

# Monoclonal Antibodies for the Treatment of Severe Asthma

Salvatore Clienti · Jaymin B. Morjaria · Elisa Basile ·  
Riccardo Polosa

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**Abstract** Patients with severe asthma have a significant unmet need with persistent symptoms and/or frequent exacerbations despite treatment with high-dose steroid and other currently available therapies. These patients are also at risk of developing steroid-related side effects, and their severe, unrelenting symptoms have a huge impact on health care resources due to frequent hospital admissions and requirement for intensive medication use. Consequently, a compelling need exists for more effective and safer pharmacotherapies to help them achieve adequate disease control. Recent novel therapies for severe asthma are now emerging, some of the most promising of which are monoclonal antibodies. Monoclonal antibodies represent a form of immunotherapy used in a wide variety of therapeutic roles. The spectrum of disease states in which monoclonal antibodies have been approved for therapeutic use now includes respiratory and allergic diseases. At present, only one drug is licensed for allergic asthmatics with severe disease, omalizumab. We review some of the

currently available biologics that are approved or under investigation for use in severe asthma. Some have shown to be useful in specifically targeted subpopulations of patients with severe asthma, whereas others have proven to be unsafe and/or unsuccessful. Despite these developments, more effort should be devoted to identifying new molecular targets, testing innovative approaches, and establishing the best use of what is available. Regarding this latter point, identifying individual characteristics that predict successful responses to these treatments is highly desirable.

**Keywords** Severe asthma · Biologics · Monoclonal antibodies

## Introduction

In 1975, Köhler and Milstein [1] developed a method that later earned them the Nobel Prize in Medicine in 1984 for the production of monoclonal antibodies from animals immunized with the substance that is to be studied or used diagnostically or therapeutically using hybridoma technology [2]. A hybridoma is a biologically engineered tumor derived from protein-producing tumor cells that have been immortalized to produce the desired antibody. Hybridomas were originally developed using mouse B cells, but with the advent of recombinant DNA technology, chimerization and humanization are being used to produce safer and more effective antibodies [3].

The use of monoclonal antibodies represents a form of immunotherapy using passive immunity in which preformed antibodies against a target antigen are injected into the body. This form of immunotherapy has opened the possibility of using these agents in a wide variety of therapeutic roles. In 1986, OKT3 anti-CD3, also known as muromonab-CD3 or Orthoclone-OKT3 (Janssen-Cilag, Titusville, NJ), used for

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S. Clienti · E. Basile  
Institute of Internal Medicine, S. Marta Hospital,  
Azienda Ospedaliero-Universitaria “Policlinico-Vittorio  
Emanuele”, Università di Catania,  
Catania, Italy

J. B. Morjaria  
IIR Division, School of Medicine, University of Southampton,  
Southampton General Hospital,  
Southampton SO16 6YD, UK

R. Polosa (✉)  
Dipartimento di BioMedicina Clinica e Molecolare,  
Università di Catania,  
Institute of Internal Medicine and Clinical Immunology,  
S. Marta Hospital,  
Via G. Clementi, 36,  
95124 Catania, Italy  
e-mail: polosa@unict.it

prevention of acute rejection in renal transplantation, became the first murine monoclonal antibody approved for human use by the US Food and Drug Administration (FDA) [4]. In 1997, the FDA approved rituximab as the first monoclonal antibody to treat B-cell, non-Hodgkin's lymphoma resistant to other chemotherapy regimens [5], which was soon followed by trastuzumab in 1998 for the treatment of certain types of breast cancer [6].

Currently, this form of immunotherapy is used for vaccination against infectious diseases, after organ transplantation for rejection prophylaxis, for cancer treatment (solid organ and blood related), and for the treatment of chronic illnesses such as rheumatoid arthritis and ulcerative colitis. The spectrum of disease states in which monoclonal antibodies have been approved for therapeutic use includes not only rheumatologic, dermatologic, autoimmune, oncologic, hematologic, cardiovascular, and gastrointestinal conditions, but also respiratory and allergologic diseases. In 2003, the FDA authorized omalizumab for use in treatment of asthma [7].

