



Prospects for new and emerging therapeutics in severe asthma: the role of biologics

Seçil Kepil Özdemir & Sevim Bavbek

To cite this article: Seçil Kepil Özdemir & Sevim Bavbek (2017): Prospects for new and emerging therapeutics in severe asthma: the role of biologics, Expert Review of Respiratory Medicine, DOI: [10.1080/17476348.2017.1326821](https://doi.org/10.1080/17476348.2017.1326821)

To link to this article: <http://dx.doi.org/10.1080/17476348.2017.1326821>



Accepted author version posted online: 02 May 2017.
Published online: 10 May 2017.



[Submit your article to this journal](#)



Article views: 23



[View related articles](#)



[View Crossmark data](#)

REVIEW



Prospects for new and emerging therapeutics in severe asthma: the role of biologics

Seçil Kepil Özdemir^a and Sevim Bavbek^b

^aDepartment of Chest Diseases, Division of Allergy and Immunology, İzmir Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital, İzmir, Turkey; ^bDivision of Immunology and Allergy, Department of Chest Diseases, Ankara University School of Medicine, Ankara, Turkey

ABSTRACT

Introduction: Asthma is a common and heterogeneous disease. While current conventional therapies are effective in the majority of the patients, a significant subgroup remain uncontrolled despite these treatments. Different biological agents are currently approved or undergoing development for treatment of asthma, including anti-IgE, anti-interleukin (IL)-5, anti-IL-13, anti-IL-4 and anti-thymic stromal lymphopoietin agents. This review will focus on the currently available evidence regarding the new and emerging biological agents in severe asthma.

Areas covered: A non-systematic review of the available English-language literature regarding severe asthma and biological agents was performed. We summarized and discussed the current evidence about the use of new and emerging biological agents in severe asthma.

Expert commentary: Because of the heterogeneity of response to therapy in refractory asthma it is of utmost importance to correctly estimate patient outcomes before starting biological therapy to make patient selection more effective. Currently, the decision of which biologic to initiate in patients with uncontrolled severe asthma should be made based on the atopic status, blood eosinophil and total IgE levels, exacerbation history, safety profile, cost, frequency and route of administration.

ARTICLE HISTORY

Received 3 February 2017
Accepted 2 May 2017

KEYWORDS

Severe asthma; uncontrolled asthma; biologic agents; biologics; new treatments

1. Introduction

Asthma is a chronic inflammatory airway disease that is characterized by heterogeneity with regard to clinical phenotype and response to therapy [1,2]. The development of inhaled corticosteroids allowing safer chronic use for asthma treatment and the guidelines recommending inhaled corticosteroids as controller medications have significantly improved the outlook of asthma [3]. While the majority of patients with asthma can be sufficiently treated with currently present medical treatments, 5–10% of patients have limited therapeutic options and significant morbidity as a result of the severity of their disease [4–6]. The European Respiratory Society and the American Thoracic Society severe asthma guidelines define severe asthma as ‘asthma that requires treatment with high-dose inhaled corticosteroids plus a second controller and/or systemic corticosteroids to prevent it from becoming uncontrolled or that remains uncontrolled despite this therapy’ when the diagnosis of asthma is confirmed and comorbidities addressed [4]. Severe or therapy-resistant asthma is recognized as a major unmet need and is a heterogeneous condition consisting of different phenotypes [4].

Research is emerging on biological therapies, most of which target the type 2 profile (often directed at interleukin (IL)-4, IL-5, and IL-13) [7], and studies of novel molecular targeted therapies are being performed mainly in the adult severe asthma population with some evidence of efficacy [4] (Figure 1, Table 1). Currently, there are several candidate asthma drugs undergoing various testing phases [3]. At

present, one anti-IgE therapeutic, omalizumab has been approved for use in patients with moderate-to-severe asthma and is recommended for Step 5 treatment in patients with moderate or severe allergic asthma with elevated IgE levels in the Global Strategy for Asthma Management and Prevention report [8]. Additionally, two anti-IL-5 agents, mepolizumab and reslizumab have been approved for add-on treatment in patients with severe eosinophilic asthma. This review will focus on the latest developments of new and emerging biological agents in severe asthma.

1.1. Currently approved biological agents

1.1.1. Anti-IgE

Omalizumab, a recombinant humanized monoclonal anti-IgE antibody, was the first monoclonal antibody used in asthma treatment [23]. Omalizumab binds to free IgE and prevents IgE from binding to its high- and low-affinity receptors on mast cells, basophils, and other cells. The clinical efficacy of this treatment in patients with moderate-to-severe and severe allergic asthma has been well documented in many clinical trials and real-life studies. There is also evidence for a response to omalizumab in nonatopic asthma patients. In a proof-of-concept trial, 41 adult patients with nonatopic, refractory asthma were randomized to omalizumab or placebo [9]. After 16 weeks, omalizumab treatment resulted in a statistically significant reduction in high-affinity IgE receptor expression on basophils and dendritic cells, an increase in forced expiratory volume in 1 s (FEV₁), and a trend toward

