

Biologics for the Treatments of Allergic Conditions

Severe Asthma



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KEYWORDS

• Severe asthma • Anti IL-33 • Benralizumab • Dupilumab • Mepolizumab
• Omalizumab • Reslizumab • Tezepelumab

KEY POINTS

- Currently marketed biologics for severe asthma provide a revolutionary treatment option by selectively targeting specific steps of the immune inflammation cascade within the Th2 high patterns.
- Upcoming molecules are able to address epithelial and innate immunity potentially allowing to a better management of severe asthma beyond Th2 high phenotypes.
- A permanent disease-modifying effect of biologics is not yet completely clear so that optimal treatment duration, the possibility of a dose treatment modulation, the place and relevance of ICS in best responders still represent controversial aspects.
- Long-term safety, especially when interacting with epithelial and innate immunity needs to be further investigated and should be carefully evaluated in patient selection.
- Both basic research and real-word evidence are needed to address the open challenges and unmet needs.

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INTRODUCTION

Patients with asthma requiring a second controller and/or systemic corticosteroids for a satisfactory disease control, although regularly treated with high-dose inhaled corticosteroids, are affected by severe asthma. Similarly, patients whose disease remains uncontrolled despite the previously mentioned pharmacologic strategies are defined as having severe asthma. This definition comes from the recent International European Respiratory Society/ American Thoracic Society (ERS/ATS) guidelines.^{1,2} According to the Global Initiative for Asthma (GINA) international recommendations, daytime symptoms (more than twice a week), night-time symptoms, activity limitation, and the need for rescue medication more than twice a week represent the hallmarks of poor asthma control. In particular, if at least 3 of the previously mentioned conditions occur, the patient is experiencing uncontrolled asthma.³

The prevalence of severe asthma lacks of univocal estimation, ranging from 1.8% to 38% in different studies.⁴⁻⁶ Differences in terms of population samples, definitions, and methodology characterizing the published reports may account for that variability. On the other hand, severe asthma, in particular when difficult to control, is undoubtedly responsible for the major burden of the disease in terms of both social and economic implications. In fact, major asthma exacerbations, asthma-related emergency room admissions, hospitalizations, and overall quality-of-life impairment are typical features of the severe phenotype in comparison with the mild or moderate ones.^{4,7} The known complex cross-talking between genetic heterogeneity and environmental triggers, and the relevance of difficult to manage comorbidities may provide an explanation to severe asthma burden despite the variety and quality of traditional treatment options. In fact, severe asthma management still represents a major challenge for clinicians and affected patients.^{1,8}

Biologic drugs are determining a true revolution in the field. Recently marketed, they are able to selectively target one or more molecular players by blocking their effect within the inflammation cascade.⁹ The currently available biologics are mostly active on Th2/eosinophilic phenotype molecules.¹⁰ The so-called Th2 high inflammatory pattern characterizes most patients affected by severe asthma; however, ongoing pharmacologic and clinical research is exploring new treatment options able to interact with Th2 low phenotypes, although regarding a smaller proportion of patients, but still difficult to treat due to reduced response to inhaled corticosteroids (ICS) and oral corticosteroids (OCS).²

Currently placed as an add on therapy for patients not satisfactory controlled by GINA step 5 treatment options, biologics provide a unique opportunity to improve the quality of life of patients with severe asthma by definitely achieving disease control and reducing/stopping their oral steroid dependence.^{2,3} Under a wider perspective, the use of biologics allows to contain indirect costs and the socio-economic burden of severe asthma.

The present work aims at providing an overview of the evidence on immunologic and clinical effects of biologic drugs, including a focus on the current unmet needs in the field.

A PubMed and Medline search was performed. The following keywords were selected: severe asthma, dupilumab, omalizumab, reslizumab, mepolizumab, benralizumab, tezepelumab, immunology of severe asthma. Papers published up to Dec 2019 were considered. Original articles, randomized clinical trials, and review papers relevant to the topic were evaluated for inclusion in the review.

