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Severe Asthma: Updated Therapy Approach Based on Phenotype and Biomarker

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Abstract

Asthma is responsible for considerable global morbidity and health-care costs affecting over 300 million people worldwide. This illness is a heterogeneous condition characterized by chronic airway inflammation and pulmonary tissue remodeling resulting in a variety of clinical manifestations and treatment responses. Recent studies have shown an increasing appreciation of heterogeneity in asthma based on molecular phenotyping, biomarkers, and differential responses to therapies. In terms of asthma classification, perhaps the most important distinction to make is whether the patient has evidence of an eosinophilic inflammatory process characterized by type 2 immune response (Th2) or not. Therefore, personalized therapies to asthmatic patients just will be a reality by identifying and characterizing biomarkers. This review approaches the advances in diagnoses and management of asthma and severe asthma and highlights those with difficult-to-treat asthma based on each phenotype and biomarkers, to assist in the optimization of conventional therapy and to guide the use of targeted therapies.

Keywords: severe asthma, phenotypes, endotypes, biomarkers, therapy

1. Introduction: severe asthma definition

Asthma is a heterogeneous disease featured by the airway chronic inflammatory process associated with airway hyper-relativity due to direct and/or indirect stimuli such as exercise,

exposure to allergens or irritants, weather change, and respiratory infections. Asthma is characterized by wheezing, shortness of breath, coughing, chest tightness, and variable expiratory airflow limitation. These symptoms may vary over time and intensity and the symptom resolution and airflow limitation can occur spontaneously or in response to pharmacotherapy [1, 2]. The clinical classification of asthma is recent onset asthma, mild and severe forms, or even asymptomatic asthma [1].

The severe asthma (SA) concept is preconized by the European Respiratory Society–American Thoracic Society, which classifies severe asthmatic patients who require treatment with high-dose inhaled (or systemic) corticosteroids (ICS) in combination with a second long-term medication (long-acting β2 agonists—LABA). This definition includes patients who either maintain or are not in control of the disease [3, 4].

The first step to identify SA is to confirm if the patient presents the basic criteria for asthma itself, that is, reversible airway obstruction and bronchial hyper-reactivity and classic clinical symptoms such as wheezing, shortness of breath, cough, and chest tightness. However, many patients with SA do not meet these criteria as those ones with associated obstructive pulmonary disease and vocal cord dysfunction. After confirming the asthmatic condition, the second step is to determine the therapeutic control of the disease, which means adding ICS/LABA combination. However, some asthmatic patients remain poorly controlled independent of therapy leading to exacerbation of clinical symptoms and airway obstruction and might indicate severe and/or frequent asthma [5].

2. Severe asthma epidemiology

Asthma spreads all over the world, affecting more than 300 million people [2, 6]. This milestone makes it one of the most common chronic inflammatory diseases worldwide [5]. Based on standard methods for assessing the asthma symptoms, its global prevalence ranges from 1 to 16% of the population in different countries, while the asthma fatality rate is about 346,000 people around the world [2]. According to epidemiological data, asthma prevalence is higher in developed countries; however, it is also presented in countries with lower economic and social indicators, that is, developing countries [7], with a prevalence of 1%. Another aspect of this disease is the higher prevalence in urban areas in comparison with rural places [2]. Indeed, asthma prevalence has increased in the world over the past decades and is in a constant increasing rate [8, 9].

Asthma development is directly related to immunological factors, immediate hypersensitivity process, age, gender, and obesity. In an overview, around 50% of children under 3 years old and 80% over 6 years old who are diagnosed with asthma are atopic individuals [2, 10]. In most cases, asthma is an inconstant disease throughout the patients' lives, along which they may have periods of remission and asthma attacks [11, 12].

SA accounts for about 5–10% of all confirmed asthma cases in developed countries. Regarding the cost associated with the management of SA, it is about six times higher than the cost of

patients with mild-to-moderate asthma [1]. In addition, SA can come up concomitantly with other chronic diseases, such as rhinosinusitis and chronic obstructive pulmonary disease (COPD) [2]. Despite the high asthma prevalence worldwide, its pathophysiology, phenotypes, endotypes, biomarkers, and treatment still need to be elucidated, therefore, being of great interest of study for the scientific community [13].

3. Pathophysiology of severe asthma

The main pathophysiological feature of asthma is the bronchial inflammation resulting from interactions between airway structural cells and the innate/adaptive immune system. Structural cells of the lung, among them, epithelial cells, endothelial cells, and fibroblasts, release inflammatory mediators, mainly chemokines, and actively participate in the inflammatory process by attracting blood cells to the inflamed site. Thus, the development of the inflammatory response initially orchestrated by the lung structural cells in asthma also depends on innate immunity cells such as eosinophils, neutrophils, macrophages, mast cells, NKT cells, γδ-Tcells, inactive lymphoid cells (ILCs) and dendritic cells, and also on adaptive immunity cells represented by T and B cells. Interactions among these cells and the release of various inflammatory proteins, including cytokines, chemokines, adhesion molecules, eicosanoids, histamine, and nitric oxide (NO), promote the bronchial inflammatory process [14–16]. This inflammatory process is a common feature to all atopic asthmatic patients including those with the severe phenotype.