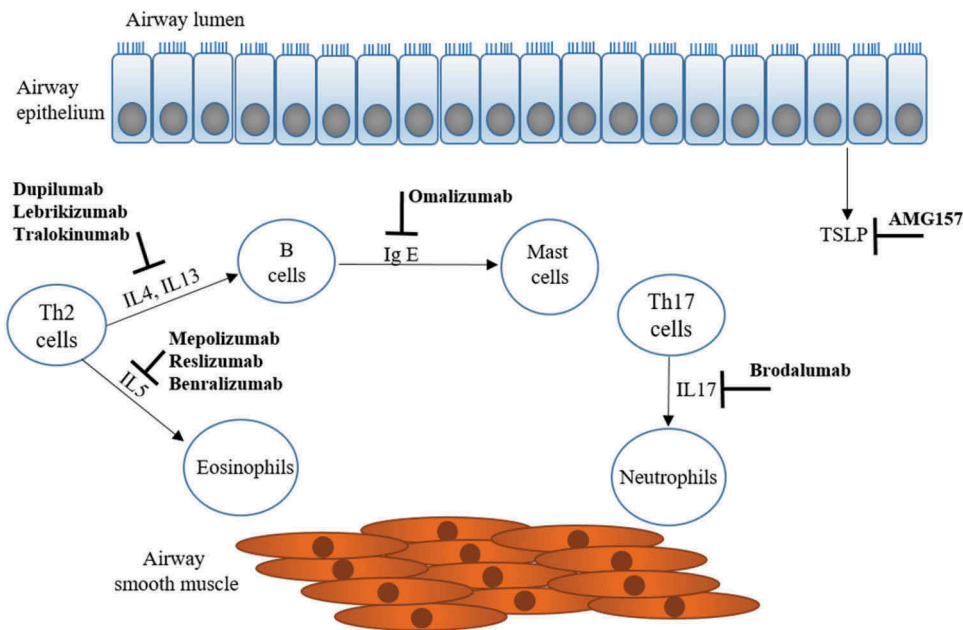


Figure 1. Targets of biological agents in asthma. IL, interleukin; TSLP, thymic stromal lymphopoietin.

improvement in asthma exacerbation rates. In another proof-of-concept study, 18 patients with symptomatic, nonatopic asthma were randomized to receive omalizumab or placebo in addition to existing therapy for 20 weeks [24]. Omalizumab therapy significantly reduced median total bronchial mucosal IgE+ cells at 12–14 weeks and improved lung function by 20 weeks despite withdrawal of conventional therapy. However, more research and larger prospective trials are needed to assess the clinical efficacy in nonatopic asthma and to identify the characteristics other than the atopic status of the patients with a response to omalizumab. A study by Hanania et al. [25] assessed the potential of fractional exhaled nitric oxide, peripheral blood eosinophil count, and serum periostin as predictors for treatment effects of omalizumab in patients with uncontrolled severe persistent allergic asthma. After 48 weeks of omalizumab treatment, reductions in exacerbation rates were greater in high versus low subgroups for all three biomarkers. In each of the biomarker-high subgroups, a significant reduction from placebo in the exacerbation rate for patients on omalizumab was observed; no significant differences versus placebo were observed in the low-biomarker subgroups. A double-blind, randomized, placebo-controlled trial included 328 patients with normal lung function and uncontrolled atopic asthma despite the use of inhaled corticosteroids [26]. The primary end point was the rate of exacerbations during the 24-week treatment period. A preplanned analysis was performed in two subgroups with high ($\geq 300/\mu\text{L}$) and low ($< 300/\mu\text{L}$) peripheral eosinophil counts at screening. Although there was a 27% reduction in exacerbation rates with omalizumab versus placebo, this effect was not statistically significant. Thus, the primary end point was not met. However, in the high-eosinophil group, omalizumab treatment resulted in a 59% reduction in the rate of exacerbations, while there was no change in the low-eosinophil group. In a pooled analysis of two double-blind,

randomized, placebo-controlled studies, including 1070 allergic asthma patients uncontrolled despite the use of moderate-to-high doses of inhaled corticosteroids, receiving high doses of inhaled corticosteroids, a history of frequent emergency asthma treatment and a low FEV₁ were predictive of best response to omalizumab [27]. A retrospective case-control study compared the pulmonary function test responses in omalizumab-treated patients with asthma with chronic rhinosinusitis and omalizumab-treated patients with asthma without chronic rhinosinusitis [28]. Allergic asthma patients treated with omalizumab showed some improvement in pulmonary function test scores, and the benefit of omalizumab was more likely to be observed in patients with asthma with chronic rhinosinusitis than in patients with asthma without chronic rhinosinusitis. However, further studies are required to investigate and confirm these findings. Confirmation of these findings will potentially guide for the selection of patients for omalizumab treatment. Additionally, nonatopic asthma patients with a type 2 high molecular phenotype would be an attractive population to explore the effects of omalizumab in nonatopic asthma [29]. Omalizumab is administered subcutaneously every 2 or 4 weeks, and the dose is determined according to pretreatment IgE levels and body weight.

The role of infections, particularly viral infections, in asthma exacerbations is well established [4]. A randomized, double-blind, placebo-controlled study including 419 inner-city children and young adults (6–20 years of age) with persistent allergic asthma found that the frequency of exacerbations was reduced with omalizumab when added to guideline-based therapy, and this effect of omalizumab being most striking during the fall season [30]. In a recent study, a 4-month treatment strategy with the addition of omalizumab beginning 4–6 weeks before the start of a school year to ongoing guideline-based treatment significantly reduced asthma exacerbations during the fall season among inner-

Table 1. Summary of new and emerging biological agents in asthma.