BIOLOGICS FOR SEVERE ASTHMA: WHAT'S ON**Omalizumab**

Mechanism

Omalizumab is a humanized monoclonal antibody, able to bind the site for high affinity of immunoglobulin (Ig)E receptor, leading to blocking interaction of the Ig with FcεRI located on mast cells, antigen-presenting cells, and basophils.^{11–13} The action on these cells reduces the production of type 2 cytokines and T2 inflammation.¹⁴ Studies carried out on omalizumab have also shown that this drug is able, through an action on IgE carrier B cells, to cause a state of anergy causing a reduction/suspension of the response to antigenic/allergenic stimulation¹⁵ (**Fig. 1**).

Target patients

Omalizumab has shown the best performance in adult and pediatric patients, with moderate-to-severe persistent asthma that a skin or in vitro positive perennial aeroallergen, whose symptoms are not adequately controlled by maximal inhalation therapy¹⁶ and with total IgE 30 to 700 IU/mL in those ages 12 and older and IgE 30 to 1300 IU/mL in those ages 6 to 11. The combined elevation of exhaled nitric oxide (FeNO) (≥ 19.5 parts per billion), peripheral blood eosinophils (≥ 260 per microliter), and periostin (≥ 50 ng/mL) was reported as a predictor of better response.¹⁷ However, according to more recent evidence, omalizumab efficacy is independent of the baseline blood eosinophilia.^{18,19}

Major outcomes

The marketed formulation is a subcutaneous injection at the dose of 0.016 mg/IgE in IU/mL $\times$ body weight in kilograms. Omalizumab has been extensively studied, both in clinical trials and in real life and has demonstrated excellent efficacy in reducing asthma exacerbations and the use of systemic corticosteroids in treated patients.²⁰ As happens also for all biological drugs in asthma, the efficacy of omalizumab is better in well-selected patients. Omalizumab was first marketed in 2003, when the US Food and Drug Administration approved the use of this molecule in the United States.¹⁶

From the analysis of 12 trials, for a total of 6427 patients, it was observed that the therapy, if used in addition to the ICS/long-acting beta2 agonists (LABA) combination, reduced the risk of exacerbations at the end of the study (relative risk, RR = 0.57) and the need for systemic corticosteroid therapy (RR 1.80, 95% confidence interval [CI] = 1.42–2.28).^{16,21} Similar promising results were also observed in improving quality of life, as measured by the Asthma Quality of Life Questionnaire, which is higher in patients treated with omalizumab than in control patients (0.33; 95% CI 0.27–0.38), but still lower than the minimally clinically important difference of 0.5.²² Similar efficacy could be observed in lung function tests.¹⁶ Therefore considering the clinical data from the randomized controlled trials, the clinician should focus on reducing systemic steroid use and exacerbations in patients treated with omalizumab, and to a lesser extent on the variation of the quality of life and respiratory function questionnaires, both results not always varied by therapy.

Mepolizumab

Mechanism

Mepolizumab is a humanized murine IgG1k monoclonal antibody. By selectively targeting the α -chain of interleukin (IL)-5 it prevents its binding to IL-5 receptor α (IL-5R α), which is expressed on the surface of eosinophils and basophils.²³ As a consequence, eosinophil differentiation, activation, and growth are inactivated²³ (see **Fig. 1**). Of note, the reported 70% block of eosinophil maturation in the bone marrow,

