



Biologic therapy for atopic asthma and beyond

Massimo Caruso, Emanuele Crisafulli, Raffaella Lizzio, and Riccardo Polosa

Purpose of review

Most asthma patients are easily managed with a standard combination of therapies consisting of inhaled controller and reliever drugs, but there remains a large unmet need at the severe end of the disease spectrum. For these patients, development of safer and more effective therapies for asthmatic patients with severe refractory disease remains a top priority. Here, drugs in development for the severe asthma sufferers and their specific mechanism-based pharmacological rationale will be reviewed with a focus on biologics. A systematic search of the literature was made using Medline, and publications were selected on the basis of their relevance to the topic. Here, the authors will review the existing efficacy and safety data from clinical trials of some of the new biologic therapies that are in development for severe asthma.

Recent findings

Despite strong preclinical data for many of the more recently identified asthma targets, especially those relating to the T-helper 2 allergic pathway, clinical trials with specific biologics have been largely disappointing. However, there is scope for their specific role in distinctively targeted subpopulations of severe asthmatic patients.

Summary

It is clear that more efforts should be devoted towards establishing new and more efficient key targets. A closer interaction between industry, academia and health workers will be required to achieve this goal effectively.

Keywords

allergic pathway, asthma, biologics, mAbs

INTRODUCTION

Asthma is a multifactorial disease characterized by various phenotypes and heterogeneous pathological mechanisms. Over the last 50 years, there has been an escalation in knowledge about the cells and mediators involved in the disease's pathogenesis. The identification of the Th 2 cell as the key 'orchestrator' of the allergic response, culminating in the interleukin (IL)-4 and IL-13 dependent generation of immunoglobulin E (IgE) by dedicated follicular B cells and plasma cells, has represented a central finding for many years [1]. However, alternative T-cell subtypes (e.g. Th1 cells, regulatory T cells and Th17 cells) are also being taken into consideration [2] and mixed endotypes are now being proposed [3].

Owing to the complex nature of the disease, it is not surprising that many asthma patients continue to have uncontrolled disease that requires either improved adherence to medications or high intensity treatment [4]. For these patients, the therapeutic arsenal is unsatisfactory and development of safer and more effective therapies for asthmatic patients

with severe refractory disease remains a top priority. Academic researchers and pharmaceutical corporations have responded to this unmet clinical need by developing a growing number of biologic agents intended to disable several key targets associated with severe asthma.

Here, we will review some of the new biologics that are in development for the severe asthma sufferers and their specific mechanism-based pharmacological rationale. Because early trials often focus on proof-of-concept for a disease and not necessarily the intended target population, most of the agents

University of Catania-AOU 'Policlinico-V. Emanuele', Department of Clinical and Molecular Bio-Medicine, Institute of Internal Medicine and Clinical Immunology, Catania, Italy

Correspondence to Riccardo Polosa, MD, PhD, University of Catania-AOU 'Policlinico-V. Emanuele', Department of Clinical and Molecular Bio-Medicine, Institute of Internal Medicine and Clinical Immunology, Catania 95124, Italy. Tel: +39 095 3781583; fax: +39 095 3781575; e-mail: polosa@unict.it

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KEY POINTS

- Asthma is a disease characterized by heterogeneous phenotypes and pathological mechanisms. The identification of the Th2 cell as the key 'orchestrator' of the allergic response, culminating in the IL-4 and IL 13-dependent generation of IgE has represented a central finding for many years, but nowadays alternative T-cell subtypes are also being taken into consideration.
- Suppressing the IL-4/IL-13 pathway not only ablates Th2-mediated responses but also modulates progression to more chronic severe form of the disease by preventing mucus hypersecretion, mucus metaplasia, smooth muscle proliferation and deposition of new matrix.
- The humanized IgG1 mAb omalizumab is the only biologic therapy recommended for patients with severe allergic asthma and increased levels of IgE, though its response is not uniform across all patients, but there is now emerging evidence that it could be effective even in nonallergic asthma.
- Antagonising the eosinophilic mitogenic factor IL-5 with specific mAbs may have beneficial advantage, given that the eosinophil may also serve a pathogenetic role in the mixed Th2/Th1/Th17 endotype of severe asthma.
- The fact that most of these new treatments are not enough to suppress inflammation and control remodelling efficiently, it is not surprising owing to the complex nature of asthma and to the limitation of blocking only one individual cellular and molecular pathway at one time.

discussed in the article may not directly relate to patients with the severe end of the disease spectrum.