Target	Therapeutic agent	Disease characteristics	Outcome summary	Author, reference, year
IgE	Omalizumab	Nonatopic severe asthma	↓ High-affinity IgE receptor expression on basophils, dendritic cells; ↑ FEV ₁	Garcia et al. [9], 2013
IL-5	Mepolizumab	Severe eosinophilic asthma	↓ Rate of clinically significant exacerbations; ↓ blood eosinophils	Pavord et al. [10], 2012
IL-5	Mepolizumab	Severe eosinophilic asthma on maintenance treatment with systemic corticosteroids	Significant corticosteroid-sparing effect; ↓ exacerbations; improved control of symptoms	Bel et al. [11], 2014
IL-5	Mepolizumab	Severe eosinophilic asthma	↓ Exacerbations; improved asthma control; ↑ FEV ₁	Ortega et al. [12], 2014
IL-5	Reslizumab	Severe eosinophilic asthma	↓ Sputum and blood eosinophils; ↑ FEV ₁	Castro et al., [13], 2011
IL-5	Reslizumab	Eosinophilic asthma inadequately controlled with inhaled steroids	↓ Exacerbations; ↑ FEV ₁ ; improvements in quality of life and asthma control	Castro et al. [14], 2015
IL-5Ra	Benralizumab	Severe asthma	↓ Exacerbations; ↑ FEV ₁ in patients with blood eosinophils ≥300/μL	Bleecker et al. [15], 2016
IL-5Ra	Benralizumab	Severe asthma	↓ Exacerbations for patients with elevated blood eosinophils	FitzGerald et al. [16], 2016
IL-13	Lebrikizumab	Moderate-to-severe asthma	↓ Exacerbations; ↑ FEV ₁ in the periostin-high patients	Hanania et al. [17], 2015
IL-13	Lebrikizumab	Severe asthma	No consistent effect on exacerbations	Hanania et al., [18], 2016
IL-13	Tralokinumab	Severe asthma	No effect on exacerbations; ↑ FEV ₁	Brightling et al. [19], 2015
IL-4Ra	Dupilumab	Moderate-to-severe eosinophilic asthma	↓ Exacerbations; ↑ FEV ₁	Wenzel et al., [20], 2013
TSLP	AMG157	Mild atopic asthma	↓ Allergen-induced percentage reduction in FEV ₁ during the early and late asthmatic response; ↓ FeNO; ↓ blood and sputum eosinophils	Gauvreau et al. [21], 2014
IL-17RA	Brodalumab	Moderate-to-severe asthma	No treatment effect	Busse et al. [22], 2013

IL: interleukin; TSLP: thymic stromal lymphopoietin; FeNO: fraction of exhaled nitric oxide; FEV₁: forced expiratory volume in 1 s.

city children with one or more recent exacerbations [31]. This study also tested the hypothesis that the beneficial effects of omalizumab on seasonal asthma exacerbations can be explained in part by an increased release of interferon- α from plasmacytoid dendritic cells on rhinovirus exposure and found that omalizumab improved interferon- α responses to rhinovirus, and within the omalizumab group, greater interferon- α responses increases were associated with fewer exacerbations. Further research is needed to evaluate the benefits of seasonal treatment with omalizumab for patients with frequent seasonal exacerbations.

A challenge to the use of biological agents in asthmatic patients is the limited information regarding their long-term efficacy, safety, and the effects of withdrawal. Few data are available regarding long-term use of omalizumab. Withdrawal of omalizumab after less than a year of treatment results in a rise in serum free IgE levels, a repopulation of the basophil surface with both IgE and Fc ϵ R1 α and a return of histamine-release responses to baseline within months [32]. However, after withdrawal of a 6-year treatment of omalizumab, the beneficial effects of the treatment were sustained in 12 out of 18 patients at 3 years after treatment with omalizumab was stopped [33]. The only randomized, double-blind, placebo-controlled withdrawal study included 176 subjects with moderate-to-severe persistent asthma receiving long-term omalizumab treatment (approximately 5 years) [34]. Significantly, more subjects in the omalizumab group had no protocol-defined exacerbation than in the placebo group (67% vs. 47.7%). A higher baseline peripheral blood eosinophil count was observed in subjects in the placebo group who experienced an exacerbation. Confirmation of this finding in further studies is important and may guide to treatment continuation or withdrawal decisions. Omalizumab is generally well tolerated [35]. However, there are

concerns about its cardiovascular risk. A postmarketing observational cohort study demonstrated a higher incidence rate of cardiovascular/cerebrovascular events in the omalizumab versus the non-omalizumab cohort [36]. After control for available confounding factors, the hazard ratio was 1.32 (95% confidence interval, 0.91–1.91). Although differences in asthma severity between cohorts (severe asthma rates were 50% versus 23% in the omalizumab versus non-omalizumab groups, respectively) likely contributed to this higher incidence, an increase in risk cannot be excluded.

1.1.2. Anti-IL-5 agents

Patients with the eosinophilic asthma phenotype have an increased frequency of exacerbations, which has been linked to eosinophilic airway inflammation [6,37]. IL-5 is a pro-eosinophilic type 2 cytokine that binds to the IL-5Ra expressed on eosinophils and basophils and promotes eosinophil recruitment, survival, and activation [38] and contributes to eosinophilic inflammation in the airways. The anti-IL-5 antibodies mepolizumab and reslizumab have been approved by the US FDA for maintenance treatment of severe asthma with an eosinophilic phenotype. Several studies in patients with severe eosinophilic asthma showed that mepolizumab reduced exacerbation risk and improved outcomes [10–12,39]. A systematic review of eight studies have suggested that mepolizumab leads to an improvement in quality of life and a reduction of asthma exacerbation rates with no significant serious adverse events on treatment [40]. In the multicenter Dose Ranging Efficacy And safety with Mepolizumab in severe asthma (DREAM) trial, 621 patients with recurrent severe asthma exacerbations and evidence of eosinophilic inflammation were randomly assigned to intravenous mepolizumab (75, 250, or 750 mg) or placebo at 4-week intervals [10]. The rate of clinically significant exacerbations

