



REVIEW

Biologics in the treatment of severe asthma



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Abstract Severe asthma is defined as asthma which requires treatment with high dose inhaled corticosteroids and with a second controller drug to prevent it from becoming uncontrolled or which remains uncontrolled despite this therapy. Patients with uncontrolled severe asthma require additional treatment options as add-on therapy, including biologics. Biologic therapies in asthma are designed to block key immune regulators, such as IgE, or certain pro-inflammatory cytokines, e.g. interleukin (IL)-5, IL-4, IL-13 or IL-17. Patients with severe asthma and eosinophilic phenotype may benefit from biologic therapies aimed at reducing blood and tissue eosinophils, such as mepolizumab, reslizumab and benralizumab. Patients with Th2-high phenotype may also benefit from therapy with anti-IL-4/anti-IL-13 monoclonal antibodies (dupilumab). The main limitations of asthma treatment with biologic agents are the crossover and overlap of the different pathways in the pathogenesis of asthma which may cause lack of complete success of these therapies, in addition of high costs, which make pharmacoeconomic studies necessary to identify the ideal target patient population to receive these biologic drugs. © 2017 Published by Elsevier España, S.L.U. on behalf of SEICAP.

Introduction

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation. It affects over 1–18% of the population in different countries.¹

According to the International European Respiratory Society (ERS)/American Thoracic Society (ATS) consensus, severe asthma is defined as “asthma which requires treatment with high dose inhaled corticosteroids (ICS) and with a second controller (and/or systemic corticosteroids) to prevent it from becoming uncontrolled or which remains uncontrolled despite this therapy”.²

Nowadays, drugs used for the treatment of asthma diminish airway inflammation and relieve bronchospasm, but they do not offer a cure, which means that when treatment is discontinued, symptoms reappear. International asthma management guidelines¹ highlight the importance

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of achieving and maintaining control with an adequate treatment. Regardless of effective treatments being widely available and the existence of treatment guidelines, gaining control of their asthma is still a challenge for many patients. Despite the use of correct treatment according to these guidelines, up to 50% of patients with asthma remain uncontrolled.³ These data suggest the necessity for alternative therapies, especially for patients with severe uncontrolled asthma. Biologic therapies are one of the most promising new treatments, particularly selective targeted monoclonal antibodies (mAb).⁴ However, we must not forget that biologics act on specific pathways, so in order to prescribe the most appropriate treatment, identification of the predominant pathophysiological alterations of each patient (phenotyping) is of utmost importance.⁵

Anti-IgE monoclonal antibodies

The development of new anti-IgE molecules, which are able to decrease free IgE levels and block its binding to the high-affinity receptor (FcεRI) offers a promising alternative therapy for patients with severe uncontrolled asthma. Currently, omalizumab is the only mAb approved for the treatment of asthma. A new human anti-IgE mAb, 8D6, binds to a conformational epitope on the CH3 domain of human IgE, can bind to already bound IgE to low-affinity receptors (FcεRII or CD23) and can compete with omalizumab for IgE binding.⁶ QGE031 (ligelizumab) is an investigational anti-IgE antibody that binds IgE with higher affinity than omalizumab. In a double-blind placebo controlled trial in 37 patients with mild allergic asthma, ligelizumab elicited a concentration- and time-dependent change in the provocative concentration of allergen causing a 15% decrease in FEV₁ that was maximal and approximately 3-fold greater than that of omalizumab at week 12.⁷ A double-blind, placebo-controlled trial has been recently completed, exploring the efficacy of ligelizumab on the reduction of severe exacerbations in patients with allergic severe asthma after one year of treatment.⁸

Anti-IL 5 biologics

Two mAbs have been developed to neutralize interleukin 5 (IL-5), mepolizumab and reslizumab, and another one, which blocks the α-subunit of the IL-5 receptor (IL-5Rα), benralizumab.