MECHANISM-DIRECTED TREATMENT OF ASTHMA

In establishing a mechanistic rationale for drug development, it is crucial to pinpoint key targets associated with the complex cellular and molecular pathways responsible for the inflammatory/immune asthmatic phenotype of type 2 inflammation. Orchestration of this type 2 inflammation is predominantly under the influence of adaptive cellular responses (i.e. activated T cells, B cells and dendritic cells) and of activation of specific signalling pathways such as IL4/IL13, IgE and IL5 (Fig. 1).

The advent of humanized mAbs has enabled the generation of highly specific therapies against several cellular and molecular targets relevant to type 2 inflammation in asthma (Table 1 [5–9,10^{***},11–15,16^{***},17–29,30^{*},31–36,37^{*},38–44,45^{***},46–52]) (<http://clinicaltrials.gov/ct2/show/>

NCT00983658, <http://www.clinicaltrials.gov/ct2/show/NCT00001909>, <http://clinicaltrials.gov/ct2/show/NCT01451450>). Below, their specific mechanism-based pharmacological rationale together with the existing efficacy and safety data from clinical trials will be discussed.

TARGETING T-CELLS

Given the important role of the Th2 cell in driving the allergic response [53], it is entirely reasonable to consider this as an attractive therapeutic target (Fig. 1). Indeed, marked suppression of T-cell proliferation with the anti-CD4 mAb keliximab in a small randomized controlled trial of severe corticosteroid-refractory asthmatic patients caused some significant effects on lung function, but other asthma outcomes were either minimally affected or unchanged [5]. In addition, there was concern of possible adverse consequences. More recently, the mAb daclizumab, which is directed at the T-cell activation marker CD25, has been trialled in moderate to severe asthma on the basis of its powerful immunosuppressive effect in organ transplant rejection [6]. The daclizumab study group [7] shows some benefit in terms of small significant improvements in forced expiratory volume in the 1st second (FEV1), daytime asthma symptoms, increased time to exacerbation and short-acting β_2 -agonist use compared with placebo. Although there were no differences in mild and moderate adverse events between the two study groups (upper respiratory tract infection, nasopharyngitis, nasal congestion, rash and nausea), there were more patients with serious adverse events in the daclizumab group including anaphylactoid reaction and viral meningitis. These somewhat disappointing clinical results of anti-T-cell therapies in chronic asthma may be explained by the recognition that other T-cell subtypes, in addition to Th2 cells, appear to be playing a more important role in asthma as it becomes more severe (e.g. Th1, Th9, Th17 and CD8⁺ cells). In principle, improved characterization of asthma endotypes could identify specific causative T-cell subsets that can be exploited as more successful drug targets (Table 1).

An alternative approach has been to target the proliferation, survival and activation of T cells by interfering with dendritic cell–T cell costimulation. In relation to this, an important target is the OX40/OX40 ligand, which is known to be regulated by the positive regulator epithelial and mast cell derived thymic stromal lymphopoietin [54]. A trial on the use of mAbs to block OX40 ligand (Oxelumab) has been completed (<http://clinicaltrials.gov/ct2/show/NCT00983658>), although the outcome is currently not published.

