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New Options for Controlling Severe Asthma

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Abstract

Asthma is a heterogeneous disease characterized by chronic airways inflammation. Most patients, using a Long Acting Bronchodilator Agent (LABA) associated with Inhaled Corticosteroids (ICS) in a single inhaler, achieve control of their symptoms. Nevertheless, cohorts of patients, defined as severe asthmatics, suffer daily symptoms and are at high risk of exacerbation and hospitalization, despite correctly adhering to an appropriate therapy regimen. Treatment for severe asthma is now focusing on tailoring to particular phenotypes driven by the endotypes.

This review will focus on some exciting new therapeutic options that are already being recommended or are soon to be so, for the management of severe asthma.

The first option is to add tiotropium, a long-acting muscarinic receptor antagonist, than can improve lung function and reduce exacerbations in patients not controlled by ICS/LABA. The second option, particularly for severe asthma with eosinophilic inflammation, is the biological treatment.

Omalizumab, a monoclonal antibody to IgE, improves asthma control in patients with a predominant allergic phenotype. Monoclonal antibodies targeted to interleukin 4α (Dupilumab) and interleukin 5 (Mepolizumab, Reslizumab, Benralizumab) have shown substantial benefit in patients with the eosinophilic asthma phenotype. Bronchial thermoplasty, a new technique to reduce airway smooth muscle mass, improves symptoms and reduce exacerbations in patients with severe uncontrolled asthma and the chronic airflow obstruction phenotype.

Only by better understanding the characteristics of asthma in uncontrolled patients will we be able to address the challenges of severe asthma with the new and innovative approaches reviewed and discussed here.

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Introduction

Bronchial asthma is a heterogeneous disease, usually characterized by chronic inflammation of the airways. It is defined by a history of respiratory symptoms, such as shortness of breath, wheezing, chest tightness and cough, which vary in terms of duration and intensity and are associated with a variable limitation of the expiratory airflow [1]. Currently, Inhaled Corticosteroids (ICS) are the first line treatment for the management of persistent asthma. ICS reduce inflammation and improve respiratory function thus reducing clinical symptoms, the rate of exacerbations and the use of bronchodilators on demand. If symptoms remain uncontrolled, guidelines recommend increasing the ICS dose or administering them in combination with a long-acting bronchodilator such as long-acting beta$_2$-agonists (LABAs). The use of slow-release antileukotrienes and theophylline, in conjunction with low-dose ICS, is also advised as an alternative therapeutic choice for patients who suffer from uncontrolled asthma.

Most patients, using a LABA associated with ICS in a single inhaler, achieve control of their symptoms. This is apparent in a high percentage of asthmatic patients [2]. Nevertheless, cohorts of patients, defined as severe asthmatics, suffer daily symptoms and are at high risk of exacerbation and hospitalization, despite correctly adhering to an appropriate therapy regimen.

The prevalence of severe asthma amongst asthmatic subjects is estimated to be between 5% and 10%. There are various definitions of severe asthma, the most agreed upon of which identifies it in asthmatic patients, who require full inhalation therapy (high dose inhaled ICS associated with a second controller agent, generally a LABA) with or without the addition of a systemic steroid, to successfully manage symptoms [3]. Despite this high dose of ICS, a proportion of patients may still suffer uncontrolled asthmatic symptoms and present with frequent exacerbations, a condition known as SUA (Severe Uncontrolled Asthma). SUA greatly compromises the patient's quality of life

and has a significant economical impact in terms of healthcare cost. SUA is characterized by patient-related factors such as comorbidity, poor adherence to therapy and psycho-social factors, as well as by therapy-related factors, in terms of efficacy and side effects, especially in cases of chronic systemic steroid therapy. Some exciting new therapeutic options are already being recommended or are soon to be so, for the management of severe asthma (Steps 4 and 5 of the 2015 Global Initiative for Asthma - GINA guidelines) [4]. The objectives of the pharmacological treatment are: reducing the severity and rate of exacerbations, improving lung function and replacing systemic steroids with equally effective but better tolerated drugs.