was decreased in all mepolizumab groups compared to placebo, and of the many variables assessed, only blood eosinophil count and the number of exacerbations in the year before baseline were associated with the reductions in the rate of clinically significant exacerbations with mepolizumab. In the multicenter Steroid Reduction with Mepolizumab Study (SIRIUS), 135 patients with severe eosinophilic asthma and at least a 6-month history of maintenance treatment with systemic glucocorticosteroids before entering the study were randomly assigned to mepolizumab (100 mg) or placebo administered subcutaneously, once every 4 weeks for 20 weeks [11]. Mepolizumab was associated with significantly greater reductions in the maintenance oral glucocorticosteroid dose than did those receiving placebo. Mepolizumab also had a significantly beneficial effect on exacerbations, asthma control, and quality of life. In the Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma (MENSA) study, 576 patients with severe asthma and evidence of eosinophilic inflammation despite high doses of inhaled glucocorticoids were assigned to mepolizumab (75 mg intravenously or 100 mg subcutaneously) or placebo every 4 weeks for 32 weeks [12]. Treatment with mepolizumab reduced exacerbations by approximately one half, improved qualities of life, and was associated with better asthma control and significant increase from baseline in FEV₁. These data are supported by the 2016 update of the Global Strategy for Asthma Management and Prevention report that recommend add-on mepolizumab as a treatment option that may be considered at Step 5 for patients aged ≥ 12 years with severe eosinophilic asthma that is uncontrolled on Step 4 treatment [8]. Another anti-IL-5 monoclonal antibody, reslizumab has shown similar efficacy to mepolizumab, though in a population that has a higher blood eosinophil count but less severe disease than those treated with mepolizumab [41]. In a multicenter trial, 106 patients with uncontrolled eosinophilic asthma, despite high-dose inhaled corticosteroid treatment, were assigned to intravenous reslizumab at 3.0 mg/kg or placebo for 12 weeks at 4-week intervals [13]. The reslizumab group had a statistically significant improvement in lung function and reduction in sputum and blood eosinophil counts and a trend toward improved asthma control. Two duplicate, multicenter, randomized controlled trials included 953 patients with inadequately controlled asthma with medium-to-high doses of inhaled corticosteroid therapy and a blood eosinophil count $\geq 400/\mu\text{L}$ [14]. Patients were assigned to intravenous reslizumab (3.0 mg/kg) or placebo every 4 weeks for 1 year. Reslizumab significantly reduced the annual rate of asthma exacerbations by 50–59% compared with placebo with significant improvements in FEV₁, quality of life, and asthma control. Two cases of anaphylaxis attributed to reslizumab were reported. Mepolizumab is administered subcutaneously 100 mg every 4 weeks, and reslizumab is administered 3 mg/kg by intravenous infusion.

1.2. Investigational biological agents

1.2.1. Anti-IL-5

In addition to IL-5, the receptor for IL-5 (IL-5R α) has been targeted using the humanized monoclonal antibody benralizumab [23]. Benralizumab is a humanized, afucosylated, monoclonal antibody against IL-5R α that induces direct and nearly complete depletion of eosinophils through enhanced antibody-dependent

cell-mediated cytotoxicity [15]. Benralizumab has been shown to reduce airway and peripheral blood eosinophils and asthma exacerbations in adults with uncontrolled eosinophilic asthma [42,43]. In two multicenter, randomized, controlled phase 3 trials, benralizumab significantly reduced asthma exacerbations and improved prebronchodilator FEV₁ in patients with severe, uncontrolled asthma with eosinophilia (blood eosinophil counts $\geq 300/\mu\text{L}$) [15,16]. In the multicenter, randomized, double-blind, parallel-group, placebo-controlled phase 3 trial (SIROCCO), 1205 adolescent and adult patients with severe asthma were assigned to benralizumab 30 mg every 4 weeks, benralizumab 30 mg every 8 weeks, or placebo for 48 weeks as add-on to their standard treatment [15]. In patients with blood eosinophil counts at least 300 cells/ μL , benralizumab reduced the annual asthma exacerbation rate and significantly improved prebronchodilator FEV₁ at week 48 with both dosing regimens. In the second multicenter, randomized, double-blind, parallel-group, placebo-controlled phase 3 trial (CALIMA), 1306 adolescent and adult patients with severe asthma and a history of at least two exacerbations in the previous year were assigned to benralizumab 30 mg every 4 weeks, benralizumab 30 mg every 8 weeks, or placebo for 56 weeks [16]. Add-on therapy with benralizumab significantly reduced the annual rate of asthma exacerbations by up to 36% for patients with elevated blood eosinophils. Patients who had experienced three or more exacerbations in the previous year had the greatest effects of benralizumab therapy.

The different anti-IL-5 agents have consistent beneficial clinical effects, appear to be safe, and have a well-defined and easily measured biomarker [41]. The efficacy of treatment with anti-IL-5 monoclonal antibodies is associated with both the exacerbation history and the blood eosinophil counts [6]. High exacerbation rates and blood eosinophil counts are associated with a better response [6]. These targeted therapies with anti-IL-5 or anti-IL-5R α are promising in short-term and medium-term treatment of selected adult patients with severe eosinophilic asthma [44]. The long-term safety of these agents needs to be addressed.

1.2.2. Anti-IL-13 and anti-IL-4 agents

IL-13 and IL-4 are involved in IgE synthesis, eosinophil activation, mucus secretion, and airway remodeling [45]. IL-13 is central to development of airway hyperresponsiveness in asthma, and its effect is mediated through the low-affinity IL-13 receptor $\alpha 1$ (IL-13R $\alpha 1$) and IL-4 receptor α (IL-4R α) complexes (IL-13R $\alpha 1$ /IL-4R α complex) [41]. IL-4 also exerts its effect through IL-4R α [46]. Lebrikizumab is an IgG4 humanized monoclonal antibody that blocks the signaling pathway through the IL-4R α /IL-13R $\alpha 1$ heterodimer by binding soluble IL-13 and preventing its link to the receptor [17,45]. Lebrikizumab was compared with placebo in a population of 219 asthmatic patients with uncontrolled disease by medium-to-high-dose inhaled corticosteroids [47]. At week 12, the mean increase from baseline in prebronchodilator FEV₁ was greater by 5.5% in the lebrikizumab group than the placebo group. Patients with higher serum levels of baseline periostin had a greater improvement in FEV₁ with lebrikizumab than in patients with low periostin levels. However, the improvement in FEV₁ was not statistically significant at 24 weeks. Treatment with lebrikizumab did not lead to significant reductions in asthma exacerbations, symptom scores, and use of rescue medication. In