Mepolizumab is a humanized IgG1 mAb against IL-5 which acts by binding with high affinity and specificity to free IL-5, preventing IL-5 from binding to its receptor on the eosinophil cell surface. A multicenter placebo-controlled trial was performed to determine the Dose Ranging Efficacy And safety of Mepolizumab in severe asthma (DREAM study).⁹ A total of 621 patients, 12–74 years of age were randomized to receive placebo or one of three doses of intravenous mepolizumab (75, 250 or 750 mg) in parallel groups for a year. There was a decrease of approximately 50% in clinical significant exacerbations in all mepolizumab groups compared to placebo without a dose–response effect reported. Mepolizumab also reduced blood and sputum eosinophil counts with a dose–response effect in the number of eosinophils in sputum.

A post hoc analysis of the DREAM trial showed that, overall, the reduction in exacerbations with mepolizumab was observed irrespective of IgE levels or atopy and were more frequent in winter months but treatment response was unaffected by season or atopy.¹⁰

Another randomized double-blind placebo-controlled trial was performed to assess the rate of exacerbations in patients receiving either intravenous (i.v.) (75 mg) or subcutaneous (s.c.) (100 mg) mepolizumab (MENSA study).¹¹ The rate of exacerbations was reduced by approximately 50% in both active groups compared to placebo. Also, an increase in FEV₁ as well as in the asthma control questionnaire (ACQ) was observed in patients receiving the drug.

Ortega et al.¹² conducted a post hoc analysis to assess the relationship between baseline blood eosinophil counts and efficacy of mepolizumab from the two aforementioned studies (DREAM and MENSA studies), stratifying patients by different baseline blood eosinophil thresholds. This analysis showed a close relationship between baseline blood eosinophil count and clinical efficacy of mepolizumab in patients with severe eosinophilic asthma and a history of exacerbations. The exacerbation rate reduction with mepolizumab versus placebo increased progressively from 52% in patients with a baseline blood eosinophil count of at least 150 cells/μL to 70% in patients with a baseline count of at least 500 cells/μL. At a baseline count less than 150 cells/μL, predicted efficacy of mepolizumab was reduced.

The Therapeutic Positioning report on mepolizumab released by the Spanish Medicines Agency (PT-mepolizumab/V1/27102016), and considering pharmacoeconomic aspects, states that mepolizumab can be used in patients with severe refractory eosinophilic asthma with eosinophil counts in peripheral blood $\geq 500/\mu\text{L}$.¹³

A trial (Steroid Reduction with Mepolizumab Study, SIR-IUS) involving 135 patients was conducted to compare the degree of oral corticosteroid reduction after receiving 100 mg of s.c. mepolizumab over a 20 week period against placebo.¹⁴ There was a significant glucocorticoid-sparing effect, a significant reduction of exacerbations and an improvement in asthma control in the group receiving mepolizumab.

A 52-week, open-label extension of the MENSA and SIR-IUS studies (COSMOS) showed a favourable safety profile of mepolizumab and indicated a durable and stable effect over time, supporting long-term treatment in patients with severe eosinophilic asthma.¹⁵

Reslizumab is a humanized IgG4κ mAb against IL-5. Two multicenter phase 3 trials were recently published. Patients aged 12–75 years, with inadequately controlled asthma with medium-to-high doses of ICS, 400 eosinophils/μL or higher in peripheral blood and at least one exacerbation the previous year, were included. They were randomized to receive either 3 mg/kg of intravenous reslizumab or placebo, for 1 year. In both trials, patients receiving reslizumab had a significant reduction in the frequency of exacerbations compared to those receiving placebo. Adverse events were similar in both groups, the most common being worsening asthma symptoms and nasopharyngitis.¹⁶