Pharmacological Intervention on Smooth Muscle

Some studies have shown that the use of Long-Acting Muscarinic receptor Antagonists (LAMAs) improves lung function and reduces exacerbation rate in asthmatic patients that have previously not responded well to ICS/LABA combinations [5]. The most significant statistical data supported the use of tiotropium, a long-acting anticholinergic bronchodilator, which has shown impressive results in several clinical studies in terms of improving lung function and reducing exacerbation rate in SUA patients who were previously treated with high dose ICS/LABA. There are diverse mechanisms of action of LAMAs in asthma. Specifically, LAMA molecules can induce the bronchodilation and inhibit the bronchoconstriction mediated by the cholinergic system, limit airway remodeling by inhibiting smooth muscle hypertrophy, limit goblet cell hyperplasia, and reduce mucous secretions (Table 1) [6].

Tiotropium administered by the 'Soft Mist Inhaler' delivery method, using the Respimat® device, was approved for bronchial asthma treatment after clinical trials demonstrated its reliability. Current indications recommend using tiotropium as an alternative to LABAs in patients with mild-to-moderate asthma who have not achieved sufficient control of symptoms in response to ICS/LABA treatment. It is also recommended to use tiotropium as an add-on therapy in those who are not adequately treated with ICS/LABA.

In a study of a population of severe persistent asthmatics, already using high dose ICS associated with LABA, the administration of Tiotropium Respimat® once daily at a dose of 5 µg showed a significant improvement in lung function, a reduction in exacerbation rate (-21% compared to placebo) and an increase in terms of time-to-first exacerbation time (+56 days) [7]. Two subsequent studies looked at 2103 patients with moderate asthma not controlled by a medium dose of ICS (400-800 µg budesonide or equivalent). These patients were treated, as add on, with Tiotropium Respimat® 5 µg in single administration or with salmeterol 50 µg twice daily. The statistically significant improvements both in lung function and quality of life were similar for both bronchodilators, confirming that tiotropium could be an effective alternative treatment to LABAs [8].

Tiotropium Respimat® as an additional maintenance treatment (used with ICS or ICS/LABA) has demonstrated a tolerability profile comparable with that of placebo amongst COPD patients even in uncontrolled bronchial asthma at different step [9].

Treatment of Th2-Mediated Inflammation

Circulating IgE

A principal therapeutic target of biological therapy, in allergic asthmatic patients, is circulating IgE, which is known to play a key role in disease progression. Omalizumab is a monoclonal antibody that binds to circulating IgE, having a pleiotropic effect on many cells involved in Th2-mediated allergic immune responses (Figure 1). Specifically, a decrease in circulating IgE reduces the expression of high affinity IgE receptors (FcεRI receptor) on the membrane surface of mast cells, lymphocytes and dendritic cells. It leads to the progressive down-regulation of Th2-mediated immunity with subsequent effects on cytokine production. This is key to managing symptoms and reducing exacerbation rate amongst allergic asthma patients [10].

Table 1: Mechanisms of action of Long Acting Muscarinic receptor antagonist in asthma [6].

Modulation of tonebronchomotor
Inhibition of sub-mucosa remodelling
Inhibition of Th2 cytokine release
Inhibition of chemotacticmediators
Inhibition of eosinophilrecritment
Modulation of globetcells
Increase of coughthreshold

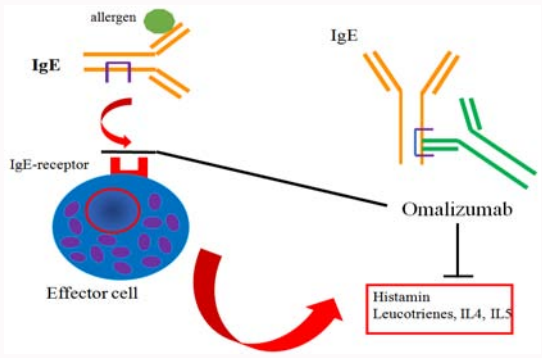

Figure 1: Mechanisms of action of omalizumab in severe atopic asthma [10].

