Selection of Biologics in Severe Asthma: A Multifaceted Algorithm

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As occurs in other diseases, asthma can now be treated with biologics. The first agent used was omalizumab (in 2004), which was followed by mepolizumab, reslizumab, and benralizumab, with dupilumab recently added to the list [1]. These biologics have different mechanisms of action: omalizumab targets immunoglobulin E (IgE); mepolizumab and reslizumab block interleukin 5 (IL-5); benralizumab binds the α chain of the IL5 receptor (IL5RA) and induces natural killer cells to drive apoptosis of cells bearing the receptor; and dupilumab targets IL-4RA, which is shared by IL-4 and IL-13, thus blocking the signaling of both cytokines.

Various algorithms for selection of biologics in severe asthma have been published [2-5]. However, since there are no head-to-head comparison studies, we propose an algorithm for the selection of biologics in adult patients with severe asthma based on clinical evidence, post hoc analysis, and available biomarkers (Figure).

1. Before 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 appropriate treatment of comorbidities should be provided.
2. The patient should be diagnosed with 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" [2]. This corresponds to GEMA (Spanish Guidelines on the Management of Asthma) treatment steps 5 and 6 [6]. The diagnosis of uncontrolled asthma should fulfill 1 of the following requirements: (*1*) Asthma Control Test <20 or Asthma Control Questionnaire >1.5; (*2*) ≥2 asthma attacks that had required ≥2 bursts of systemic corticosteroids; (*3*) at least 1 hospitalization, 1

intensive care unit stay, or mechanical ventilation in the previous year; (*4*) FEV_1 <80% predicted, with a reduced FEV_1/FVC, defined as a value below the lower limit of normal [7]. The prevalence of uncontrolled severe asthma in Spain has been estimated at around 4% [8].

3. The diagnosis of severe asthma should be followed by determination of the patient's phenotype [7]. We propose phenotype-based targeted therapy with biological agents. The selection of the most suitable biological drug for each patient should be multifaceted, considering clinical and physiological data (frequency of severe exacerbations, corticosteroid 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 diseases, such as chronic urticaria, atopic dermatitis, nasal polyposis, aspirin-exacerbated respiratory disease, eosinophilic esophagitis, and obesity (complete evidence for these aspects is presented in the online repository). For example, concomitant chronic urticaria would point to omalizumab as a choice, and concomitant atopic dermatitis would point to dupilumab. In addition, the main clinical outcomes should be taken into consideration for each patient. Therefore, if the main clinical target is to reduce the maintenance dose of oral corticosteroids, omalizumab and reslizumab seem not to be the first choice, since clinical trials have not proved their usefulness as corticosteroid-sparing agents. Furthermore, the cost should be taken into account, particularly in patients with high body mass index and total IgE levels.
4. In patients with severe allergic asthma, defined as 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 drug chosen should be omalizumab or dupilumab. Before omalizumab can be selected, total serum IgE levels should be 75-1500 kU/L and body weight should be taken into account. 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, responses have been reported in patients with total IgE under this threshold. We believe that the choice between omalizumab and dupilumab should include FeNO levels, as Castro et al [10] showed no statistically significant differences with placebo in terms of reduced frequency of exacerbations or lung function in patients with FeNO levels <25 ppb treated with dupilumab. The level of eosinophils should also be taken into account, as dupilumab did not prove efficacious in the population of patients with <150 eosinophils/μL.
5. Asthmatic patients with relevant perennial allergen sensitization and eosinophil levels >300/μL (150/μL in those receiving treatment with oral corticosteroids) and total IgE of 75-1500 kU/L can qualify for all available biologics. In the case of omalizumab, a recent post hoc analysis of 2 pivotal clinical trials has shown greater efficacy in patients with higher eosinophil counts, 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 choice between omalizumab, dupilumab, and IL5/IL5RA agents (and between IL5/IL5RA agents themselves) should be based on the previously mentioned multifaceted approach [12].
6. Patients with severe asthma and no specific relevant perennial allergens but with peripheral blood eosinophilia ≥300/μL (≥150/μL in corticosteroid-dependent asthma) are candidates for biologics targeting IL-5, such as subcutaneous mepolizumab [13], intravenous reslizumab [14], subcutaneous benralizumab [15], and dupilumab [12]. All of these agents significantly reduce the number of severe asthma exacerbations and improve lung function, although only mepolizumab, benralizumab, and dupilumab have been shown to have a systemic corticosteroid–sparing effect in double-blind, placebo-controlled clinical trials [11,13,15]. Benralizumab has a dual mechanism against eosinophils because it neutralizes the key survival signal provided by IL-5 and directly activates FcγRIIIa-induced, antibody-dependent cytotoxicity, which is driven by NK cells, leading to complete depletion of eosinophils and a significant reduction in basophil count. Differences in the mechanism of action may play a role, although further studies are required to confirm whether there are differences between IL5/IL5RA biologics. The frequency and route of administration should also be taken into account. Dupilumab should be considered in patients with FeNO ≥25 ppb. Dupilumab can increase eosinophil levels [12], and this should be taken into account in patients with very high eosinophil counts.

