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REVIEW

Biologics in the treatment of severe asthma

S. Quirce[a,b,*], E. Phillips-Angles[c], J. Domínguez-Ortega[a,b], P. Barranco[a,b]

[a] Department of Allergy, Hospital La Paz Institute for Health Research (IdiPAZ), Madrid, Spain
[b] CIBER de Enfermedades Respiratorias, CIBERES, Spain
[c] Department of Allergy, Hospital Universitario La Paz, Madrid, Spain

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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.

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 guidelines[1] highlight the importance

* Corresponding author.
E-mail address: santiago.quirce@salud.madrid.org (S. Quirce).

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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 od 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 FEV_1 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 FEV_1 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/μL.[13]

A trial (Steroid Reduction with Mepolizumab Study, SIRIUS) 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 SIRIUS 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 study[17] further characterizes the efficacy and safety of reslizumab in patients aged 12–75 years with asthma inadequately controlled by at least a