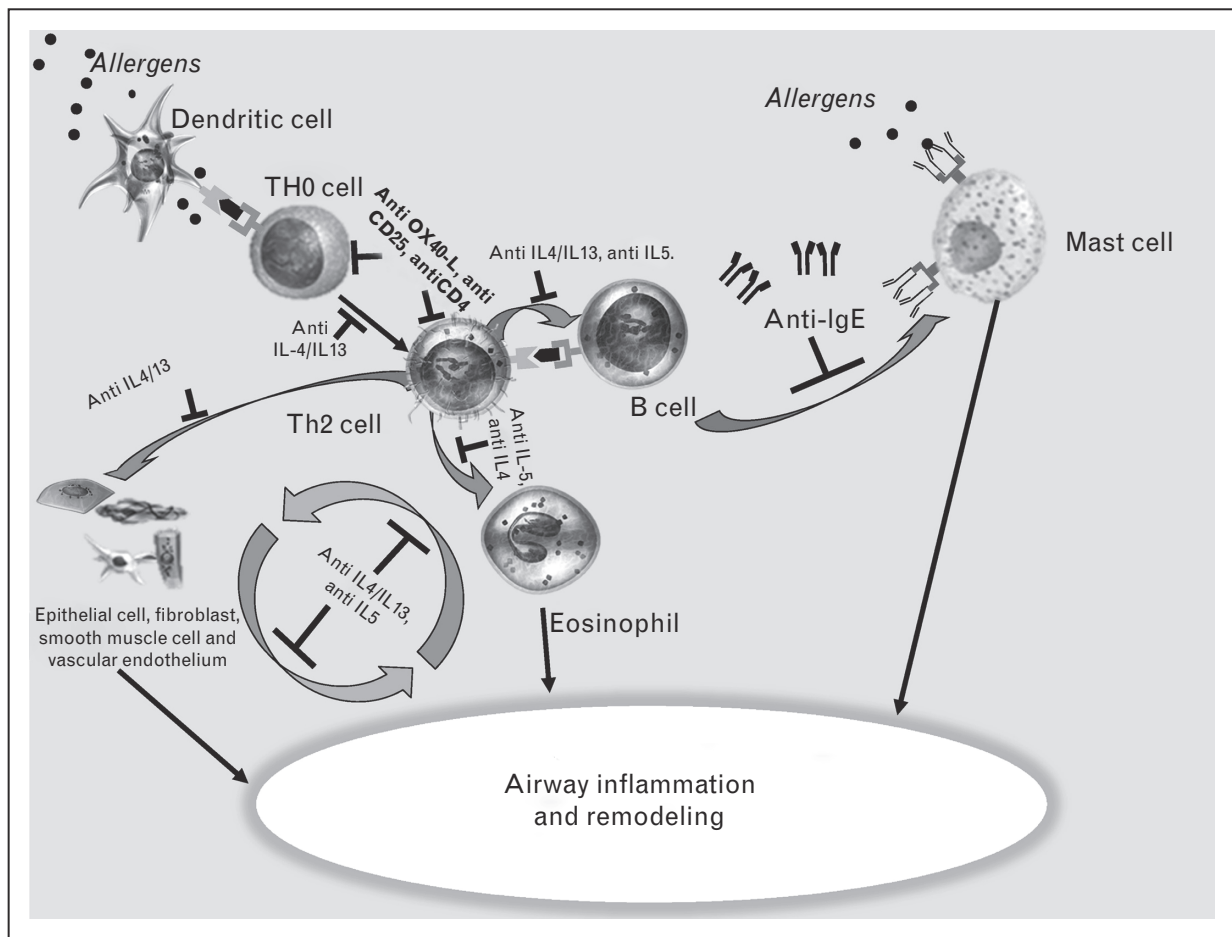


FIGURE 1. Cellular and molecular mechanisms promoting asthma inflammation and remodelling and related mechanism-based pharmacological rationale of biologic therapy for the treatment of asthma.

TARGETING THE INTERLEUKIN-4/INTERLEUKIN-13 SIGNALLING PATHWAY

IL-4 and IL-13 are molecular targets of particular interest in asthma (Fig. 1) based upon the ability of these two cytokines to drive Th2 (IL-4) cell differentiation and activation, to enhance inflammatory responses by upregulating vascular cell adhesion protein 1 [in concert with tumour necrosis factor alpha (TNF α)] involved in eosinophil and basophil recruitment (IL-4 and IL-13) and to prime inflammatory cells for secretion of mediators (IL-4 and IL-13) [55,56]. IL-4 and especially IL-13 also modulates progression to several aspects of airway remodelling in asthma by inducing mucus hypersecretion, mucus metaplasia, smooth muscle proliferation, fibroblast activation and deposition of new matrix [55,56]. Both IL-4 and IL-13 induce their effects by signalling through the IL-4R α /IL-13R α 1 complex [57,58].