The clinical effects of Omalizumab can be predicted by monitoring the biomarkers that indicate Th2 activity: blood eosinophil count, Exhaled Nitric Oxide (FeNO) level and serum periostin level. It has been shown that allergic asthmatic patients, with the highest levels of these biomarkers at baseline, are those with the best chances of having a therapeutic response to Omalizumab [11]. This supports the theory of there being multiple endotypes within the same phenotype and their potentially diverse impacts on therapeutic outcome. It has been shown that the efficacy of Omalizumab is lower in allergic asthmatic patients that present with comorbidities, such as nasal polyposis, where some of the eosinophilic inflammatory infiltrate is sustained by type 2 Innate Lymphoid Cells (ILC2) and is less responsive to the effects of anti-IgE [12].

Omalizumab has also been shown to alleviate the effects of airway remodeling in bronchial asthma by reducing basement membrane thickness [13].

Cytokines in Th2-Type Inflammation

In addition to targeting the effects of IgE, it is also possible to act directly on specific molecular targets that are involved in Th2-mediated inflammatory processes. These targets include several cytokines and their receptors. Th2 cytokines include IL-4 and IL-13, which are produced by Th2 lymphocytes and regulate many

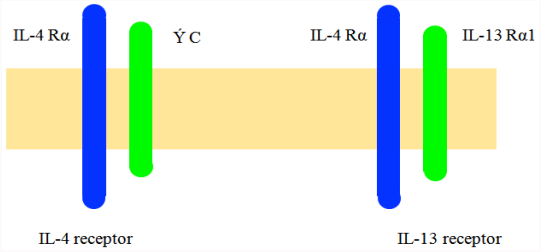

Figure 2: Human monoclonal IgG4 antibody Dupilumab binding the shared alpha subunit of the IL-4 receptor, thus inhibiting IL-4 and IL-13 signal transduction [17].

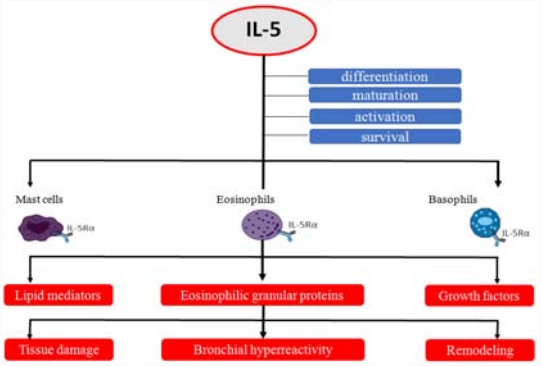

Figure 3: Role of IL-5 is a cytokine for the differentiation, maturation, circulating migration and survival of eosinophils in tissues [20,21].

interactions within the immune system as well as acting on epithelial cells and bronchial muscle cells. A major role of both IL-4 and IL-13 is in regulating the proliferation of Th2 lymphocytes. They are also involved in the expression of adhesion molecules on endothelial cells and the contraction of bronchial smooth muscle [14].

Lebrikizumab is a monoclonal antibody that binds circulating IL-13 and removes it from the circulation. Lebrikizumab was the first monoclonal to demonstrate efficacy in severe asthmatic patients who had increased Th2 activity coupled to the following characteristics: treatment with high-dose inhaled corticosteroids, severe non-specific bronchial hyper responsiveness, elevated total serum IgE level and increased levels of circulating eosinophils, both in the presence or absence of allergy. Any significant effect on FEV_1 and exacerbation rate was only apparent in the subgroup of asthmatic patients that had demonstrated increased Th2 activity and expressed high levels of serum periostin, a biomarker of type 2 inflammation. Periostin is produced by the bronchial epithelium after IL-13 stimulation and is involved in the interaction between epithelial cells and the basement membrane. This would suggest that the therapeutic activity of Lebrikizumab is limited to a subgroup of asthmatic patients who have demonstrated increased Th2 activity [15].