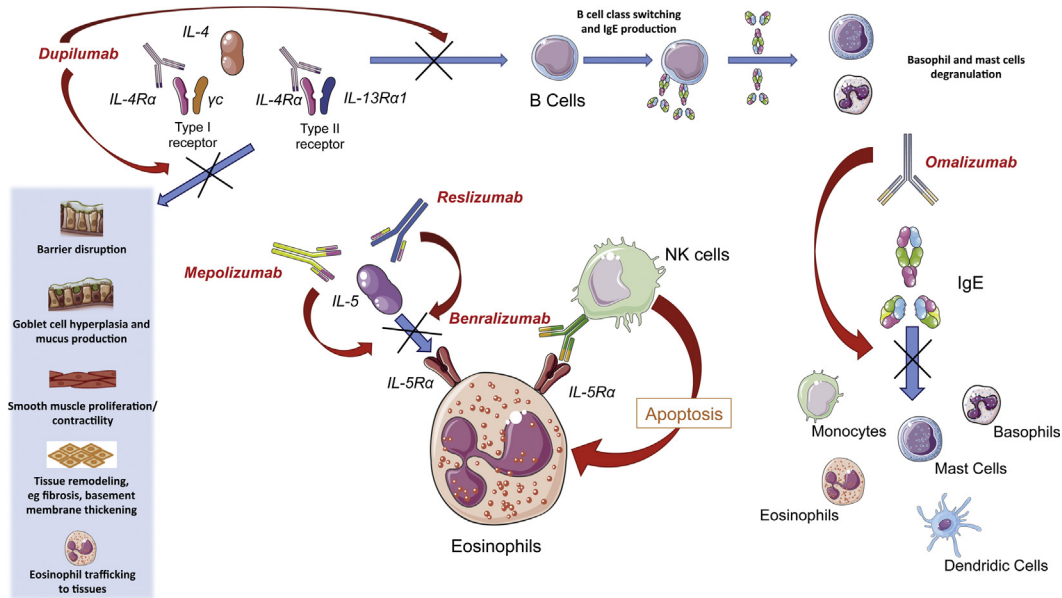


Fig. 1. Overview of main mechanisms of the currently available biologic drugs.

including a partial but significant depletion of eosinophil myelocytes and metamyelocytes, has been described when a dose of 750 mg was administered intravenously.²⁴ On the opposite, the marketed dosing regimen did not show to impact on eosinophil progenitors in the blood or bone marrow while a restart of physiologic eosinophil maturation has been detected approximately 3 months after mepolizumab discontinuation. It may account for the fast airway inflammation and asthma symptoms relapse.^{24–26} Concerning bronchial district, a dose-dependent but still partial (and not significant with mepolizumab 100 mg)²⁴ eosinophil depletion has been observed.^{25,27} Of note, IL-5 cannot be considered the only cytokine regulating the eosinophil bronchial homing; in fact other molecules including eotaxin, which are not targeted by mepolizumab, may play a relevant role.^{9,25}

Target patients

Blood eosinophil count ≥ 300 cells/ μ L has been identified as the minimum requirement for the best response to mepolizumab within the population with severe asthma.^{23,27} Higher eosinophil count may predict even better response regarding specific parameters. A post hoc analysis of DREAM and MENSA trials highlighted that the lung function increase was more evident for patients with baseline eosinophil counts ≥ 500 cells/ μ L.²⁸ Also, the exacerbation rate reduction was greater in patients with 3 or ≥ 4 (but not in that with 2) exacerbations in the previous year.²⁷

On the opposite, body mass index did not result to be a covariate for exacerbation rate in the analysis of the DREAM trial.²⁷ The presence of nasal polyps does not seem to affect mepolizumab benefit on asthma, although the drug effect on that comorbidity is controversial.^{29,30}

Major outcomes

The approved dose of mepolizumab is 100 mg every 4 weeks. The major clinical outcomes demonstrated by the published trials and subsequent analyses include asthma exacerbations and systemic glucocorticoid.³¹ A 30% to 50% reduction in number of exacerbations and a 50% decrease of oral steroid (OCS) dose (odds ratio 2.39 for mepolizumab vs placebo [95% CI 1.25–4.56; $P = .008$]), were overall described in treated patients.^{32,33} More in detail, SIRIUS trial reported a 90% to 100% OCS reduction in 23% of patients and a 75% to less than 90% OCS reduction in 17%. In 36% of active group (vs 56% of placebo group) no OCS change was observed.³²