Initial studies of IL-4 antagonism in asthma employed a soluble recombinant human IL-4R α (Altrakinept; Nuvance, Immunex Corp., Seattle,

USA) designed to block the interaction between circulating IL-4 and its receptor. Using an inhaled formulation in moderate asthma prevented worsening in symptoms and reductions in FEV1 on withdrawal of inhaled corticosteroids (ICS) [8,9]. No significant adverse events or development of anti-IL-4R antibodies were detected. However, in a large phase II study, efficacy in moderate to severe asthma could not be confirmed (<http://www.clinicaltrials.gov/ct2/show/NCT00001909>). Dupilumab, another human mAb targeting the α subunit of the IL-4, hinders the Th2 immune response through blocking IL-4 and IL-13. It demonstrated efficacy in asthma exacerbations and was well tolerated in patients with elevated eosinophil levels, reducing measurable levels of Th2 inflammatory mediators [10¹¹]. Attempts at blocking IL-4 directly with an mAb such as pascolizumab (SB 240683; PDL BioPharma, Inc., Incline Village, Nevada, USA) and similar mAbs made by PDL BioPharma also resulted in disappointing clinical results [11].

Table 1. Overview of biologic therapies approved or in development for use in asthma

Biologic	Target	Mechanism of action
Keliximab [5]	Anti-CD4 mAb	Induces apoptosis of peripheral T cells
Daclizumab [6,7]	Anti CD-25	Plays against the alpha subunit of the high-affinity IL-2 receptor
Oxelumab (http://clinicaltrials.gov/ct2/show/NCT00983658)	Anti OX40-ligand	Exerts its main action by hindering T-cell activation by APCs and disturbs OX40l costimulatory signals. This drug regulates T-cell tolerance, peripheral T-cell homeostasis and T-cell mediated inflammatory diseases, disabling amplification of Th2 cell differentiation
Altrakinecept [8,9] (http://www.clinicaltrials.gov/ct2/show/NCT00001909)		
Dupilumab [10 ^{***}]		
Pascolizumab [11]	Anti IL-4	They block the interaction between IL-4 and its cellular receptors (IL-4R α). Interferes with the differentiation of Th0 cells to Th2 cells, B-cell class switching to IgE and MHC class II production
IMA-026 [12], QAX576 [13]		
Tralokinumab (CAT354) [14–16 ^{**}]		
Lebrikizumab (MILR 1444A) [17]		
Anrukinzumab (IMA-638) [12,18]	Anti IL-13	IL-13 neutralizing mAbs turn off IL13-mediated reactions (which redundant with those of IL-4); costimulate Th2 immune response; have entered Phase I/II clinical trials
Pitrakinra [19,20]	Dry powder formulation of the IL-4 mutein pitrakinra	Inhibits per competition the IL4 pathways; shows attenuation of the allergen-induced asthmatic response; phase 2 clinical trial was completed
AMG-317 [21]	IL-4R α	It blocks both the IL-4 and IL-13 pathways
Omalizumab [22–29,30 [*] ,31–36]	Anti IgE	Inhibits the binding of IgE to the high-affinity IgE receptor (Fc ϵ RI) on the surface of mast cells and basophils
QGE031 (http://clinicaltrials.gov/ct2/show/NCT01451450)	Anti-IgE	This Ab binds to IgE preventing them to bind the Fc ϵ RI receptor
Quilizumab [36,37 [*]]	Anti-IgE	Antibody against the M1 prime segment of membrane IgE inhibits the production of IgE by B cells
Mepolizumab [38–44,45 ^{**} ,46]		
Reslizumab [47–49]	Anti IL-5	They work by blocking the bond between IL5 and the alpha chain of its receptor. They hinder eosinophils activation and degranulation, and they also interfere with the activation of B-cells and with their production of Ig
Benralizumab [50–52]	Anti IL5-R α	mAb binding the α subunit of the receptor to IL-5. It showed enhanced eosinophil-depleting activity

Next, a number of human IL-13 neutralizing mAbs, including Anrukinzumab, IMA-026, QAX576, tralokinumab and Lebrikizumab, have entered Phase I/II clinical trials of asthma.