Tralokinumab is another anti-interleukin-13 human monoclonal antibody developed for the treatment of severe, uncontrolled asthma. Tralokinumab reduced Annualized Asthma Exacerbation Rate (AAER) in participants with severe asthma with baseline FeNO 37 ppb or higher in STRATOS 1, but not in STRATOS 2. These inconsistent effects on AAER do not support a key role for interleukin 13 in severe asthma exacerbations [16].

Dupilumab is an interleukin 4 (IL-4) receptor α-antagonist that inhibits IL-4 and IL-13 signaling through blockade of the shared IL-4α subunit. Blockade of the IL4/13 is effective in reducing Th2 response [14]. Dupilumab has shown efficacy in both atopic dermatitis and bronchial asthma studies, suggesting that the targeted action of an endotype can lead to a significant clinical response regardless of phenotypic expression [16,17]. Asthmatic patients with uncontrolled asthma that is unresponsive to topical steroids given together with a long-acting bronchodilator, showed reduced incidence of exacerbations and a significant effect on respiratory function, as demonstrated by a rapid improvement in FEV_1 upon receipt on the drug. This differentiates Dupilumab from other biological drugs used to treat Th2-mediated phlogosis (Omalizumab and Lebrikizumab). The clinical response was associated with a marked reduction in FeNO, demonstrating an important effect on local airway Th2-mediated inflammation as has also been shown with topical steroid treatment in some patients [17]. The efficacy and safety of Dupilumab was assessed in patients with uncontrolled asthma [18]. In this trial, patients who received Dupilumab had significantly lower rates of severe asthma exacerbation than those who received placebo, as well as better lung function and asthma control [18]. The efficacy of Dupilumab was evaluated in reducing oral glucocorticoid use in patients with severe asthma. The percentage change in the glucocorticoid dose was −10.1% in the Dupilumab group, as compared with -41.9% in the placebo group ($p<0.001$). The treatment reduced oral glucocorticoid use while decreasing the rate of severe exacerbations and increasing the FEV_1 [19].

The Regulatory Cytokines of Eosinophils

The role of eosinophils in allergic inflammation and in bronchial asthma is widely reported, especially their presence in the respiratory mucous membranes of asthmatic subjects. The relationship between elevated sputum and blood eosinophil levels and, its associated risk in developing asthmatic exacerbations is well-documented [20]. IL-5 is a cytokine that is essential for the differentiation, maturation, circulating migration and survival of eosinophils in tissues (Figure 2) [20,21]. Eosinophils are typical effector cells of Th2-mediated immune responses and, once activated, exhibit an autocrine production of IL-5 which inhibits their apoptosis thus prolonging their life-span and activity.

Two humanized monoclonal antibodies that bind circulating IL-5 are currently available (Mepolizumab and Reslizumab). A further monoclonal antibody (Benralizumab) binds to the IL-5 receptor on eosinophils (Figure 3). This blockade of IL-5 activity results in the reduced production and activation of eosinophils presenting an innovative way to treat the many types of asthma with an associated eosinophilia.

Mepolizumab is an unglycosylated humanized monoclonal antibody (IgG1, kappa), which inhibits the activity of IL-5 by preventing its binding to the α-chain of the IL-5 receptor. Recent studies have shown that Mepolizumab can be effective in reducing eosinophil count by reducing eosinophilic progenitors in the bronchial mucosa and suppressing the rate of maturation in the bone marrow of asthmatic patients [22].

Some clinical studies with Mepolizumab showed better symptom control, improved respiratory function and a significant reduction in exacerbations in asthmatic patients with blood eosinophilia >300 eosinophils/μl [23,34].