A significant improvement of lung function, more consistent in patients with baseline eosinophil counts ≥ 500 cells/ μ L, was shown by most of studies.^{28,33,34}

Reslizumab

Mechanism

Reslizumab is a recombinant humanized IgG4k monoclonal antibody able to block IL-5 and interfere with its functions.¹⁰ Its mechanism of action is similar to mepolizumab (see Fig. 1). The only substantial difference with mepolizumab is regarding the intravenous way of administration. Tailoring the dose through a weight-adjusted approach seems to provide an additional opportunity and a more robust pharmacologic effect according to some evidence³⁵; a further reduction of airways eosinophilia (sputum eosinophilia), in comparison with mepolizumab, has been described; however the topic is under debate.³⁶

Target patients

Blood eosinophil count ≥ 400 cells/ μ L and 12% forced expiratory volume in 1 second (FEV1) reversibility characterize the best responders to reslizumab among patients

with severe asthma.³⁷ The coexistence of (self-reported) chronic sinusitis with nasal polyposis (CSwNP) seems to enhance reslizumab effect on asthma control.

Major outcomes

Reslizumab is approved at the dosage of 3 mg/kg every 4 weeks. It demonstrated to determine a 50% to 59% reduction of the annual exacerbation rate when compared with placebo.³⁷ The same effect rises to 83% in patients with CSwNP and higher blood eosinophilia level (400 cells/ μ L). A significant increase in time to first exacerbation and in the number of patients with a year free of exacerbations has also been described,³⁸ together with pre-bronchodilator FEV1 improvement. Reslizumab was also responsible for a 70% to 50% decrease in OCS daily dose.

Benralizumab

Mechanism

Benralizumab, a fully humanized afucosylated IgG1 κ monoclonal antibody, selectively binds an IL-5 receptor α (IL-5R α) epitope and interferes with IL-5 signaling, independently of the ligand presence.³⁹ IL-5 R α is restrictedly expressed on eosinophils and basophils, but also on their progenitors in the bone marrow, thus it provides the right target for selective cell depletion.⁴⁰ Benralizumab depletes IL-5R α -expressing cells through a second way, that is an antibody-directed cell-mediated cytotoxicity (see Fig. 1). The previously mentioned afucosylation of the monoclonal antibody oligosaccharide core significantly enhances the affinity to human Fc γ receptor IIIa (Fc γ RIIIa), mainly expressed on natural killer (NK) cells. When activated by interaction with benralizumab, NK cells contribute to a robust depletion of eosinophils in the bone marrow and blood, and to an almost complete depletion in sputum and tissues.³⁹ No evidence of a similar effect, which seems to sustain a more consistent clinical effect,³⁹ is currently available for other anti-IL-5 drugs.

Target patients

Benralizumab has demonstrated the greatest effect in patients with severe asthma and blood eosinophils ≥ 300 cells/ μ L.⁴¹ A pooled analysis of the SIROCCO and CALIMA studies looked for predictors of enhanced response to benralizumab.⁴² Besides peripheral eosinophils, OCS dependence, the presence of nasal polyposis, and forced vital capacity less than 65% of predicted were identified as relevant parameters. More precisely, according to a similar post hoc analysis,⁴³ patients combining at baseline high blood eosinophils and a history of 3 or more exacerbations in the previous year experienced a more robust reduction of annual exacerbation rate during the treatment course. In addition, the coexistence of obesity or fixed airflow obstruction before the treatment start did not hamper the positive impact of benralizumab on lung function.⁴¹