The anti-IL-13 mAb anrukinzumab (IMA-638; Wyeth, now Pfizer, New York, USA) attenuated the allergen-provoked allergic reaction in a Phase II study [12] of 56 patients with mild atopic asthma, but interestingly, a related mAb, IMA-026, directed to the same target but a different epitope, did not. Both mAbs failed to attenuate allergen-induced airway hyperresponsiveness (AHR) or to reduce sputum eosinophilia. A search for the reasons for this difference has been informative with regard to how the IL-4/IL-13 receptor complex functions. IMA-638

binds IL-13 in such a way that it still allows it to bind to both the IL-13Ra1 and IL-13Ra2 subunits but inhibits the docking of the IL-4Ra to the IL-13/IL-13Ra1 complex [18]. In contrast, IMA-026 binds to IL-13 at a point that blocks its interaction with IL-13Ra1 and IL-13Ra2. Thus, when compared with IMA-026, the efficacy of IMA-638 in depleting IL-13 indicates that IL-13Ra2 on the cell surface is important for the removal of IL-13. This clearly has implications for the design of any future IL-13 inhibitors.

The effect of the anti IL-13 mAb, QAX576 (Novartis International AG, Basel, Switzerland), was studied on a clinical experimental model of allergic inflammation following nasal allergen

challenges in patients with seasonal allergic rhinitis [13]. No apparent effects were detected in the QAX576 group on nasal lavage eosinophil levels or nasal symptom scores compared with placebo. A Phase II study of QAX576 in moderate to severe atopic asthmatic patients was withdrawn due to complexity of design and lack of enrolment.

Phase I studies with the humanized anti-IL-13 mAb, tralokinumab (CAT-354; MedImmune, LLC, Gaithersburg, Maryland, USA), in individuals with moderate asthma have demonstrated that the drug administered intravenously has an acceptable safety and tolerability profile, with good bioavailability and linear pharmacokinetics [14]. A recent Phase II clinical trial with Tralokinumab shows no overall benefit in either the Juniper Asthma Control Questionnaire or lung function over a range of three doses [15]. However, in a small subset of patients who had elevated sputum IL-13 levels measured at baseline, this drug did show efficacy against both end-points, suggesting that the sputum level of IL-13 might be a good biomarker for anti-IL-13 responsiveness. In a recent placebo-controlled study [16²²] with 194 adult patients with moderate to severe asthma, tralokinumab, in addition to other asthma controller medication, showed some therapeutic benefit in individuals.

Lebrikizumab [MILR 1444A; Genentech (Roche Group), South San Francisco, California, USA] is a humanized anti-IL-13 mAb, currently undergoing Phase II clinical trials in inadequately controlled asthmatic individuals. Corren *et al.* [17] reported an improved FEV1 (but not symptoms) in patients with moderate to severe asthma, including those on long-acting β -agonists. Dividing the individuals into those with higher blood eosinophils and/or IgE did not improve the identification of responders. However, when a median split of serum periostin levels was used to divide the population, those in the upper 50th percentile had a much more robust response to treatment than those in the lower half. Periostin is highly expressed in airway epithelial cells (and probably other cells) in response to IL-13, acting as a functional biomarker that may be exploited to predict responders.

Targeting IL-4 or IL-13 alone may be ineffective because of redundant mechanisms shared with the two cytokines, and alternative approaches that suppress the activity of both IL-4 and IL-13 may be more beneficial. On the basis of this concept, pitrakinra (Aerovant; Aerovance Inc., San Francisco Bay Area, Berkeley, California, USA), an IL-4R α double mutein involved in both IL-4 and IL-13 signalling, was developed for asthma clinical trials [19]. When administered intravenously (and also by inhalation), pitrakinra attenuated the allergen-induced

late allergic reaction, as well as reducing sputum and circulating eosinophilia with no safety concerns [20]. Larger trials are now in progress in clinical asthma.

