is expressed by a variety cell types in certain inflammatory conditions [158]. Targeting eotaxin with bertilimumab has been shown to reduce mast cell infiltration in the cardiac tissue of transplanted rat hearts, which possibly has resulted in decreased myocardial fibrosis and improved contractile function after heart transplantation [159]. Canakinumab (ACZ885) is a human anti-IL-1 β monoclonal antibody developed for the neutralization of 1 β signaling. Canakinumab has attenuated late asthmatic responses in mild asthmatics after allergen challenge [160].

RECENT PATENTS

Programmed death-1 (PD-1) is characterized as negative regulator of CD4+ T cells. PD-1 ligands, B7H1 (PD-L1) and B7DC (PD-L2), have opposing roles in modulating and polarizing T-cell functions in airway hyper-reactivity [161]. Recently a human monoclonal antibody that specifically binds to PD-1 with high affinity is patented. The invention provides methods for detecting PD-1, as well as methods for treating various diseases, including cancer and infectious diseases, using anti-PD-1 antibodies. Possible usage has been suggested in the treatment of allergy and asthma, as well [162]. As mentioned previously binding of the CD40 ligand to the CD40 antigen on the B cell membrane provides a co-stimulatory signal that stimulates B cell activation and proliferation. Antagonist anti-CD40 monoclonal antibodies may find use in the treatment of asthma [163]. On the other hand, as IL-31 is associated with chronic skin inflammation and pruritus, monoclonal antibodies directed against IL-31 can be promising in treating allergic skin disorders [164-166].

CURRENT & FUTURE DEVELOPMENTS

Specific targeting and individualized treatments are essentials of today's advanced therapy strategies. Thus, understanding the mechanisms of allergic immune response is mandatory to plan the treatment of allergic disorders. Monoclonal antibodies may serve as the most favorable agents in this respect. Variable outcomes for monoclonal antibody therapies must be encountered and treatment with monoclonal antibodies must be tailored to well-characterized patient populations. Efficacy, safety measures, long-term tolerability and cost concerns shape the feasibility of monoclonal antibody treatments. Close monitoring is essential in patients

following the administration of monoclonal antibodies. Moreover, besides efficacy, safety measures have to be applied to limit possible adverse side-effects including hypersensitivity reactions, immune or cytokine imbalance syndromes, autoimmunity, immunosuppression and neoplasia development. It is widely accepted that larger randomized, controlled trials are needed to further clarify the efficacy and safety of mentioned monoclonal antibodies and to describe their roles in the long-term management of patients with allergic disorders for our daily clinical practice.

CONFLICT OF INTEREST

The author confirm that this article content has no conflict of interest.

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DISCLOSURE

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