Major outcomes

The recommended dose of benralizumab is 30 mg every 4 weeks for the first 3 doses, and then every 8 weeks.⁴¹ In patients with ≥ 300 blood eosinophils/ μ L, 3 main clinical outcomes were reported and confirmed by different studies: (1) asthma exacerbation rate. According to SIROCCO and CALIMA trials,^{44,45} benralizumab reduced asthma exacerbations by approximately 50% and 36% (28% for the every 8-week dosing arm), respectively. (2) Oral steroid intake. A median OCS reduction 75%, versus 25% in the placebo group was observed during the treatment ($P < .001$).⁴⁶ (3) Lung function. A clinically significant improvement of pre-bronchodilator FEV1 was reported by the BISE study. The change was greater than 80 mL (95% CI 0–150; $P = .04$) after 3 months of therapy.⁴⁷

Of note, due to its peculiar mechanism, benralizumab action is independent of IL-5 levels, which can increase during asthma exacerbation. It provides the rationale for treating acute asthma exacerbations with benralizumab as well, although little evidence is available on that at the moment.⁴⁸

Dupilumab

Mechanism

Dupilumab is a fully humanized molecule able to bind, with high affinity and specifically, the α subunit of the IL-4 receptor, shared by the IL-4 type I receptor complex (IL-4 α / γ c) and IL-4/IL-13 type II receptor complex (IL-4 α /IL-13R α), and to inhibit the signal of both cytokines.⁴⁹ Therefore, due to the crucial role that these 2 cytokines play in type 2 inflammation, their inhibition is able to reduce/suppress the inflammatory response, the cytokine and chemokine cascade induced by their activity⁴⁹ (see [Fig. 1](#)).

Target patients

From the subanalysis carried out observing the characteristics of the patients enrolled in the registration studies, it was concluded that subjects with a more marked type 2 inflammation, characterized by high values of eosinophilia and exhaled nitric oxide (FeNO), are those who better respond to treatment with dupilumab.^{50–52} In particular, a post hoc study of QUEST⁵⁰ showed that patients with eosinophils and FeNO values above 150 cell/ μ L and 25 ppb, respectively, had better benefits. On the other hand, in the VENTURE⁵² study the biomarker statistics were not as clear-cut, with the exception of severe exacerbations, which can be influenced overall by the FeNO value (with better outcome in the case of FeNO $\geq$ 50 ppb or $\geq$ 25 to < 50 ppb compared with < 25 ppb). A possible cause of these differences between the 2 studies could be the use of OCS by patients in the VENTURE⁵² study. Therefore studies show that dupilumab is able to modify the previously mentioned endpoints, statistically differently from placebo, in patients with blood eosinophilia less than 150 cell/ μ L or FeNO less than 25 ppb in QUEST⁵⁰ or in patients with less than 150 EOS/ μ L in VENTURE.⁵²

Major outcomes

As with other biological drugs developed for asthma, the effects of the molecule on exacerbations of disease and reduction of systemic corticosteroid use were primarily assessed in dupilumab studies.

In the main randomized controlled trials, dupilumab (200 or 300 mg every 2 weeks) was shown to significantly reduce the annual exacerbation rate by almost 50% in 52 weeks in the QUEST study, where this outcome was placed as the primary endpoint,⁵⁰ data confirmed by even shorter 24-week studies (DRI12544)⁵¹ and VENTURE.⁵² The hospitalization/response rate was also found to be reduced by 46.8% in QUEST. In addition to the already mentioned reduction of exacerbations, dupilumab has proven to be able to save OCS in dependent patients in the VENTURE study.⁵² In this study, dupilumab (300 mg every 2 weeks) made it possible to reduce the daily OCS dose significantly more than placebo at week 24 (end of OCS maintenance phase) with baseline (after OCS dosage optimization).

Further subanalysis showed that dupilumab was also able to reduce the steroid dose to < 5 mg prednisone in more than 50% of cases.^{52,53} Because it is a drug developed for a respiratory disease, pulmonary function, although not always as the primary outcome, has also been evaluated. Dupilumab was found to increase lung function in all studies, at both 200 and 300 mg every 2 weeks. The function values measured by FEV1 showed a significant increase after 12 and 24 weeks of treatment.^{50,51} The same

results were also observed after only 2 weeks of dupilumab therapy^{52–54} ($P < .001$ vs placebo where reported^{53,54}).