Asthma is a complex syndrome characterized by several clinical, functional, and inflammatory phenotypes [8]. The bulk of asthma patients have mild to moderate disease that can be easily controlled by regular use of inhaled corticosteroids (ICS) combined with short-acting inhaled  $\beta_2$ -agonists for relief of symptoms. However, for some patients, asthma continues to be poorly controlled with regard to persistent symptoms, frequent exacerbations, significant airway obstruction, and regular requirement for  $\beta_2$ -agonists despite treatment with high-dose systemic steroids and other available therapies [9]. These patients are at risk of developing steroid-related side effects [10], and account for about 60% of asthma-related health care costs [11–13]. Despite the unmet need in this group of patients, the evidence base for the assessment and management of asthmatics with severe or refractory disease is small, and many unanswered questions remain [14]. Addressing problems such as persistently poor compliance, comorbidities, psychosocial factors, and persistent environmental exposure to allergens or toxic substances, all of which require complementary diagnostic and therapeutic approaches [15–17], may relieve some of the challenges posed by unmet needs in severe refractory asthma. Nevertheless, the need for safe and effective therapeutic approaches for severe refractory asthma is beyond doubt; the development of such therapies should be a main priority for the academic world and the pharmaceutical industry. Advances in our understanding of the complex cellular and molecular networks that characterize the inflammatory and immune phenotype of the most severe forms of chronic asthma may provide a mechanistic rationale and molecular targets for optimal drug development.

Thus, mast cells, eosinophils, epithelial cells, macrophages, neutrophils, dendritic cells, B cells, and activated T

cells (T-helper type 1 [Th1], Th2, regulatory T cells, Th17 cells) and their associated molecular pathways have been actively investigated as targets for novel therapeutics. Because of their specificity, monoclonal antibodies can efficiently target an antigen on a cell of interest and work by blocking the binding of cytokines, immunoglobulins, hormones, or proteins that promote certain unwanted functions (e.g., the inflammatory response) [18]. In the context of severe asthma, this has been recently translated into several biologic agents that interfere with several aspects of inflammatory signaling. Herein we review some of the currently available biologics that are approved or under investigation for use in treatment of severe asthma.

### Omalizumab Studies

The sentinel role of IgE in increasing allergen uptake by dendritic cells and activating mast cells and basophils for mediator release is central in the pathogenesis of allergic inflammation [19]. IgG antibodies specific for the C3 domain of IgE that block IgE binding to Fc $\epsilon$ RI (and Fc $\epsilon$ RII, CD23) were shown to inhibit allergen-induced inflammatory responses in mice and humans [20].

Omalizumab (Xolair; Genentech, South San Francisco, CA and Novartis, Basel, Switzerland) is a recombinant DNA-derived humanized, IgG $_1\kappa$ , nonanaphylactoid monoclonal antibody that selectively binds to circulating human IgE. Once bound, the circulating IgE become biologically inert and is progressively removed from the circulation via the reticuloendothelial system. The level of free circulating IgE decreases rapidly, reducing mast cell and basophil degranulation and downregulating the Fc $\epsilon$ RI binding site on these effector cells [21, 22].

Subcutaneous administration of omalizumab has been shown to decrease the frequency of asthma attacks, reduce occurrence of exacerbations, improve symptom control, and reduce the need for ICS and  $\beta$ -agonists in phase 2 and 3 trials of severe atopic asthmatics who have symptoms despite receiving maximal treatment [23, 24].

Omalizumab is safe and currently the only monoclonal antibody approved as add-on therapy for use in severe, persistent allergic asthma [25]. Key criteria for omalizumab use include documented evidence of frequent exacerbations, serum total IgE between 30 and 700 IU/mL, and evidence of specific allergen sensitivity (by skin testing or radioallergosorbent test). Despite growing evidence that anti-IgE treatment may also be beneficial to patients suffering from other IgE-related conditions (including allergic rhinitis, peanut allergy, latex sensitivity, atopic dermatitis, and allergic bronchopulmonary aspergillosis) and from some IgE-unrelated diseases (e.g., autoimmune chronic urticaria) [26], to date, omalizumab is not approved for treatment of nonasthma conditions.

The positive performance of omalizumab in early registrative trials has been replicated in recent studies. In a double-blind, placebo-controlled (DBPC) study of 315 Japanese patients with uncontrolled moderate to severe asthma, the use of omalizumab for 16 weeks elicited a statistical increase in the morning peak expiratory flow and a reduction in the odds of experiencing an asthma exacerbation compared with placebo [27]. Improvements in asthma symptom scores, daily life activity scores, sleep scores, and rescue medication usage in favor of omalizumab were reported, but they were not significant. Nonsevere adverse events were similar in both groups, but more injection site reactions were reported in the omalizumab group.

