Selection of biologics in severe asthma: a multifaceted algorithm

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As in other disorders, biologics have also been introduced in the treatment of severe asthma. Firstly, omalizumab in 2004, then mepolizumab, reslizumab and benralizumab followed, with dupilumab recently added to the list [1]. These biologics have different mechanisms of action: omalizumab is directed against immunoglobulin E (IgE); mepolizumab and reslizumab block interleukin 5 (IL-5); benralizumab binds the alpha chain of the IL5 receptor (IL5RA) and induces Natural Killer cells to drive apoptosis of cells bearing the receptor; and dupilumab is directed against IL-4RA, which is shared by IL-4 and IL-13, so blocking the signaling of both cytokines.

Recently, different algorithms on the selection of biological for severe asthma have been published [2-5]. However, head to head comparison studies are not available, so we aimed to propose an algorithm of selection of biologics in adult patients with severe asthma based in clinical evidence, post hoc analysis and available biomarkers (fig 1).

1. Previously to the treatment with biologics, the diagnosis of asthma should be reconsidered, proper adherence and inhalation technique should be ensured, allergen and trigger avoidance should be tried, and a proper treatment of comorbidities should be provided.

2. The patient should have a diagnosis of uncontrolled severe asthma. Severe asthma is defined as “asthma that requires treatment with high dose inhaled corticosteroids and with a second controller and/or systemic corticosteroids to prevent it from becoming uncontrolled or which remains uncontrolled despite this therapy”. This corresponds to GEMA (Spanish Guidelines on the Management of Asthma) treatment steps 5 and 6 [6] (2). The diagnosis of uncontrolled asthma should fulfill one of the following requisites: (i) ACT<20 or ACQ>1.5; (ii) two or more asthma attacks that had required two or more burst of systemic corticosteroids (CS); (iii) at least one hospitalization, ICU stay or mechanical ventilation in the previous year; (iv) FEV1 <80% predicted, with a reduced FEV1/FVC, defined as less than the lower limit of normal [7]. The prevalence of uncontrolled severe asthma in Spain has been estimated around 4% [8].

3. After a diagnosis of severe asthma, determination of the patient’s phenotype should follow [7]. We propose a phenotype-based targeted therapy with biological agents. The selection of the most suitable biological drug for each patient should be multifaceted, considering clinical and physiologic data (frequency of severe exacerbations, cortico-dependence, lung function), specific biomarkers (allergic status with sensitization to perennial allergens and total serum IgE levels, blood or airway eosinophilia, and fractional exhaled nitric oxide –FeNO–), and associated pathologies, such as chronic urticaria, atopic dermatitis, nasal polyposis, AERD, eosinophilic esophagitis and obesity (complete evidence basis of these aspects is presented in the repository). For example, a concomitant chronic urticaria would point to omalizumab as a choice, as a concomitant atopic dermatitis would point to dupilumab. In addition, it is advisable that main clinical outcomes be considered for each patient. Thus, if the main clinical target were reducing the maintenance dose of oral corticosteroids, omalizumab or reslizumab seem not to be the first choice, as clinical trials have not...
proved their capability as steroid-sparing agents. Also, the cost should be taken into account, particularly when related to BMI and total IgE levels.

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4. In patients with severe allergic asthma, defined by sensitization to a perennial allergen and relevant symptoms upon exposure to the allergen, with eosinophil levels under 300/µL (150/µL in those receiving treatment with oral corticosteroids), the election should be omalizumab or dupilumab. To select omalizumab, total serum IgE levels should be between 75 and 1,500 kU/L and body weight should be considered. The limit of 75 kU/L is supported by the analysis of Bousquet et al. [9], who found that patients with total serum IgE levels under 76 kU/L had a lower response to omalizumab. Nevertheless, there have been described responses in patients with total IgE under this threshold. We believe that the election between omalizumab and dupilumab should consider FeNO levels, as Castro et al. [10] showed no statistically significant differences with placebo in the reduction of exacerbations or in lung function in patients with FeNO levels < 25 ppb treated with dupilumab. Also, the level of eosinophils should be taken into account, as dupilumab did not show efficacy in the population of patients with <150 eosinophils/µL.

5. Asthmatic patients with relevant perennial allergen sensitization, with eosinophil levels over 300/µL (150/µL in those receiving treatment with oral corticosteroids) and total IgE between 75-1,500 kU/L, can qualify for all available biologics. In the case of omalizumab, a recent post hoc analysis of two pivotal clinical trials has shown greater efficacy in patients with greater levels of eosinophils, although a significant response was observed in patients with <300 and ≥300 eosinophils/µL) [11]. Dupilumab should be considered for patients with FeNO≥25 ppb. Again, the election between omalizumab, dupilumab and IL5/IL5RA (and among these ones) should be based in the previously mentioned multifaceted approach [12].

6. Severe asthmatics without specific relevant perennial allergens, but with peripheral blood eosinophilia ≥300 eosinophils/µL (≥150 eosinophils/µL in corticosteroid dependent asthma) are candidates to receive biologics targeting IL-5, such as subcutaneous mepolizumab [13], intravenous reslizumab [14], or IL5RA subcutaneous benralizumab [15], or dupilumab [12]. All of these agents were able to significantly reduce the number of severe asthma exacerbations and to improve lung function, although only mepolizumab, benralizumab and dupilumab have a DBPC trial demonstrating a systemic steroid sparing effect [11,13,15]. Benralizumab possess a dual mechanism against eosinophils because it neutralizes the key survival signal provided by IL-5, and also directly activates FcγRIIIa-induced antibody dependent cytotoxicity, driven by NK cells, leading to a complete depletion of eosinophils and a significant reduction of basophils. This different mechanism of action could be taken into account, although further studies are required to confirm whether there are differences among IL5/IL5RA biologics. The frequency and via of administration can also be taken into account. Dupilumab should be considered in patients with FeNO≥25 ppb. Dupilumab can increase eosinophil levels [12] which needs to be considered in patients with very high eosinophil counts.
Once the biologic has been selected, a follow up at six months should be done. The response should consider exacerbations, lung function, control of asthma, and reduction of oral corticosteroids when appropriated. FeNO levels could be also useful as well as eosinophil counts. Also, adverse effects should be taken into account. If a good response were observed, the treatment should be maintained, with continuous safety and efficacy monitoring throw-out the hole therapy duration. Otherwise, the biologic should be discontinued and the patient re-evaluated. In these patients, the previously discarded biologic should be considered. In the particular case of anti-IL5/IL5RA agents, if one of them had failed, another one can be tried.
REFERENCES

Figure 1. Algorithm for the selection of biologics in severe asthma

EoE: Eosinophilic Esophagitis; EGPA: Eosinophilic Granulomatosis with Polyangiitis; ABPA: Allergic Bronchopulmonary Aspergillosis

* (≥150 eosinophils/µL in corticosteroid dependent asthma)

** These limits can vary in the different countries. In addition, omalizumab have showed some results with IgE levels out of these limits (Ref 13 Suppl. Material)

*** In the case of ANTI-IL5/ANTI-IL1A consider changing among them, as there has been responses after switching. Consider also the mechanism of action