The subsequent SIRIUS study evaluated the effect of Mepolizumab (100 mg) as a steroid sparing in asthmatic patients

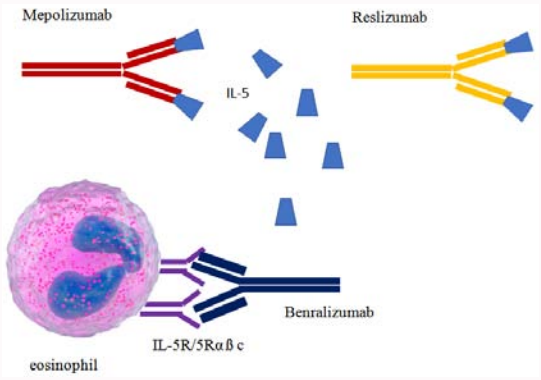

Figure 4: Monoclonal antibodies aimed to inhibit eosinophil functions include mepolizumab and reslizumab, which bind to and neutralize iL-5, as well as benralizumab, which targets and blocks IL-5Rα [14].

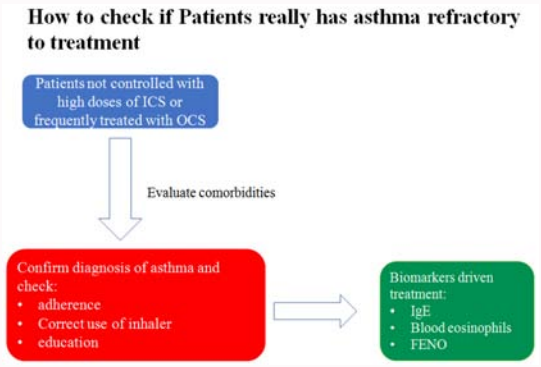

Figure 5: Operative proposal to identify patients to be treated with biological agents.

receiving oral corticosteroids for at least six months per year (mean dose of 12.5 mg prednisone/day) [25]. In addition to reducing the rate of exacerbations and the extent of symptoms, patients treated with Mepolizumab halved their systemic steroid intake. The number of exacerbations was also significantly reduced in the MENSA study, which included patients with a blood eosinophilia of at least 150/µl at screening or 300/µl in the previous year [26]. In both the MENSA and SIRIUS studies, patients treated with Mepolizumab, reported similar adverse events to those who received placebo.

Reslizumab binds to the ERRR region of IL-5, which is critical for its interaction with its receptor, thus resulting in the inhibition of its activity [26,27]. Administered at a dose of 3.0 mg/kg e.v. every 4 weeks, Reslizumab has been shown to decrease exacerbations, lower eosinophilia in the sputum, and to improve quality of life by alleviating symptoms in asthmatic subjects with a pre-treatment blood eosinophilia of >400/µl, who had previously been treated with high dose ICS [28,29].

Benralizumab is a fully humanized afucosylated anti-human IL-5Rα antibody that binds to an epitope on the IL-5 receptor alpha (IL-5Rα). Benralizumab has been shown to reduce the levels of blood eosinophils and of eosinophil bone marrow precursors by means of anti-cell-mediated cytotoxicity using a molecular mechanism different from that of similar antibodies that bind circulating interleukins [30]. Benralizumab has shown efficacy against exacerbations in cases of severe uncontrolled eosinophilic asthma, where peripheral eosinophil values are >300/µl. Two trials have studied Benralizumab in severe eosinophilic asthma, administering a fixed subcutaneous dose of 30 mg every four weeks for three times, and after this first period every eight weeks regularly [31,32]. It was reported that Benralizumab improved FEV_1 when compared to placebo, and reduced the symptoms and the number of exacerbations in patients with uncontrolled asthma who had an eosinophil count >300/µl.

The effect of these monoclonal antibodies in steroid-dependent asthmatic patients, especially in those with a severe asthma phenotype, which includes nasal polyposis and NSAID intolerance, presents an intriguing therapeutic avenue. Interestingly, eosinophilia corresponding with activation of innate Th2-mediated inflammatory responses linked to the presence of ILC2 cells was reported amongst this patient cohort.