In another DBPC study, 576 children 6–12 years of age with a positive skin prick test to perennial allergens and a clinical history of multiple respiratory exacerbations despite medium to high doses of ICS were randomly assigned to receive omalizumab or placebo 2:1 in a 24-week fixed-steroid phase. This was followed by a 28-week adjustable-steroid phase [28•]. During the 24-week period, patients treated with omalizumab had a 31% reduction in clinically significant exacerbations compared with those receiving placebo, which increased to 43% over the whole 52-week study period. These reductions were noted in patients whether they were on long-acting bronchodilator agents or not. Global evaluation of treatment effectiveness scores were significantly improved in the omalizumab group, and no major safety issues were reported in the study. No significant improvements were noted in any other measured objective or subjective parameters, but changes were generally in favor of patients on omalizumab.

In a pooled analysis examining the efficacy of omalizumab in adolescents (12–17 years of age) with moderate to severe asthma inadequately controlled with ICS, it was reported that mean use of systemic corticosteroids for asthma exacerbations was markedly lower in the omalizumab group compared with placebo, with a relative risk of 0.47 [29]. Additionally, significant improvements in the actual and predicted forced expiratory volume in 1 s (FEV<sub>1</sub>) and symptom and global evaluation of treatment effectiveness scores, as well as a reduction in the number of missed school days were shown in those on omalizumab when compared with placebo.

Omalizumab dose is calculated to result in neutralization of free IgE to levels less than 5% at baseline (0.016 mg/kg of omalizumab per IU/mL per 4 weeks) and takes into consideration the patient's baseline total serum IgE and body weight. The decision on the dose and frequency of administration can be made by simply using standardized dosing tables. However, it is uncertain whether such models can invariably predict clinical response [30, 31]. Slavin et al. [32] used a pharmacokinetic/pharmacodynamic model to examine the relationship between omalizumab, free IgE,

and clinical outcomes in patients with severe, persistent allergic asthma from a large DBPC study (INNOVATE [Investigation of Omalizumab in Severe Asthma Treatment]) and from a bioequivalence study (single-dose, parallel-group study of omalizumab in healthy atopic individuals with IgE levels of 30–300 IU/mL). The model accurately fitted omalizumab and free total IgE, correlating well with changes in clinical measures of asthma (symptom scores, peak expiratory flow, and rescue medication usage). Notably, whereas administration of omalizumab caused free total IgE to fall rapidly below the target of 50 ng/mL, clinical improvements occurred after an extended period of time, indicating a clear time-dependent and concentration-dependent relationship between total IgE and clinical outcomes (particularly in omalizumab-treated responders). This relationship displayed characteristic hysteresis loops, indicating a significant disconnection between decreases in total IgE levels and downstream physiologic events such as clinical asthma symptoms. In a further recent pharmacokinetic/pharmacodynamic omalizumab study, Lowe et al. [33] confirmed the observations made by Slavin et al. [32] given that their model also accurately predicted that reduction in free total IgE levels correlated well with improvements in clinical asthma symptoms. However, in this study, a target level of 14 ng/mL of free IgE at the midpoint of the 4-week clinical observation period was considered to be the marker for determining the dose and regimen for omalizumab. Given the clear clinical end point–linked biomarker criterion, this model aids in deducing doses and regimens for narrow subsets of patients, thus potentially improving on currently available dosing tables.

Recent international asthma guidelines advise the use of omalizumab as an alternative or in addition to oral corticosteroids in step V patients and in uncontrolled patients with severe allergic disease and increased levels of IgE [34]. However, the capacity of this drug to exert a significant steroid-sparing effect has been tested in several studies but remains to be established, given that omalizumab was studied mainly as add-on therapy in moderate and severe asthma patients not routinely receiving oral corticosteroids. In a recent uncontrolled clinical study of corticosteroid-dependent severe asthma, a substantial safe decrease in oral corticosteroid requirements was observed resulting to at least some extent from omalizumab therapy [35].

## Monoclonal Antibodies Against Tumor Necrosis Factor- $\alpha$

As for the pathogenic mechanisms of rheumatoid arthritis, Crohn's disease, and psoriasis, strong evidence now exists for tumor necrosis factor (TNF)- $\alpha$  playing a key role in the

pathogenesis of chronic inflammatory disorders of the airways, such as severe asthma and chronic obstructive pulmonary disease [36, 37]. TNF- $\alpha$  is a multifunctional proinflammatory cytokine. As asthma severity increases, there is predilection toward a Th1 inflammatory profile and an overexpression of TNF- $\alpha$  [8, 38]. Considering the need for alternative treatments for asthmatic patients with severe disease who are particularly resistant to conventional therapy, molecules targeted at blocking the effects of TNF- $\alpha$  may be useful.