another study, 212 patients with asthma who were not receiving inhaled corticosteroids and had a prebronchodilator FEV₁ of 60–85% of predicted value were randomized to lebrikizumab or placebo [48]. No significant improvement was detected in FEV₁ in 12 weeks, even in the subgroup analysis of the patients with high serum periostin levels. Two replicate, multicenter, randomized, double-blind, placebo-controlled trials included 463 patients with uncontrolled asthma despite the use of medium-to-high dose of inhaled corticosteroids and a second controller [17]. Treatment with lebrikizumab, with a median duration of 24 weeks, reduced the rate of asthma exacerbation and improved FEV₁ at week 12 (9.1% placebo-adjusted improvement) in the periostin-high patients. Two recent large phase 3 studies (LAVOLTA 1 and 2) of lebrikizumab included 2149 patients with severe asthma [18]. The studies failed to provide consistently significant results for the primary end point of a significant reduction in the rate of asthma exacerbations over 52 weeks or a clear dose–response even in the biomarker-high (periostin concentration of at least 50 ng/mL or a blood eosinophil count of at least 300 cells/ μ L) group. Tralokinumab is another IgG4 monoclonal antibody to IL-13. In a proof-of-concept study, 194 subjects with moderate-to-severe uncontrolled asthma were randomized [49]. The primary end point of the change from baseline in Asthma Control Questionnaire scores was not different between groups, but the statistically insignificant increases in FEV₁ with dose–response observed across the tralokinumab doses tested and the reduction in the use of short-acting β 2-agonists in tralokinumab-treated subjects suggested a treatment effect. In another randomized, double-blind, placebo-controlled trial, tralokinumab treatment had an acceptable safety and tolerability profile but did not statistically reduce the primary end point of annual asthma exacerbation rates at week 52 in patients with severe uncontrolled asthma [19]. Improvements in FEV₁ were noted in patients receiving the drug every 2 weeks, but not in those receiving tralokinumab every 4 weeks. Improvements in lung function were greatest in patients in the high baseline serum dipeptidyl peptidase-4 and high baseline serum periostin subgroups.

Dupilumab is a fully human monoclonal antibody to the IL-4R α that inhibits both IL-4 and IL-13 signaling [20]. In a multicenter, randomized, double-blind, placebo-controlled phase 2a study, 104 patients with moderate-to-severe asthma not well controlled with medium-to-high-dose inhaled glucocorticoids plus long-acting β 2 agonists, and an elevated blood eosinophil or an elevated sputum eosinophil level was randomized [20]. Dupilumab therapy was associated with fewer asthma exacerbations compared to placebo when long-acting β 2 agonists and inhaled glucocorticoids were withdrawn. A phase 2b dose-ranging study included 776 adult patients with uncontrolled persistent asthma and showed that dupilumab added to medium-to-high-dose inhaled corticosteroids and long-acting β 2 agonists significantly improved lung function and reduced the rate of severe exacerbations, regardless of baseline eosinophil counts [50]. There were also significant improvements in patient-reported outcomes such as Asthma Quality of Life Questionnaire scores and asthma symptom scores at week 24 with dupilumab.

The anti-IL-13 monoclonal antibody lebrikizumab did not show significant clinical efficacy in severe asthma. When taken together with the disappointing results of the studies with the

other anti-IL-13 monoclonal antibody tralokinumab and the promising results obtained in phase 2 studies of dupilumab suggest that there may be advantages in suppressing the activity of both IL-4 and IL-13.

1.2.3. Anti-thymic stromal lymphopoietin

Thymic stromal lymphopoietin (TSLP) is an epithelial cell-derived cytokine, and its levels are increased in the airways of patients with asthma [21]. In a proof-of-concept, multicenter, randomized, double-blind, placebo-controlled study, treatment with anti-TSLP monoclonal antibody (AMG157) significantly attenuated the allergen-induced percentage reduction in FEV₁ during the early and the late asthmatic response on days 42 and 84 [21]. Treatment with anti-TSLP monoclonal antibody for 12 weeks was also associated with a reduction in the fraction of exhaled nitric oxide and blood and sputum eosinophils in patients with mild atopic asthma.

1.2.4. Prospects in type 2 low asthma

Although previous studies suggest that monoclonal antibodies targeting IgE, IL-5, IL-4, and IL-13 may be effective for some patients with asthma with type 2 inflammation, nearly half of the patients with asthma do not have type 2 inflammation [23,51]. Additionally, type 2 low asthma, especially neutrophilic asthma was associated with more severe disease [29,52]. Type 2 low asthma responds poorly to current therapies, and responsiveness to inhaled corticosteroids is poor in patients with type 2 low asthma compared to patients with a type 2 high asthma molecular phenotype [51]. Thus, there is a need for effective anti-inflammatory therapies for patients with type 2 low asthma. However, very few targets for therapy are identified in type 2 low asthma, especially in patients with severe, uncontrolled disease [23].

Th17 cells produce a number of cytokines, especially IL-17A and IL-17F, and the Th17-derived cytokines are important in the induction and activation of neutrophils [53]. Additionally, increased expression of IL-17A and IL-17F has been shown in the airway tissues in severe asthma [53]. Brodalumab is an anti-IL-17 receptor type A monoclonal antibody [22]. In a randomized study, 302 patients with inadequately controlled moderate-to-severe asthma taking inhaled corticosteroids received brodalumab or placebo [22]. Treatment with brodalumab did not produce a treatment effect compared to placebo. Only a subgroup with high bronchodilator reversibility demonstrated an improvement in Asthma Control Questionnaire scores. However, a follow-up phase 2b study focusing the subgroup with high bronchodilator reversibility was stopped due to a lack of observed efficacy [54]. Further studies about the mechanisms of type 2 low asthma may lead to novel therapies in this subgroup of asthma with an unmet need for better treatments.