BIOLOGICS FOR SEVERE ASTHMA: THE NEAR FUTURE

The most recent advances in the field have suggested epithelial barrier dysfunction as the *primum movens* of asthma pathogenesis.⁹ Besides anatomic integrity, mainly related to genetic predisposition and smoking habit, epithelial barrier efficiency relies on innate immunity competence. An impaired immunologic first-line response may trigger an unbalanced inflammation, meaning Th2 polarized response and altered tissue repair processes leading to airway remodeling and further epithelial physical inefficiency.⁵⁵

In the light of that evidence, master cytokines regulating the cross talk between epithelial cells and innate/adaptive immunity have been identified as potential pharmacologic treatment targets. Among them, TSLP (thymic stromal lymphoprotein) and IL-33 are currently under investigation in clinical trials and will provide new therapeutic options in the near future.⁹

Tezepelumab

Mechanism

Tezepelumab is a humanized monoclonal antibody blocking TSLP by preventing the interaction with its receptor complex.⁵⁶ This cytokine expresses the innate immunity activation. Produced by the epithelium, it regulates dendritic cell functions, polarizes the differentiation of naive T cells into mature CD4 T cells, activates B cells, and regulates Th2 cytokine production (mainly IL-4, IL-5, IL-13). The last effect is also mediated by direct activation of ILC2 (innate lymphoid cells).⁵⁷

Target patients

When considering tezepelumab mechanism of action, its efficacy on both Th-2 high and low asthma phenotypes is quite clear. In fact, when activated by allergens or environmental stimuli, including viruses and pollutants, it interferes with the impaired immune response before its evolution in a Type 2 high or Type 2 low pattern and regardless the individual atopic status.^{9,56}

No specific markers of Th2 phenotype such as IgE or eosinophils were considered when selecting the study population of a recent phase 2b trial.⁵⁸ The study, the only one currently available, included adult patients with uncontrolled asthma (at least 2 exacerbations requiring systemic glucocorticoids in the previous year) despite medium-dose to high-dose inhaled glucocorticoid and long-acting β -agonist, FEV1 between 40% and 80% of predicted and at least a 12% and 200 mL improvement with bronchodilator.

Major outcomes

Exacerbation rate was 61%, 71%, and 66% lower than the placebo in the low-dose (70 mg subcutaneously every 4 weeks), medium-dose (210 mg subcutaneously every 4 weeks), and high-dose groups (280 mg subcutaneously every 2 weeks) respectively, regardless of initial eosinophil level. Also a significantly longer time to first exacerbation in patients receiving the medium-dose and high-dose tezepelumab versus placebo was observed, and all tezepelumab groups experienced a relevant pre-bronchodilator FEV1 increase versus placebo.⁵⁸

Anti-Interleukin-33

IL-33 belongs to alarmins family and is produced by epithelial cells in response to the interactions with environmental triggers or inflammatory factors. Its activation

depends on protease digestive process of its pro-cytokine form.⁵⁹ In view of its functions, IL-33 is believed to play a key role both in type 1 and type 2 inflammation. In fact it interacts with innate immunity, particularly dendritic cells and it is also able to initiate a type 2 immunity inflammatory cascade by polarizing Th2 cells and ILC2 cells.⁶⁰ Very recently, a phase 2 12-week proof-of-concept trial, that enrolled 296 adult patients with moderate-to-severe asthma who were not well controlled on LABA and ICS therapy, evaluated IL-33 as a therapeutic target in severe asthma.⁶¹ REGN 3500, a humanized monoclonal antibody to all IL-33 molecules regardless of amino terminus, demonstrated its superiority versus placebo in significantly improving asthma control and lung function, with an optimal safety profile. The greatest effect was observed in patients with blood eosinophil levels ≥ 300 cells/ μ L. The potential use of anti-IL-33 antibody has not yet been evaluated by any regulatory authority, and an asthma clinical trial program is currently under development.⁶¹