AMG-317 is a fully human mAb with high affinity to IL-4R α , which functionally blocks the action of IL-4 and IL-13. A large Phase II was conducted to determine the safety and efficacy of subcutaneous AMG-317 (75, 150 or 300mg) in patients with moderate to severe asthma [21]. Treatment did not have clinical efficacy with no improvements in the control of asthma, β -agonist use or lung function. However, AMG-317 did suppress exacerbations, particularly in patients on the higher dose of AMG-317 (300mg) and with higher asthma symptom scores (Table 1).

TARGETING IMMUNOGLOBULIN E SIGNALLING PATHWAYS

Allergen-specific IgE is the mechanism through which the acute mast cell/basophil-mediated allergic response is generated, by cross-linking of IgE bound to its high-affinity receptors (Fc ϵ R1). When allergen binds to cell-bound IgE, it undergoes a major conformational change to initiate the secretory response, involving the release of pre-formed mediators, cytokines, chemokines and growth factors and the generation of newly formed products, including prostaglandin D2 and leukotriene C4, as well as cytokines such as IL-4, IL-5, IL-13, thymic stromal lymphopoietin, TNF α and a range of chemokines (Fig. 1) [59,60]. However, there is now emerging evidence for a nonspecific role of IgE in persistent forms of airway inflammation. Direct stimulation of T cells by superantigens – mainly of bacterial origin – is known to lead to local polyclonal IgE responses and cytokine release promoting and sustaining inflammation [61]. Thus, mAbs directed against IgE might not only inhibit allergic inflammation in asthma, rhinitis and atopic dermatitis but could also have a role in nonallergic persistent forms of inflammation as recently reported for other diseases (such as autoimmune chronic urticaria) [62].

The humanized anti-IgE mAb omalizumab (Xolair, Novartis) has been engineered to target the Fc ϵ 3 region of IgE that normally binds Fc ϵ R1 on mast cells, basophils and dendritic cells forming polymeric IgE that contain immune complexes [22]. Omalizumab administration causes the free circulating IgE to fall rapidly, whereas complexed IgE initially increases before being effectively removed by the reticulo-endothelial system [23]. This rapid fall in free circulating IgE leads to progressive Fc ϵ R1 internalization in mast cells, basophils and dendritic

cells, thereby enhancing its therapeutic efficacy [24]. Loss of circulating IgE together with reduction in FcεR1 expression markedly attenuates mast cells' and basophils' potential to release preformed and newly generated mediators and facilitates allergen uptake by dendritic cells [25], making the omalizumab an attractive drug for an overall attenuation of allergic inflammation.

Omalizumab is approved in the EU for the treatment of patients aged at least 6 years with severe persistent allergic asthma who remain symptomatic and experience severe exacerbations, despite the use of high-dose ICS and long-acting β₂-agonists (LABAs) [26], and in the U.S. for the treatment of patients aged at least 12 years with moderate to severe persistent allergic asthma inadequately controlled with ICS [27].

Recent expert panel guidelines now also recommend omalizumab in step V patients with severe allergic asthma and increased levels of IgE either as an alternative or in addition to oral corticosteroids [28]. However, there is little evidence about the ability of omalizumab to have significant steroid-sparing effect, with the exception of an uncontrolled clinical trial in which a substantial dose reduction in oral corticosteroid requirements was shown [29]. Furthermore, omalizumab has been recently shown to be effective even in nonallergic asthma [30[■]]. Although the drug's pharmacological activity and clinical benefits are well known, several questions remain unanswered: for instance, when and how the drug can be withdrawn, and which clinical or biological markers may be useful for monitoring.

As for most biologics, a further limitation of add-on omalizumab treatment is that substantial clinical efficacy is observed in only about one-third of the patients [31,32]. There has been much speculation about why such a variable response exists including the relative importance of IgE signalling vs. other non-IgE Th2-related inflammatory pathways in the disease, the lack of potency/tissue penetration and the importance of the ratio of antigen-specific IgE to total IgE [33]. These possibilities will be testable for the more potent form of anti-IgE (e.g. QGE031) currently in clinical development (<http://clinicaltrials.gov/ct2/show/NCT01451450>). In absence of clear indications, it is generally advised that patients taking omalizumab therapy are to be clinically assessed at 16 weeks after starting therapy to decide whether to continue or cease therapy [34].