1.3. Conclusion

Currently, the anti-IgE therapeutic omalizumab and anti-IL-5 antibodies mepolizumab and reslizumab have been approved for the treatment of asthma in selected patients. Omalizumab has been proved to be effective in patients with moderate-to-severe and severe allergic asthma in many clinical trials and real-life studies. While no longer a new biological agent for

severe asthma, there are preliminary promising data with new utilizations of omalizumab in nonatopic asthma and in reducing viral exacerbations. Studies in patients with uncontrolled eosinophilic asthma showed that mepolizumab, reslizumab, and benralizumab reduced exacerbation risk and improved outcomes. Additionally, different biological agents are undergoing development for treatment of asthma, including anti-IL-13, anti-IL-4, and anti-TSLP agents. Studies on dupilumab (anti-IL4/13) have revealed beneficial clinical improvements. Detection of eosinophilic airway inflammation is important in severe asthma because it affects therapeutic consequences. Currently, the biological agents are mostly targeting the type 2 pathway, and patients with type 2 low asthma have few therapeutic options.

2. Expert commentary

Asthma is a heterogeneous disease with different phenotypes, and it is clear that the presentation, natural history, pathophysiological mechanisms, and response to treatment differ between patients and this is particularly true for severe asthma. Although most patients can be treated with conventional therapies, a subgroup of patients has more severe and difficult-to-control disease. This group of patients represents a major unmet need for emerging therapies. Better identification of asthma phenotypes and endotypes will guide to provide novel personalized therapeutic approaches, especially in patients with severe, poorly controlled disease.

There are several candidate asthma therapies and potential biomarkers associated with a better response to these agents. Several biological agents targeting the cytokines implicated in asthma pathophysiology have been developed. Agents such as monoclonal antibodies to the main cytokines associated with asthma (e.g. IL-5, IL-13, and TSLP) and monoclonal antibodies targeted to receptors of these cytokines (e.g. IL-5R α and IL-4R α) are currently under investigation in asthma treatment. Biological agents targeting type 2 inflammation are promising for type 2 high asthma. The clinical efficacy of omalizumab therapy in patients with moderate-to-severe and severe allergic asthma has been well documented in clinical trials and real-life studies, and preliminary findings suggest that high blood eosinophil counts, frequent emergency asthma treatment, and impaired lung function may predict better response to omalizumab treatment. Monoclonal antibodies against IL-5 are effective in severe eosinophilic asthma. High exacerbation rates and blood eosinophil counts are associated with a better response to anti-IL-5 monoclonal antibodies. In addition, benralizumab (anti-IL-5R α) has significantly reduced asthma exacerbations and improved prebronchodilator FEV₁ in severe eosinophilic asthma. However, longer studies are required to determine the long-term efficacy and safety of the anti-IL-5 and anti-IL-5R α agents. Although the results of the studies with the anti-IL-13 monoclonal antibodies lebrikizumab and tralokinumab are disappointing in severe asthma, dupilumab that inhibits both IL-4 and IL-13 signaling has shown promising results in preliminary studies. Early trials seem encouraging with anti-TSLP in asthma; future studies are needed to evaluate its efficacy in severe asthma.

As increased number of biological agents become available, and because of the heterogeneity of response to therapy in

refractory asthma, it is of utmost importance to correctly estimate patient outcomes before starting biological therapy to make patient selection more effective and cost saving. Therefore, appropriate use of biomarkers and evaluating each patient's underlying phenotype to guide clinical decisions are necessary. Currently approved biologics have shown benefit in type 2 high asthma phenotype. Further studies evaluating the predictors of response to approved biological agents are required to select the optimal biological agent for appropriate populations. Head-to-head comparative trials of the approved biological agents are also necessary to make clinical decisions between different biological agents directed to type 2 high asthma phenotype. With our current knowledge, the decision of which biologic to initiate should be made based on the atopic status, blood eosinophil and total IgE levels, exacerbation history, safety profile, cost, frequency, and route of administration. As our knowledge about the use of biological agents improves, studies exploring the synergistic effects of combination therapy with biological agents may be anticipated.

Most of the emerging biological agents target the type 2 profile; however, nearly half of the patients with asthma do not have type 2 inflammation. Furthermore, type 2 low asthma responds poorly to current therapies and corticosteroids. However, patients with type 2 low severe asthma have few therapeutic options. The anti-IL-17 receptor type A monoclonal antibody, brodalumab was evaluated in moderate-to-severe asthma, and only a subgroup with high bronchodilator reversibility demonstrated an improvement in Asthma Control Questionnaire scores. However, a study focusing this subgroup with high bronchodilator reversibility was stopped due to a lack of efficacy. It remains possible that a more specific subgroup of severe asthma with an indication of IL-17 involvement may benefit from anti-IL-17 receptor type A monoclonal antibody. Further research is certainly needed to better understand the mechanisms of type 2 low asthma, and this may lead new targeted therapeutic agents to develop in this subgroup.

Identification of potential specific subgroups, specific biomarkers, and subject characteristics with an optimal treatment response is of key importance with therapeutic agents that target specific mechanisms. All clinical trials showing beneficial clinical effects of the new biological agents point a specific subgroup of patients with response to therapy. A tailored approach in severe asthma treatment will be possible in the near future with the improvement of our knowledge about asthma phenotypes and the improved understanding of the optimum phenotypes with a response to these biological agents.

3. Five-year review

We anticipate further research over the next 5 years to better characterize asthma phenotypes, the distinct pathophysiological mechanisms involved, and the biomarkers predictive of optimal response to new targeted therapies. This will help to establish more appropriate treatment strategies in asthma and is particularly important in severe and difficult-to-control disease. Comparative efficacy trials and real-life data with the use of the approved biological agents will be critical in treatment decisions.