A recent phase 3 study¹⁷ further characterizes the efficacy and safety of reslizumab in patients aged 12–75 years with asthma inadequately controlled by at least a

medium-dose ICS and with a blood eosinophil count ≥ 400 cells/ μ L. Patients were randomized to receive reslizumab 0.3 or 3.0 mg/kg or placebo administered once every 4 weeks for 16 weeks. The primary end point was change from baseline in pre-bronchodilator FEV₁ over 16 weeks. Secondary end points included FVC, forced expiratory flow at 25–75% of FVC (FEF_{25%–75%}), patient-reported control of asthma symptoms, short-acting β -agonist (SABA) use, blood eosinophil levels, and safety. Reslizumab significantly improved lung function, asthma control and symptoms, and quality of life. It was well tolerated in patients with inadequately controlled asthma (despite standard therapy) and elevated blood eosinophil levels. Overall, the 3.0-mg/kg dose of reslizumab provided greater improvements in asthma outcomes vs. the 0.3-mg/kg dose, with comparable safety.

Benralizumab is a humanized IgG1 κ mAb which targets IL-5R α , an IL-5 receptor expressed on eosinophils and basophils. It has been shown to deplete eosinophils through antibody-dependent cellular cytotoxicity. It exhibited an acceptable safety profile in a phase I multicenter, double-blind, placebo-controlled study, in which 13 patients were randomized to receive a single intravenous dose of benralizumab 1 mg/kg or placebo and 14 patients to receive three monthly subcutaneous doses of placebo or, either 100 mg or 200 mg of benralizumab. Both cohorts (single intravenous dose and multiple subcutaneous doses) presented a reduction in eosinophil counts in the airway mucosa and submucosa, as well as, in sputum. The percentages of eosinophil reduction in airway mucosa between placebo and benralizumab were statistically significant when both cohorts were combined in a post hoc analysis. There was also suppression in eosinophil levels in the bone marrow and peripheral blood.¹⁸

A phase 2B study was performed on 18–75-year-old patients with uncontrolled asthma treated with a medium or high-dose of ICS and LABA who had suffered from two to six exacerbations over the last year. Patients were randomized to receive placebo or one of three doses of benralizumab: 2 mg, 20 mg or 100 mg. They were given subcutaneous injections every four weeks for the first three doses and afterwards every eight weeks for a year. The study conclusion was that benralizumab at 20 mg and 100 mg doses reduced asthma exacerbations in patients with eosinophilic uncontrolled asthma with at least a baseline blood eosinophil count of 300 cells/ μ L.¹⁹ In both studies the most common adverse effect was nasopharyngitis.

In a placebo-controlled, double-blind, phase 3 trial the safety and efficacy of benralizumab was evaluated.²⁰ Patients ($n = 1205$) aged 12–75 years with a physician-based diagnosis of asthma for at least 1 year and at least two exacerbations while on high-dosage ICS plus LABA in the previous year were recruited. Patients were assigned to benralizumab 30 mg either every 4 weeks or every 8 weeks, or placebo every four weeks for 48 weeks as an addition on to their standard treatment. Patients were stratified 2:1 according to blood eosinophil counts of at least 300 cells/ μ L and less than 300 cells/ μ L. The primary endpoint was annual exacerbation rate ratio versus placebo, and key secondary endpoints were prebronchodilator FEV₁ and total asthma symptom score at week 48, for patients with blood eosinophil counts of at least 300 cells/ μ L. Compared with placebo, benralizumab

reduced the annual asthma exacerbation rate over 48 weeks when given every 4 weeks (rate ratio 0.55, 95% CI 0.42–0.71; $p < 0.0001$) or every 8 weeks (0.49, 0.37–0.64; $p < 0.0001$). Both benralizumab dosing regimens significantly improved prebronchodilator FEV₁ in patients at week 48 compared with placebo. Compared with placebo, asthma symptoms were improved by the every 8 weeks regimen, but not the every 4 weeks regimen. These results confirm the efficacy and safety of benralizumab for patients with severe asthma and elevated eosinophils, which are uncontrolled by high-dosage ICS plus LABA, and provide support for benralizumab to be an additional option to treat this disease in this patient population.