One proof-of-concept study [39], one controlled clinical trial [40], and one DBPC [41•] study have been conducted using the soluble TNF receptor etanercept; although the former two showed marked improvements in subjective and objective asthma measures, the latter only showed some subjective improvements. A large, randomized controlled, multicenter study assessing the efficacy and safety of etanercept (25 mg twice weekly) in patients with moderate to severe persistent asthma was recently completed [42•]. Akin to the other studies, it was carried out over 12 weeks. However, no improvements were observed in any of the subjective or objective parameters measured. An important finding was that there were no safety issues, and the drug was well-tolerated. Unfortunately, no studies have investigated the efficacy/safety of the well-known chimeric mouse/human monoclonal anti-TNF- $\alpha$  antibody infliximab in chronic severe asthma. More recently, in 309 patients with severe, persistent asthma randomly assigned to receive placebo or three increasing doses (50, 100, and 200 mg) of the humanized monoclonal antibody golimumab, no significant improvement in any of the efficacy measurements was reported, and the study was terminated prematurely due to the number of severe infections and solid malignancies in the golimumab groups compared with the placebo group [43•]. Of note, post-hoc analysis indicated that patients on golimumab (100 and 200 mg) with a 12% or greater prestudy reversibility of FEV<sub>1</sub> with ICS and a history of sinusitis were less likely to experience severe asthma exacerbations.

It should be noted that patients enrolled in the larger studies by Morjaria et al. [41•], Holgate et al. [42•], and Wenzel et al. [43•] had milder disease compared with those investigated in the smaller studies by Howarth et al. [39] and Berry et al. [40]. Also, if a severe asthma patient fails one anti-TNF drug, he or she may still respond to others, as in rheumatoid arthritis. Therefore, it is possible that in patients with more severe disease, anti-TNF- $\alpha$  therapy may still be efficacious. It is unfortunate that in view of the conflicting efficacy findings and potential safety problems encountered in the published studies, no further trials with anti-TNF- $\alpha$  agents for treatment of severe asthma have been planned.

## Monoclonal Antibodies Against Interleukin-5

Eosinophil infiltration and degranulation in bronchial airways has been implicated in the pathology of asthma [44]. Interleukin (IL)-5, which is most specific to eosinophils, is responsible for eosinophilic growth, differentiation, mobilization, recruitment, activation, and survival [45]. Hence, antagonizing IL-5 with monoclonal antibodies may be a beneficial therapy for asthma, particularly for eosinophilic-predominant asthma. However, early clinical trials in individuals with mild to moderate asthma failed to show significant clinical or functional improvement [46–48].

Recently, two small DBPC trials have reassessed the role of the eosinophil–IL-5 pathway in more severe forms of asthma by testing the effect of the anti-IL-5 monoclonal antibody mepolizumab on asthma exacerbations in subgroups of patients with persistent airway eosinophilia despite systemic corticosteroid therapy [49•, 50•]. In the study by Nair et al. [50•], 20 patients with prednisone-dependent asthma and sputum eosinophilia received intravenous infusions of mepolizumab or placebo on a monthly basis. The protocol design included a prednisone tapering phase, which was started soon after the second infusion. At the 8-week follow-up, the authors reported a significant reduction in asthma exacerbations; clinically important dose reductions in prednisone use; improvements in FEV<sub>1</sub> and patient's related outcome measures (e.g., Juniper's Asthma Control Questionnaire [ACQ]); and, as expected, a clear reduction in blood and sputum eosinophil counts from baseline in the mepolizumab arm. The clinically important prednisone-sparing effect without the development of asthma exacerbations or deterioration of other physiologic and clinical factors is perhaps the most important finding; the size of the effect observed with mepolizumab is far greater than those reported in the large majority of the trials with immunomodulatory therapies [51]. In the study by Haldar et al. [49•], patients with refractory eosinophilic asthma and recurrent, severe exacerbations of their disease were recruited to receive 12 doses of intravenous mepolizumab ( $n = 29$ ) or placebo ( $n = 32$ ) on a monthly basis. These authors reported a significant mean 12-month reduction in asthma exacerbations and improvement in Juniper's Asthma-related Quality of Life Questionnaire in favor of mepolizumab. No improvements were observed in any of the other clinical parameters assessed. Akin to the study by Nair et al. [50•], they showed a significant reduction in blood and sputum eosinophil counts in the patients receiving mepolizumab compared with placebo. No serious risks or adverse events associated with the administration of mepolizumab were reported in either study.