Key issues

- The heterogeneous nature of severe asthma constitutes a therapeutic challenge.
- Because of the heterogeneity of response to therapy in refractory asthma it is of utmost importance to correctly estimate patient outcomes before starting biological therapy to make patient selection more effective.
- Omalizumab treatment should be considered in patients with severe uncontrolled allergic asthma.
- Mepolizumab and reslizumab treatment should be considered in patients with severe uncontrolled eosinophilic asthma.
- The decision of which biologic to initiate should be made based on the atopic status, blood eosinophil and total IgE levels, exacerbation history, safety profile, cost, frequency and route of administration.
- Further research is needed to better understand the mechanisms of type 2 low asthma, and this may lead new targeted therapeutic agents to develop in this subgroup.

Funding

This paper was not funded.

Declaration of interest

S. Bavbek is an advisory board member for Novartis and GlaxoSmithKline. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

References

Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.

- Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. *Nat Med*. 2012;18:716–725.
- Gonem S, Berair R, Singapuri A, et al. Fevipiprant a prostaglandin D2 receptor 2 antagonist, in patients with persistent eosinophilic asthma: a single-centre, randomized, double-blind, parallel-group, placebo-controlled trial. *Lancet Respir Med*. 2016;4:699–707.
- Rank MA. Preparing for the next big thing in asthma management. *J Allergy Clin Immunol Pract*. 2015;3:991–992.
- Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J*. 2014;43:343–373.
- Moore WC, Bleecker ER, Curran-Everett D, et al. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. *J Allergy Clin Immunol*. 2007;119:405–413.
- Trivedi A, Pavord ID, Castro M. Bronchial thermoplasty and biological therapy as targeted treatments for severe uncontrolled asthma. *Lancet Respir Med*. 2016;4:585–592.
- Abrams EM, Szefer SJ, Becker AB. Effect of asthma therapies on the natural course of asthma. *Ann Allergy Asthma Immunol*. 2016;117:627–633.
- Global initiative for asthma. Global Strategy for asthma management and prevention, 2016. Available from: www.ginasthma.org
- Garcia G, Magnan A, Chiron R, et al. A proof-of-concept, randomized, controlled trial of omalizumab in patients with severe, difficult-to-control, nonatopic asthma. *Chest*. 2013;144:411–419.

- Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicenter, double-blind, placebo-controlled trial. *Lancet*. 2012;380:651–659.
- Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med*. 2014;371:1189–1197.
- This randomized, placebo-controlled study reports the effect of mepolizumab therapy in reducing the use of maintenance oral corticosteroids in patients with severe eosinophilic asthma.**
- Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med*. 2014;371:1198–1207.
- This study reports the results of a phase 3, randomized, placebo-controlled trial, with its primary outcome the rate of exacerbations in patients with severe eosinophilic asthma.**
- Castro M, Mathur S, Hargreave F, et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized placebo-controlled study. *Am J Respir Crit Care Med*. 2011;184:1125–1132.
- Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicenter, parallel double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med*. 2015;3:355–366.
- Bleecker ER, FitzGerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2 -agonists (SIROCCO): a randomized, multicenter, placebo-controlled phase 3 trial. *Lancet*. 2016;388:2115–2127.
- FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomized double-blind, placebo-controlled phase 3 trial. *Lancet*. 2016;388:2128–2141.
- This study reports the results of a phase 3, randomized, placebo-controlled trial, with its primary outcome annual rate ratio versus placebo of asthma exacerbations in patients with severe eosinophilic asthma.**
- Hanania NA, Noonan M, Corren J, et al. Lebrikizumab in moderate-to-severe asthma: pooled data from two randomized, placebo-controlled studies. *Thorax*. 2015;70:748–756.
- Hanania NA, Korenblat P, Chapman KR, et al. Efficacy and safety of lebrikizumab in patients with uncontrolled asthma (LAVOLTA I and LAVOLTA II): replicate, phase 3, randomised, double-blind, placebo-controlled trials. *Lancet Respir Med*. 2016;4:781–796.
- Brightling CE, Chanez P, Leigh R, et al. Efficacy and safety of tralokinumab in patients with severe uncontrolled asthma: a randomized, double-blind, placebo-controlled, phase 2b trial. *Lancet Respir Med*. 2015;3:692–701.
- Wenzel S, Ford L, Pearlman D, et al. Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med*. 2013;368:2455–2466.
- Gauvreau GM, O'Byrne PM, Boulet LP, et al. Effects on an anti-TSLP antibody on allergen-induced asthmatic responses. *N Engl J Med*. 2014;370:2102–2110.
- Busse WW, Holgate S, Kerwin E, et al. Randomized, double-blind, placebo-controlled study of brodalumab, a human anti-IL-17 receptor monoclonal antibody, in moderate-to-severe asthma. *Am J Respir Crit Care Med*. 2013;188:1294–1302.
- Fajt ML, Wenzel SE. Development of new therapies for severe asthma. *Allergy Asthma Immunol Res*. 2017;9:3–14.
- A recent, comprehensive review on new therapies for severe asthma.**
- Pillai P, Chan YC, Wu SY, et al. Omalizumab reduces bronchial mucosal IgE and improves lung function in non-atopic asthma. *Eur Respir J*. 2016;48:1593–1601.
- Hanania NA, Wenzel S, Rosén K, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. *Am J Respir Crit Care Med*. 2013;187:804–811.
- The study reports the results of the analyses evaluating treatment effects of omalizumab in relation to exhaled nitric oxide fraction, blood eosinophils, and serum periostin levels in a large cohort of patients with severe allergic asthma.**