Recently, a comparison of anti-IL-5 therapies in patients with severe asthma using global and indirect meta-analyses of randomized placebo-controlled trials has been published.²¹ The authors identified all RCTs with anti-IL5 treatments for patients with asthma over the 1990–September 2015 period. Only differences between each drug and placebo were studied since no direct comparisons between these drugs have been published. A global meta-analysis of ten trials involving 3421 patients was conducted followed by an indirect comparison of each IL-5-targeting drug: benralizumab, reslizumab and mepolizumab. IL-5 blockade significantly reduced annual exacerbation rates vs. placebo by 40% [29–50] ($p < 0.01$). ACQ-5 was significantly improved vs. placebo but below the recognized minimal clinically important difference level (−0.31 [−0.41, −0.21], $p < 0.01$). FEV₁ changes from baseline were improved vs. placebo by 0.09 L [0.05–0.12] ($p < 0.01$). The subgroup analysis identified a slight additional improvement in mean treatment effects in eosinophilic (> 300 eosinophils/ μ L) patients with severe asthma. Similar patterns and rates of adverse events and severe adverse events were reported with the three drugs. IL-5 blockade appears to be a relevant treatment strategy to improve severe asthma management, particularly for eosinophilic patients. No clear superiority appeared between the drugs when appropriate doses were compared.²¹

Anti-IL-4 and anti-IL-13 monoclonal antibodies

IL-4 and IL-13 play a significant role in the pathogenesis of asthma. Due to the strong evidence of their involvement from genetic studies and the convincing intervention data from animal studies, a broad range of biological agent against these targets has been developed, although only a few have been evaluated in asthmatic patients.

Lebrikizumab is an IgG4 humanized monoclonal antibody that specifically binds to IL-13 inhibiting its function. Corren et al.²² conducted a randomized, double-blind, placebo-controlled study. They randomized 219 patients with moderate to severe persistent uncontrolled asthma, in spite of treatment with ICS, to receive 250 mg of subcutaneous lebrikizumab monthly for 6 months. There was a significant increase in baseline FEV₁ of 5.5% in the active group compared to the placebo group at 12 weeks. There was not a significant reduction in the number of exacerbations. However, in the Th2-high subgroup (total IgE > 100 IU/ml and eosinophilia > 140 cells/ μ L) the rate of

exacerbations was 60% lower in patients receiving lebrikizumab compared to those receiving placebo. These data suggest that a selected group of patients (Th2-high phenotype) may obtain a greater benefit from therapy with anti-IL13 mAbs. However, in phase 3 studies lebrikizumab did not consistently show significant reduction in asthma exacerbations in biomarker-high patients, and the clinical development of lebrikizumab for asthma treatment has been halted.²³

Dupilumab is a humanized mAb which targets the α -subunit of IL-4 receptor also shared with IL-13, and thus inhibits interleukin-4 and interleukin-13 signalling, key drivers of type-2-mediated inflammation.

A phase 2A, randomized, double-blind, placebo-controlled study was performed to evaluate the safety and efficacy of dupilumab for the treatment of patients with persistent asthma with elevated eosinophilic levels (≥ 300 eosinophils/ μ L in blood or $\geq 3\%$ in sputum).²⁴ A total of 104 patients were randomized, 52 to receive 300 mg of dupilumab and 52 to receive placebo, subcutaneously, in a weekly dose, for 12 weeks or until the patients suffered from a moderate to severe exacerbation. Patients had to discontinue LABAs at week 4 and decrease and discontinue ICS during weeks 6 through 9. A statistically significant reduction in asthma exacerbations of 87% was found in the active group compared to placebo. After the second week there was an increase of 200 ml in FEV₁ at baseline associated with dupilumab, which was maintained until the end of the study. Dupilumab was also found to reduce biomarkers associated with Th2-driven inflammation. Authors conclude that it is confirmed that IL-4 and IL-13 contribute to airway inflammation in patients with persistent asthma despite treatment with ICS. They also highlight the effect of dupilumab in reducing asthma exacerbations, even after ICS and LABA withdrawal; despite the particular definition of exacerbation they use in their protocol which differs from clinical practice. Nevertheless they recommend larger studies to be performed.