Once the biologic has been selected, the patient should be followed up at 6 months. Assessment of the response should be based on exacerbations, lung function, control of asthma, and reduction of oral corticosteroids when appropriate. FeNO levels could be also useful, as could eosinophil counts. Furthermore, adverse effects should be taken into account. If the response is good, treatment should be maintained, with continuous safety and efficacy monitoring throughout therapy. Otherwise, the biologic should be discontinued and the patient re-evaluated. In these cases, the previously ruled out biologic should be considered. In the case of anti-IL5/IL5RA agents, if one of the drugs fails, it can be replaced by another from the same family.

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Conflicts of Interest

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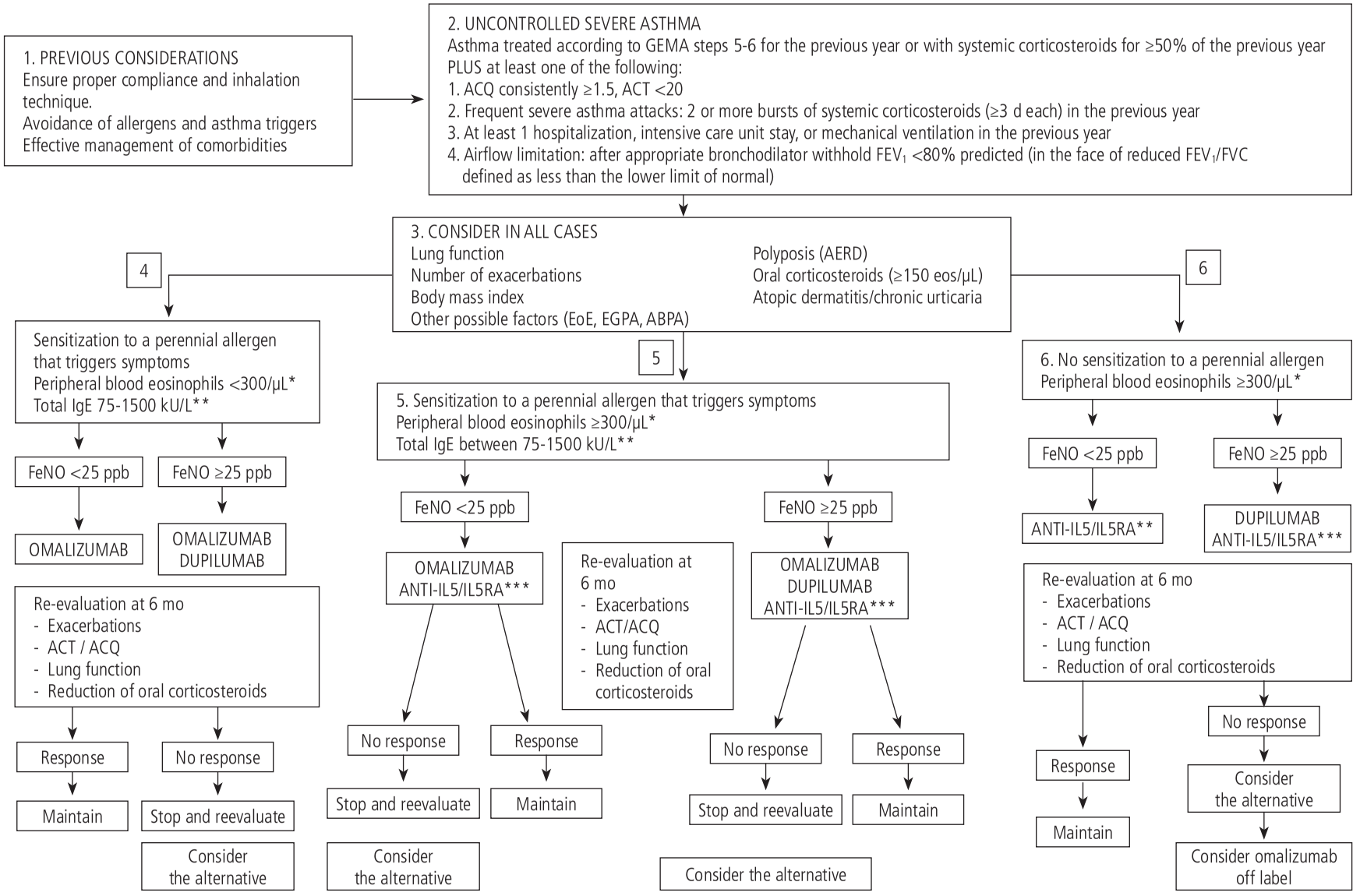

Figure. Algorithm for the selection of biologics in severe asthma. The order of the boxes does not imply preference. ACQ indicates Asthma Control Questionnaire; ACT, Asthma Control Test; FeNO, fractional exhaled nitric oxide; AERD, aspirin-exacerbated respiratory disease; EoE indicates eosinophilic esophagitis; EGPA, eosinophilic granulomatosis with polyangiitis; ABPA, allergic bronchopulmonary aspergillosis.
*≥150 eosinophils/µL in corticosteroid-dependent asthma
**These limits vary by country. In addition, IgE levels outside these limits have been reported with omalizumab (Ref 13 Suppl. Material)
***In the case of anti-IL5/anti-IL5RA agents, if one drug fails, it can be replaced by another from the same family, as responses after switching have been reported. Consider also the mechanism of action.

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