26. Busse W, Spector S, Rosén K, et al. High eosinophil count: a potential biomarker for assessing successful omalizumab treatment effects. *J Allergy Clin Immunol.* **2013**;132:485–486.
27. Bousquet J, Wenzel S, Holgate S, et al. Predicting response to omalizumab, an anti-IgE, in patients with allergic asthma. *Chest.* **2004**;125:1378–1386.
28. Clavenna MJ, Turner CJ, Samuelson M, et al. Differential effect of omalizumab on pulmonary function in patients with allergic asthma with and without chronic rhinosinusitis. *Allergy Asthma Proc.* **2016**;37:23–26.
29. Gaga M, Zervas E, Humbert M. Targeting immunoglobulin E in non-atopic asthma: crossing the red line? *Eur Respir J.* **2016**;48:1538–1540.
30. Busse WW, Morgan WJ, Gergen PJ, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *N Engl J Med.* **2011**;364:1005–1015.
31. Teach SJ, Gill MA, Togias A, et al. Preseasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations. *J Allergy Clin Immunol.* **2015**;136:1476–1485.
32. Saini SS, MacGlashan DW, Sterbinsky SA, et al. Down-regulation of human basophil IgE and FcεR1α surface densities and mediator release by anti-IgE-infusions is reversible in vitro and in vivo. *J Immunol.* **1999**;162:5624–5630.
33. Nopp A, Johansson SGO, Adedoyin J, et al. After 6 years with Xolair; a 3 year withdrawal follow-up. *Allergy.* **2010**;65:56–60.
34. Ledford D, Busse W, Trzaskoma B, et al. A randomized multicenter study evaluating Xolair persistence of response after long-term therapy. *J Allergy Clin Immunol.* **2016** Nov 5. doi:10.1016/j.jaci.2016.08.054.
- **This is the first randomized controlled trial to compare the risks and benefits of continuing versus discontinuing omalizumab after long-term use in patients with allergic asthma.**
35. Mansur AH, Srivastava S, Mitchell V, et al. Longterm clinical outcomes of omalizumab therapy in severe allergic asthma: study of efficacy and safety. *Respire Med.* **2017**;124:36–43.
36. Iribarren J, Rahmaoui A, Long AA, et al. Cardiovascular and cerebrovascular events among patients receiving omalizumab: results from EXCELS, a prospective cohort study in moderate to severe asthma. *J Allergy Clin Immunol.* **2016** Sep 14. DOI:10.1016/j.jaci.2016.07.038.
37. Green RH, Brightling CE, McKenna S, et al. Asthma exacerbations and sputum eosinophil counts: a randomized controlled trial. *Lancet.* **2002**;360:1715–1721.
38. Kim AS, Doherty TA. New and emerging therapies for asthma. *Ann Allergy Asthma Immunol.* **2016**;116:14–17.
39. Haldar P, Brightling CE, Hargadon B, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med.* **2009**;360:973–984.
40. Powell C, Milan SJ, Dwan K, et al. Mepolizumab versus placebo for asthma. *Cochrane Database Syst Rev.* **2015**;7:CD010834.
41. Pavord ID, Hilvering B, Shrimanker R. Emerging biologics in severe asthma. *Immunol Allergy Clin N Am.* **2016**;36:609–623.
42. Lavolette M, Gossage DL, Gauvreau G, et al. Effects of benralizumab on airway eosinophils in asthmatic patients with sputum eosinophilia. *J Allergy Clin Immunol.* **2013**;132:1086–1096.
43. Castro M, Wenzel SE, Bleecker ER, et al. Benralizumab an anti-interleukin 5 receptor α monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomized dose-ranging study. *Lancet Respir Med.* **2014**;2:878–890.
44. Varricchi G, Bagnasco D, Borriello F, et al. Interleukin-5 pathway inhibition in the treatment of eosinophilic respiratory disorders: evidence and unmet needs. *Curr Opin Allergy Clin Immunol.* **2016**;16:186–200.
45. Bagnasco D, Ferrando M, Varricchi G, et al. A critical evaluation of anti-IL-13 and anti-IL-4 strategies in severe asthma. *Int Arch Allergy Immunol.* **2016**;170:122–131.
46. Sulaiman I, Lim JCW, Soo HL, et al. Molecularly targeted therapies for asthma: current development, challenges and potential clinical translation. *Pulm Pharmacol Ther.* **2016**;40:52–68.
- **A comprehensive review on molecularly targeted therapies for asthma.**
47. Corren J, Lemanske RF, Hanania NA, et al. Lebrikizumab treatment in adults with asthma. *N Engl J Med.* **2011**;365:1088–1098.
48. Noonan M, Korenblat P, Mosesova S, et al. Dose-ranging study of lebrikizumab in asthmatic patients not receiving inhaled steroids. *J Allergy Clin Immunol.* **2013**;132:567–574.
49. Piper E, Brightling C, Niven R, et al. A phase II placebo-controlled study of tralokinumab in moderate-to-severe asthma. *Eur Respir J.* **2013**;41:330–338.
50. Wenzel S, Castro M, Corren J, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high dose inhaled corticosteroids plus a long-acting β2 agonist: a randomized double-blind placebo-controlled, pivotal phase 2b dose-ranging trial. *Lancet.* **2016**;388:31–44.
- **This study reports the results of a randomized, placebo-controlled, phase 2b dose-ranging trial, having as primary outcome change from baseline at week 12 in forced expiratory volume in 1 s in patients with uncontrolled persistent asthma.**
51. Woodruff PG, Modrek B, Choy DF, et al. T-helper type 2-driven inflammation defines major subphenotypes of asthma. *Am J Respir Crit Care Med.* **2009**;180:388–395.
52. Moore WC, Hastie AT, Li X, et al. Sputum neutrophils are associated with more asthma phenotypes using cluster analysis. *J Allergy Clin Immunol.* **2014**;133:1557–1563.
53. Ramli WA, Prefontaine D, Chouiali F, et al. Th17-associated cytokines (IL-17A and IL-17F) in severe asthma. *J Allergy Clin Immunol.* **2009**;123:1185–1187.
54. Chung KF. Targeting the interleukin pathway in the treatment of asthma. *Lancet.* **2015**;386:1086–1096.