A phase 2B dose-ranging trial was conducted to assess the efficacy and safety of dupilumab as add-on therapy in patients ($n=769$ patients) with uncontrolled persistent asthma on medium-to-high-dose ICS plus a LABA, irrespective of baseline eosinophil count.²⁵ Patients were randomly assigned to receive subcutaneous dupilumab 200 mg or 300 mg every 2 weeks or every 4 weeks, or placebo, over a 24-week period. The primary endpoint was change in FEV₁ from baseline at week 12, in patients with baseline blood eosinophil count of at least 300 eosinophils/ μ L. In the subgroup with at least 300 eosinophils/ μ L, the greatest increases in FEV₁ compared with placebo were observed at week 12 with doses every 2 weeks in the 300 mg group and in the 200 mg group compared with placebo. Similar significant increases were observed in the overall population and in the fewer than 300 eosinophils/ μ L subgroup, and were maintained to week 24. Likewise, dupilumab every 2 weeks produced the greatest reductions in annualized rates of exacerbation in the overall population (70–70.5%), the subgroup with at least 300 eosinophils/ μ L (71.2–80.7%), and the subgroup with fewer than 300 eosinophils/ μ L (59.9–67.6%). The most common adverse events with dupilumab compared with placebo were upper respiratory tract infections and injection-site reactions.

This study showed that dupilumab increased lung function and reduced severe exacerbations in patients with uncontrolled persistent asthma irrespective of baseline eosinophil count and had a favourable safety profile, and hence in addition to ICS plus LABA therapy could improve the lives of patients with uncontrolled persistent asthma compared with standard therapy alone.

Anti-IL-17 monoclonal antibodies

IL-17 pathway contributes to the pathogenesis of asthma by acting through IL-17 receptor A (IL-17RA) which expresses in smooth muscle cells in the airway. Even though, IL17RA may play a role in the disease pathology of asthma, IL-25 signalling is also involved, mediating downstream Th2 events such as IL4, IL5 and IL13 secretion by Th2 cells. It is believed this is the reason for which cytokine-targeted strategies to block IL-17RA may benefit patients with asthma.

Brodalumab is a human, anti-IL17RA IgG2 mAb which binds with high affinity to the receptor thus blocking IL-17 and IL-25 biological activities. A randomized, double-blind, placebo-controlled study of Brodalumab was conducted in patients with moderate to severe asthma.²⁶ A total of 302 patients were randomized to brodalumab (140 mg, 210 mg or 280 mg) or placebo. No treatment effect was found in the overall population, but a high bronchodilator reversibility group was identified as a potential subpopulation which could respond to the treatment with clinically significant responses. These results in the high-reversibility subgroup analysis are of uncertain significance, requiring further study of brodalumab in this asthma subpopulation.

Conclusions

Patients with uncontrolled severe asthma have limited therapeutic options, so the perspective of selective and clinically effective targeted therapies would be enviable for them. Over the last years there has been an important development of different therapeutic agents but until recently only omalizumab had been introduced into daily practice, with very satisfactory results in patients with severe allergic asthma. Biologics targeting IL-5, such as mepolizumab and reslizumab (recently approved by FDA and EMA) are now already available, but there is still scarce experience with them in daily clinical practice.

Notwithstanding, there are different obstacles in asthma treatment with biologic agents, such as the crossover of the different pathways in the pathogenesis of asthma which may cause lack of complete success of these therapies in addition of high production costs and potential side effects. Nevertheless it is hoped that these new therapies will progressively find their way into clinical practice, at least in selected groups of patients.

Ethical disclosures

Confidentiality of data. The authors declare that no patient data appears in this article.

Right to privacy and informed consent. The authors declare that no patient data appears in this article.

Protection of human subjects and animals in research. The authors declare that no experiments were performed on humans or animals for this publication.

Conflict of interest

Dr. S. Quirce has received consultation fees from Novartis, GSK and AstraZeneca, and has participated in company sponsored speaker's bureau of TEVA Pharmaceuticals and Sanofi.

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