Taken together, these findings suggest that antagonizing IL-5 with monoclonal antibodies may be beneficial in carefully selected subgroups of patients with refractory asthma and evidence of eosinophilic airway inflammation. Unfortunately, most patients with severe asthma do not have eosinophilia, and even in patients with eosinophilic asthma, mepolizumab appears to have only a negligible effect on other physiologic and clinical factors.

Given that clinically important steroid tapering is highly desirable in this population, larger studies should also establish the steroid-sparing effect of mepolizumab in unselected patients with severe refractory asthma. A DBPC, dose-ranging, efficacy and safety study with intravenous mepolizumab (75, 250, and 750 mg) administered every 4 weeks over a 52-week treatment period in patients with severe, uncontrolled, refractory asthma is currently ongoing [52].

### Monoclonal Antibodies Against T Cells

Activation of distinct T-cell endotypes has been largely implicated in the initiation, maintenance, and progression of the chronic inflammatory response of the airways in asthma [53]. The nonspecific reduction in the number of circulating T cells achieved by the chimeric anti-CD4 monoclonal antibody keliximab may have an overall beneficial effect in patients with severe corticosteroid-refractory asthma [54]. Keliximab yielded a significant increase in morning and evening peak expiratory flow compared with placebo, and these changes were accompanied by a decrease in symptom scores, but use of this drug did not reach statistical significance in patients with corticosteroid-refractory asthma [55].

Specifically, elevated CD25<sup>+</sup> T cells, IL-2, and soluble (s) IL-2 receptor- $\alpha$  chains (sCD25) have been demonstrated in the airways of patients with severe asthma [56–58]. With this in mind, Busse et al. [59] conducted a study to evaluate the efficacy and safety of a humanized monoclonal antibody directed against the  $\alpha$  (CD25) subunit of the high-affinity IL-2 receptor, daclizumab, in patients with moderate to severe asthma. A total of 115 patients on medium- to high-dose ICS were switched to an equivalent dose of inhaled triamcinolone and then randomly assigned to receive infusions of daclizumab ( $n = 88$ ) or placebo ( $n = 27$ ) every 2 weeks for 12 weeks. The protocol design included an ICS tapering phase of 8 weeks while on the study drug and a follow-up phase of 16 weeks off the study drug. These authors reported small but significant improvements in FEV<sub>1</sub>, daytime asthma symptoms, increased time to exacerbation, and short-acting  $\beta_2$ -agonist use in the daclizumab study group. 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 reactions and viral meningitis. This small study demonstrated that daclizumab may have a role in asthma, but further studies are needed to identify subsets of severe asthmatics in whom there may be a role for daclizumab as add-on therapy.

### Monoclonal Antibodies Targeting the Interleukin-4/Interleukin-13 Pathway

IL-4 and IL-13 have been reported to promote IgE production, mucus hypersecretion, bronchial hyperresponsiveness, acute inflammatory processes, and underlying structural changes to the airways [60–62]. Both IL-4 and IL-13, which share the IL-4 receptor  $\alpha$  (IL-4R $\alpha$ ) subunit in their cognate receptors, activate signal transducer and activator of transcription factor 6 to manifest their biological activity [62, 63]. Biological compounds targeting these molecules may provide a new therapeutic modality for patients with uncontrolled severe asthma.

Using this concept, a mutant IL-4 protein that inhibits the binding of IL-4 and IL-13 to IL-4R $\alpha$  complexes, pitrakinra (AER 001; Aerovant, Aerovance, Berkeley, CA), has entered phase 2 clinical trials for the treatment of asthma. Encouraging preliminary proof-of-concept data from a phase 2a trial have been reported from an antigen challenge study wherein a dry powder formulation of pitrakinra (60 mg delivered via inhalation) reduced the severity of late asthmatic response by 72% [64]. A large, multicenter, dose-ranging, randomized controlled trial in patients with severe uncontrolled asthma is currently in progress [65].