REAL-LIFE PERSPECTIVE: RATIONALE AND MAJOR EVIDENCE

In parallel to the randomized controlled clinical trials, several real-life trials have been described. The importance of these evaluations also in real life is strategic for a better and greater understanding of the effects of a drug, otherwise studied only in selected patients. In fact, it is well known that patients in randomized clinical trials are usually younger, with better fitness and, above all, with fewer comorbidities than those who, once the drug is marketed, will use experimental drugs.^{62,63} The importance of real-life studies is also revealed with regard to the duration of treatment. The timing of randomized controlled trials is in fact generally short, with a mean duration of 6 to 12 months, inadequate to assess the long-term effects of the drugs, those of withdrawal after long periods of treatment, and disease control after discontinuation of treatment.

Particularly, it has been observed that patients with severe asthma, treated in real life, are very different from those in clinical trials, both for omalizumab²⁰ and mepolizumab.⁶⁴ Because of its long-standing commercialization, omalizumab has long been studied not only in randomized controlled trials, but also in real life.^{20,63} This type of study has made it possible to clarify and deepen what emerged in the trials regarding the safety, even after long periods of administration, the efficacy of the drug in patients with comorbidities and its impact on the latter.²⁰ Although there are unavoidable differences between the real-life population and randomized patients in the trials, with the former having a significantly lower FEV1 and a higher IgE level, the efficacy of the drug in symptom control, exacerbations and improvement of respiratory function is confirmed even after only 4 months of treatment.^{65–67} As said, one of the aims of studies in RL is to assess what happens when therapy is discontinued, and consequently to seek an optimal duration of therapy. In this respect, the results for omalizumab are not entirely straightforward. In fact, the data in real life are limited; recently a study conducted on 49 patients showed a persistent effect of more than 4 years after OMA interruption, extended to 6 years in 60% of cases.⁶⁸

Although mepolizumab has been developed and marketed, some data about real life are available. The efficacy in reducing exacerbations, OCS daily dose and steroid dependence has been demonstrated in a 1 year observational study performed on 138 patients.⁶⁹ Similar results were subsequently confirmed also in another observational trial performed on 61 patients with severe asthma.⁷⁰ The first study also described side effects of 12 months of administration, with few side effects and already well described in clinical trials, confirming a comforting safety profile.⁶⁹ Regarding safety profile, another study, on 143 patients, described only 6 discontinuations of the drug, 5 of them due to poor efficacy and only 1 because of the occurrence of adverse

events (urticaria).⁷¹ Real-life experience permitted also the observation of the effect of mepolizumab on patients previously treated with other biologic drugs, particularly omalizumab. Despite this has been performed in a clinical trial evaluating the effect of this therapeutic switch,⁷² usually in trials the previous administration of another monoclonal antibody is an exclusion criteria for randomization, and for this reason the data from these patients is quite poor. In a 1-year observational study, performed on 27 patients previously treated with omalizumab and switched to mepolizumab due to poor efficacy of the anti-IgE drug, a significant reduction of exacerbations, OCS intake, improvement of FEV1 has been proven.⁷³ As for omalizumab, also mepolizumab has been investigated in real life for its effect on lung function. In a multicenter observational Italian study, involving 134 patients with severe asthma, the effect of the administration of anti-IL-5 drug for 6 months on lung function tests has been observed, with an increase of FEV1 of approximately 200 mL.⁷⁴

Among the main objectives of research in severe asthma and in biologic therapies, there is the discovery of biomarkers able to predict the response to the drugs. In a sub-analysis of the DREAM study,²⁷ Ortega and colleagues²⁸ described the relationship between the baseline eosinophil level before mepolizumab administration and the response to the drug. In a subanalysis of an Italian real-life study instead has not confirmed a similar trend.⁷⁵

About reslizumab, a trial on 26 patients evidenced an efficacy of the drug in reducing exacerbations, glucocorticoid doses, and being also able to improve the control of the disease (measured with ACQ-6 questionnaire).⁷⁶ About benralizumab and dupilumab, due to their recent commercialization, only a few data about their efficacy in real life are available.