An alternative approach in antagonizing the IgE signalling pathway is that to interfere directly with the activity of IgE switched B cells, which potentially offers additional benefits beyond neutralization of

serum IgE. Indeed, although omalizumab is effective in reducing free serum IgE, it must be dosed regularly to maintain suppression of free IgE, as IgE production does not appear to be affected in most patients who are treated with omalizumab for a year or two [35]. In addition, due to dosing constraints, patients with very high baseline levels of IgE are not eligible for treatment with omalizumab. A therapy that specifically targets cells that are responsible for IgE production and IgE memory may overcome these limitations. IgE-switched B cells express a membrane form of IgE, which is known as M1 prime. Antibodies against the M1 prime segment of membrane IgE inhibit the production of IgE in preclinical studies by depleting membrane IgE-expressing IgE-switched cells [36].

Quilizumab (Genentech) is a humanized mAb against M1 prime. In a small clinical study [37[■]] in mild allergic asthmatic individuals subjected to allergen challenge, quilizumab inhibited the production of new allergen-specific IgE and reduced total serum IgE levels compared with placebo. The reductions in total serum IgE were sustained for over 4 months following the last dose of the antibody. In addition, quilizumab treatment reduced allergen challenge induced increases in blood and sputum eosinophils. These pharmacodynamic effects were accompanied by reductions in early and late phase asthmatic responses in quilizumab-treated patients, compared with placebo (Table 1).

TARGETING INTERLEUKIN-5 SIGNALLING PATHWAYS

Eosinophil infiltration and activation may serve a pathogenetic role not only in allergic asthma [63], but it is also associated with the mixed Th2/Th1/Th17 endotype of severe asthma [64]. Upon activation, eosinophils degranulate and release lytic enzymes, lipid mediators, cytokines, cytotoxins, leukotrienes and pro-fibrogenic factors that induce tissue inflammation, mucus hypersecretion, remodelling and AHR [65,66]. Growth, differentiation, recruitment, activation and survival of eosinophils are very much dependent on the Th2 inflammatory cytokine IL-5 [63], which is why it is an obvious candidate to target (Fig. 1) [67[■]]. In preclinical mouse asthma models, anti-IL-5 treatment reduces eosinophilic inflammation and airway hyperreactivity [68–70]. Hence, antagonizing IL-5 with mAbs may have beneficial advantage for asthma with several anti-IL-5 strategies being in clinical development for allergic diseases, particularly those characterized by an eosinophilic predominant form. Two humanized mAbs that neutralize IL-5 activity, mepolizumab and reslizumab, have been tested in

clinical studies of asthma patients with mild-to-moderate disease.

Early studies using the anti-IL-5 mAb mepolizumab (Bosatria; GSK, Brentford, Middlesex, UK), administered intravenously, almost completely removed circulatory and sputum eosinophils in asthma but, somewhat surprisingly, failed to demonstrate significant clinical or functional improvement [38–40]. Subsequent studies showed that mepolizumab decreased tissue [41] and bone marrow eosinophils [42] by 50% at most. Partial depletion of airway eosinophils was argued to be responsible for the unexpected lack of efficacy of mepolizumab in asthma, with mepolizumab-resistant eosinophils being dependent upon other factors for their survival (e.g. granulocyte macrophage colony-stimulating factor). Another explanation for the lack of efficacy of mepolizumab is that patients were selected on clinical and physiological parameters rather than eosinophilic inflammation. More recently, two small [43,44] and a large [45^{***}] randomized controlled trials of mepolizumab have incorporated criteria to select for severe asthmatic individuals with evidence of eosinophilic disease (sputum eosinophilia of >3%, fractional exhaled nitric oxide of >50 ppb and/or peripheral blood eosinophils of $>0.3 \times 10^9/l$) and a history of exacerbations. In all three studies, mepolizumab significantly reduced exacerbations, but did not have significant effects on FEV1 or symptom scores. Specifically, in the large ($n=616$) multicentre, double-blind study [45^{***}], infusion of mepolizumab reduced the rate of clinically significant asthma exacerbations by 48, 39 and 52%, respectively in the 75, 250 and 750 mg treatment group. Visits to emergency department and admissions also fell, although with variable results in the three arms of the study; 60% reduction with 75 mg, 42% with 250 mg and 48% with 750 mg. No significant adverse effects were reported.