Antagonizing the effects of IL-13 could also be achieved by administering IL-13 receptor-specific monoclonal antibodies. Corren et al. [66•] recently published the results of a phase 2 DBPC, multiple-dose, clinical trial in moderate to severe asthmatics evaluating the efficacy and safety of AMG 317, a fully human monoclonal IgG<sub>2</sub> antibody that binds with high affinity to IL-4R $\alpha$ . A total of 294 individuals on ICS (200–1,000  $\mu$ g) were randomly assigned to receive subcutaneous AMG 317 at doses of 75 ( $n = 73$ ), 150 ( $n = 73$ ), or 300 mg ( $n = 74$ ), or placebo ( $n = 74$ ) for 12 weeks. Overall, there were no significant differences in the primary end point (ACQ scores) or any of the secondary clinical end points among any of the doses of AMG 317 and placebo. However, patients on AMG 317 experienced numerically fewer asthma exacerbations, and those on the higher dose of AMG 317 (300 mg) and in the top tertile of ACQ scores had a constant trend of more clinically meaningful effect in changes in ACQ, FEV<sub>1</sub>, morning peak flows, and asthma exacerbations.

## Targeting Stem Cell Factor Receptor (c-kit)/Platelet-derived Growth Factor Receptor Tyrosine Kinase Inhibitor

Dendritic and mast cells have been implicated in severe asthma; they are activated via the binding of stem cell factor receptor c-kit [8, 67, 68]. Antagonism of the stem cell factor/c-kit pathway leads to a reduction in mast cells, histamine levels, eosinophil infiltration, IL-4 synthesis, and bronchial hyperresponsiveness [68]. Furthermore, growth factors such as platelet-derived growth factor have been reported to contribute to airway remodeling [69, 70]. Masitinib is a tyrosine kinase inhibitor that effectively and specifically inhibits c-kit and platelet-derived growth factor receptors [71].

Using this principle, Humbert et al. [72] conducted a phase 2a, 16-week, DBPC, multicenter study in 44 individuals with severe persistent asthma to assess the efficacy and safety of masitinib in this population. The participants were randomly assigned to receive oral masitinib at doses of 3 ( $n = 12$ ), 4.5 ( $n = 11$ ), or 6 ( $n = 10$ ) mg/kg per day, or placebo ( $n = 11$ ) in 3 phases: a 4-week stable corticosteroid dose, 8-week oral corticosteroid reduction phase, and 4-week stabilization period for observation. They reported no significant difference with respect to oral corticosteroid weaning, which was the primary end point, or airway function parameters (secondary end points). However, there was a significant improvement in the ACQ score in favor of masitinib. Due to the small sample size, no intradose comparisons were possible, but among patients on high-dose oral corticosteroids ( $>15$  mg of prednisolone equivalent) who received masitinib, six were able to be weaned of oral corticosteroids, compared with none in the placebo group. Moreover, patients receiving masitinib had more minor and serious (nonrespiratory) adverse events compared with those on placebo. Although the authors have suggested that larger studies need to be conducted to evaluate the role of masitinib in severe asthma, this pilot study only showed an improvement in asthma control despite oral corticosteroid withdrawal. It was small, had many dropouts due to drug-related causes, and poor outcomes on objective markers assessed.

## Conclusions

Even though understanding of the disease has improved considerably over the past 10–20 years, this has not been translated into a notable clinical advantage for severe asthma sufferers. In fact, findings with current biologics in the treatment of severe asthma have not been very exciting overall. This could be because medicines blocking the action

of individual biological pathways may not be enough to efficiently suppress inflammation and control remodeling. There are also concerns about long-term safety (i.e., the possibility of increased infections and malignancies).

Careful patient selection coupled with meticulous monitoring for adverse effects would appear to make these therapeutic options useful add-on alternatives, but only in a few selected patients. Nonetheless, the definitive importance of careful phenotypic classification of patients with severe asthma will be established only when detailed characterization of hundreds of patients is completed and analyzed, as proposed in the newly established pan-European consortium Unbiased Biomarkers for the Prediction of Respiratory Disease Outcome (U-Biopred) [73]. Whatever the outcomes of these research programs, pharmacoeconomic concerns also should be taken into account given the elevated acquisition costs of recombinant human monoclonals and of the diagnostic screening procedures for the identification of potential responders.

**Disclosure** Dr. Polosa has received grant support from CV Therapeutics and NeuroSearch A/S; has served as a speaker for CV Therapeutics, Novartis, Merck & Co., and Roche; has served as a consultant for CV Therapeutics, Duska Therapeutics, and NeuroSearch A/S; has received payment for development of educational presentations (including service on speakers' bureaus) from MSD Pharma and Pfizer; and has had travel/accommodations expenses covered/reimbursed by CV Therapeutics, NeuroSearch A/S, MSD Pharma, and Pfizer. Drs. Cliente, Morjaria, and Basile reported no potential conflicts of interest relevant to this article.

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