SUMMARY AND UNMET NEEDS

The opportunity to selectively interfere with specific steps of the immune inflammatory cascade and consequently achieve better or complete asthma control is something completely new in the field, and the revolution is still ongoing, including drugs under development and others very recently marketed.^{9,10} Despite a relatively limited experience, robust evidence supports a strong safety and efficacy profile for each one of the available biologics. On the other hand, whether these molecules are able to provide a long-lasting disease-modifying effect independent of treatment continuation, and when it occurs, is still under debate.⁹ For that reason, the optimal treatment duration, the possibility of a dose treatment modulation in high or poor responders, the place and relevance of ICS in best responders still represent controversial aspects. Among the everyday challenges clinicians using biologics have to face, the optimal patient selection represents a major one. In fact, low-nonresponders among patients matching prescription criteria and the theoretic best responder profile of that biologic are rather frequent, as well as subjects characterized by overlapping eligibility.^{8,77} A number of biomarkers have been explored but up to now no one is able to specifically predict the response to one biologic drug.⁷⁸ The research is still ongoing; focusing on composite indexes, including patients' comorbidities, could improve patients' selection accuracy and more in general biologic therapy sustainability.

Management of the so-called Th2 low phenotypes represents another major challenge. In fact, although regarding a smaller proportion of patients with asthma, they are usually characterized by poor response to steroids, whether systemic or inhaled, and frequent exacerbations. The currently available biologics are not able to specifically address Th2 low phenotypes.⁷⁹ However, the upcoming molecules targeting epithelial-innate immunity besides beyond eosinophilic pattern,

namely anti-TSLP and anti-IL-33, could provide an opportunity for some Th2 low phenotypes.

Most importantly, so far no one of the biologics currently in use have been related to major safety issues. In particular, eosinophil partial or complete depletion has not been related to any specific disease or dysregulation, in terms of infections, tumors, or autoimmune diseases, in animal models and human subjects.^{10,31} Although the premarketing research and real-life evidence when available have provided for all of them an optimal safety profile, which is also conceptually supported by their extremely selective way of action, the long-term safety remains something to be carefully investigated in the real-life setting. With regard to some upcoming molecules, interfering with innate and epithelial immunity may raise potential issues and suggest a very careful patient selection especially when other immune-mediated diseases coexist. However, apart from speculative considerations, the currently available evidence cannot support any warning or specific recommendation on the topic.

In conclusion, biologics for severe asthma have substantially contributed to increase the standard of care, to reduce drug (particularly OCS)-related morbidity, and most importantly to ameliorate patients' quality of life.

Both basic research and real-world evidence are needed to address the open challenges and unmet needs.

CLINICAL CARE POINTS

- Monoclonal antibodies targeting cytokines or their receptors within the severe asthma inflammation cascade are able to allow to achieve better or complete asthma control and to significantly reduce or interrupt the use of systemic steroids.
- According to the evidence coming from clinical trials and real-life studies, biologic therapies for severe asthma provide an optimal safety and tolerability profile; however, the potential long-term effects need to be carefully monitored.
- Some practical aspects related to the management of biologic therapies for severe asthma remain under discussion: the optimal treatment duration, the possibility of a dose treatment modulation in high or poor responders, the place and relevance of ICS in best responders.
- The optimal candidate selection to each biologic treatment still remains challenging, especially in patients with overlapping eligibility. A number of biomarkers have been explored but up to now no one is able to specifically predict the response to one biologic drug.

DISCLOSURE

The authors have nothing to disclose.

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