The Effects of Non-Pharmacological Intervention on Smooth Muscle

Bronchial Thermoplasty (BT) represents an innovative approach in the treatment of severe asthma that aims to control disease by reducing the smooth muscle thickening in the airways that causes reduced airway flow [33]. BT was first approved by the Food and Drug Administration (FDA) in 2010 and remains the only device-based non-pharmacological treatment approach for severe asthma [34]. The most appropriate indication seems to be for the treatment of severe non-eosinophilic asthma, characterized by a neutrophilic or paucicellular inflammatory infiltrate.

This novel technique releases thermal energy, in a controlled manner, into the airways during a bronchoscopy, using an electric radiofrequency generator. The electrical energy is converted into heat upon meeting tissue resistance [35]. BT is performed in three sessions scheduled approximately three weeks apart. The first session treats the airways of the right lower lobe, the second treats the airways of the left lower lobe and the final session treats the airways in both upper lobes. The right middle lobe is excluded from treatment and a patient may only partake in this entire procedure once [36].

Each BT session takes approximately 30 min to 45 min. Each bronchus is treated along its entire visible length, beginning at the periphery and moving proximally. A full treatment consists of about 30 to 70 activations per lobe (depending on the patient's anatomy). The effectiveness of the treatment may depend on how thoroughly the procedure is performed. If a segment of tissue is left untreated, it could, in theory, continue to constrict when stimulated, potentially negating the benefits of the treatment. Meticulous technique and airway mapping is vital for the effectiveness of this treatment [37].

This selective ablation is believed to reduce airway hyper-reactivity and airway obstruction with a concurrent improvement in asthma symptoms. It has been shown to improve patient quality of life and to reduce the number of exacerbations over a prolonged 5-year observation period [35,38]. The limitations of this technique include its inability to access and treat any symptomatic distal airways due to their small diameter. Contraindications include patients with implanted medical devices [39], chronic obstructive pulmonary disease, bronchiectasis, recurrent respiratory infections or any other significant uncontrolled respiratory disease [40]. Serious heart and lung diseases also render the patient unsuitable for bronchoscopy as well as sensitivity to the anesthetics that are necessary to perform bronchoscopy. Active bleeding and coagulation dysfunction also affect candidate suitability [41].

Several aspects of BT require further clarification, especially regarding its mechanism of action, the long-term pathophysiological effects and the realistic role this non-pharmacological treatment could play in severe asthma therapy.

Considering the possible side effects (high incidence of acute post-operative inflammation and pulmonary consolidations, extending far beyond the treated airways) [42], the ERS/ATS task force recommend that BT should only be performed in adults with severe asthma as determined by an Institutional Review Board-approved independent systematic registry or a clinical study [43].

Conclusions

An era of new therapeutic treatments in severe asthma is emerging, warranting an in-depth review by the physicians involved in patient management. The prospect of using biological drugs, which reduce the activity of IgE or Th2-mediated eosinophilic phlogosis, requires a reliable therapeutic algorithm to verify definitively whether the patient truly suffers from bronchial asthma. It must also be taken into account whether the patient is compliant in the correct use of their medication, has comorbidities (that can potentially worsen symptoms) and whether or not eosinophilic inflammation is present (Figure 4).

Treatment with biological drugs is an exciting prospect in the treatment of asthma. An increase in therapeutic options has allowed us to further explore the topic of phenotyping and personalized therapy, an approach that must also consider the sustainability of the National Health Services. The use of economical and validated biomarkers, in addition to physiopathological and clinical evaluation, are the cornerstones for the correct classification of the differing phenotypes identified amongst asthmatic patients. Only by better understanding the characteristics of asthma in uncontrolled patients will we be able to address the challenges of severe asthma with the new and innovative approaches reviewed and discussed here.

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