Another anti-IL-5 mAb that has recently entered clinical development is Reslizumab (Cinquil or SCH55700; Ception Therapeutics, Malvern, Pennsylvania, USA), which is very similar to mepolizumab. Reslizumab significantly reduced peripheral blood eosinophils in severe asthmatic individuals in an initial clinical study [47] ($n=26$), but was not associated with significant improvements in FEV1. In a larger, more recent study [48] in uncontrolled severe asthmatic individuals ($n=106$), which incorporated criteria to select for patients with eosinophilic disease (sputum eosinophilia of >3%) and AHR or bronchodilator reversibility, reslizumab treatment was associated with improvements in lung function and a nonsignificant trend towards greater disease control, compared with placebo. The

beneficial response to reslizumab was especially noted in those patients with concomitant nasal polyposis. Indeed, in a separate randomized controlled trial, reslizumab significantly suppressed corticosteroid-resistant polyps in proportion to IL-5 levels in nasal lavage [49]. Given that eosinophil infiltration is common to both asthma and nasal polyposis, a recent small placebo-controlled trial with mepolizumab has likewise shown efficacy against nasal polyposis [46].

An alternative approach in antagonizing the IL-5 signalling is that to engineer blocking mAb to the IL-5 receptor. Benralizumab (MEDI-563; Medimmune) is a fucosylated humanized mAb directed against the α chain of the IL-5 receptor (anti-IL-5R α IgG1) that induces apoptosis of eosinophils and basophils by antibody-dependent cell-mediated cytotoxicity [50]. An initial proof-of-concept and safety study [51] of Benralizumab administered as single, escalating, intravenous doses (0.0003–3 mg/kg) to patients with mild asthma has demonstrated a dose-dependent reduction in blood eosinophils, with total ablation lasting for 8–12 weeks occurring at the highest dose. A subsequent study [52] in patients with acute severe asthma ($n=110$) showed that a single infusion of benralizumab reduced the number and severity of exacerbations compared with placebo during 12 weeks of follow-up that included outpatient standard of care (Table 1).

CONCLUSION

A plethora of new biologic therapies targeting specific type 2 inflammation associated cells or receptors are currently under investigation in clinical studies of asthmatic individuals, and in particular in severe asthma patients to improve their symptoms control and quality of life.

The fact that most of these new treatments are not enough to suppress inflammation and control remodelling efficiently, it is not surprising owing to the complex nature of asthma and to the limitation of blocking only one individual cellular and molecular pathway at one time.

Even when these highly specific therapies prove effective in some patient subsets, new challenges arise. In fact, improving segregation of asthma patients into subgroups most likely to respond to a particular therapy requires addressing pharmacoeconomic concerns, given the elevated acquisition costs of biologic therapies and of the diagnostic screening procedures necessary for the identification of potential responders.

Last but not least, when clinical benefits are well established for a specific biologic therapy, the issue of when/how the drug can be reduced or withdrawn,

and which clinical or biological markers may be useful for monitoring will remain uncertain.

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Conflicts of interest

R.P. has received grant support from CV Therapeutics, NeuroSearch A/S, Sandoz, MSD and Boehringer-Ingelheim; has served as a speaker for CV Therapeutics, Novartis, MSD and Roche; has served as a consultant for CV Therapeutics, Duska Therapeutics, Neuro-Search A/S, Boehringer-Ingelheim and Forest Laboratories and has received payment for developing educational presentations (including service on speakers' bureaus) from MSD and Pfizer. None of the remaining authors has any competing interests to declare and no funding was received in the preparation of this manuscript.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

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