Histological addresses indicate that bronchial biopsies of asthmatic individuals reveal tissue structural changes, such as collagen deposition under the epithelium, which is described as the thickening of the basement membrane and of the smooth muscle layer of the airways due to the hyperplasia and the hypertrophy of the smooth muscle, which is most commonly observed in patients with severe asthma [17].

Further, there is an increase if the number of blood vessels (angiogenesis) in response to increased secretion of the vessel-endothelial growth factor (VEGF) [18] as well as an increase in mucus secretion commonly observed in biopsies of asthmatic patients, due to an increase in the number of secreting-mucus goblet cell in the epithelium and in the size of submucosal glands [19].

Once asthma presents a complex inflammatory process regulated by immune cells and structural bronchial cells collaborating for the initiation, exacerbation, and maintenance of the inflammatory process, all of these events might lead to irreversible bronchial structural changes and the airway remodeling which strongly contribute to severe development of asthma [15].

3.1. Airway remodeling

Airway remodeling can be defined as a set of changes in the composition, content and organization of the cellular and molecular constituents of the airway wall. The airway remodeling includes epithelial damage, cilial dysfunction, increased thickness of sub-epithelial basement membrane, angiogenesis, and neuronal proliferation. Also, it increases airway smooth muscle

mass and goblet cell hyperplasia with mucus production which causes stress and injury to epithelial cells [20, 21].

Epithelial damage is characterized by the thickening of the sub-epithelial basement membrane with deposition of collagens type I, III, V and VI, periostin, tenascin, osteopontin and fibronectin. Periostin is expressed in epithelial and matrix cells, upregulated by type 2 cytokines, and is implicated in the basement membrane fibrosis [22]. In addition, the epithelium is a source of members of the epidermal growth factor family (neurotrophins, angiogenic factors, and TGF-β) that promotes the neuronal and microvascular proliferation present in the airway remodeling. This process leads to mucosal fibrosis, muscle hyperplasia, and the reduction in distance between airway smooth muscle cells and the epithelium [20].

4. Phenotypes, endotypes and biomarkers

Traditionally, two clinical forms of asthma have been defined: allergic asthma and non-allergic asthma. About 80% of children and 50% of adults have allergic asthma characterized by an allergic sensitization defined by the presence of serum immunoglobulin E (IgE) and/or a positive allergy skin test for common proteins of inhaled allergens such as house dust mites, animal dander, fungal spores, plant pollen, or ingested allergens as peanuts. In 80% of the cases, patients with allergic asthma have concomitant allergic rhinitis. The "united airway disease" hypothesis proposes that allergic rhinitis and asthma are manifestations of the same underlying disease process and that each influences the severity of the other. Non-allergic asthma usually develops later in life with no IgE reactivity to allergens or any obvious involvement of the adaptive immune system such as Th2 cells. This form of disease is more common in women and it is often associated with chronic rhinosinusitis, nasal polyps, obesity, and is difficult to treat, often requiring long-term treatment with systemic steroids [15].

Currently, the division of asthma into only two clinical forms is oversimplified due to the discovery of diverse asthma phenotypes, each one with a distinct pathophysiology as better described further in this chapter. The asthma phenotypes differ in terms of genetic susceptibility, environmental risk factors, onset age, clinical presentation, prognosis, and response to therapies [23]; therefore, asthma is seen as a syndrome rather than a single disease [20]. It is also described as a considerable clinical overlap with COPD among smokers with asthma [2]. On the other hand, endotypes represent molecular mechanisms' underlying observable characteristics of phenotypes and characterization of mediators (biomarkers) as the pharmacological target for each phenotype is desirable to personalize each asthma syndrome [24, 25].

According to the spectrum of asthma, SA affects a group of patients with high medical needs, whose pathophysiology and clinical characteristics vary widely [7, 23]. Therefore, the clinical aspects of SA vary from those based purely on airway obstruction [13, 26] to those related to corticosteroid resistance [1, 3, 27] and to those based on life-threatening (or life-ending) diseases. Therefore it becomes sine qua non to classify SA by specific phenotype(s), endotype(s), and their biomarkers [28, 29].

4.1. Phenotypes of severe asthma

Phenotypes of SA involve a complex interaction of many genetic and environmental factors in association with observable characteristics, such as specific IgE responsiveness (biomarker) to particular allergens and lung functions [7, 23, 30] (**Figure 1**). Therefore, characterization of these phenotypes has involved biased and unbiased approaches to grouping clinical, physiologic, and hereditary characteristics [7, 31–33]. Nowadays, SA phenotypes are mainly composed of the following classification: type 2 asthma and non-type 2 asthma (**Figure 1**).

4.1.1. Type 2 asthma

Allergic asthma, which has been described as Th2 immune response (type 2), is a hallmark with an increase of CD4$^+$ T cells that produce IL-4, IL-5, and IL-13 detected on the bronchoalveolar fluid as well as on mucosal biopsies and correlated with blood and airway eosinophilia and
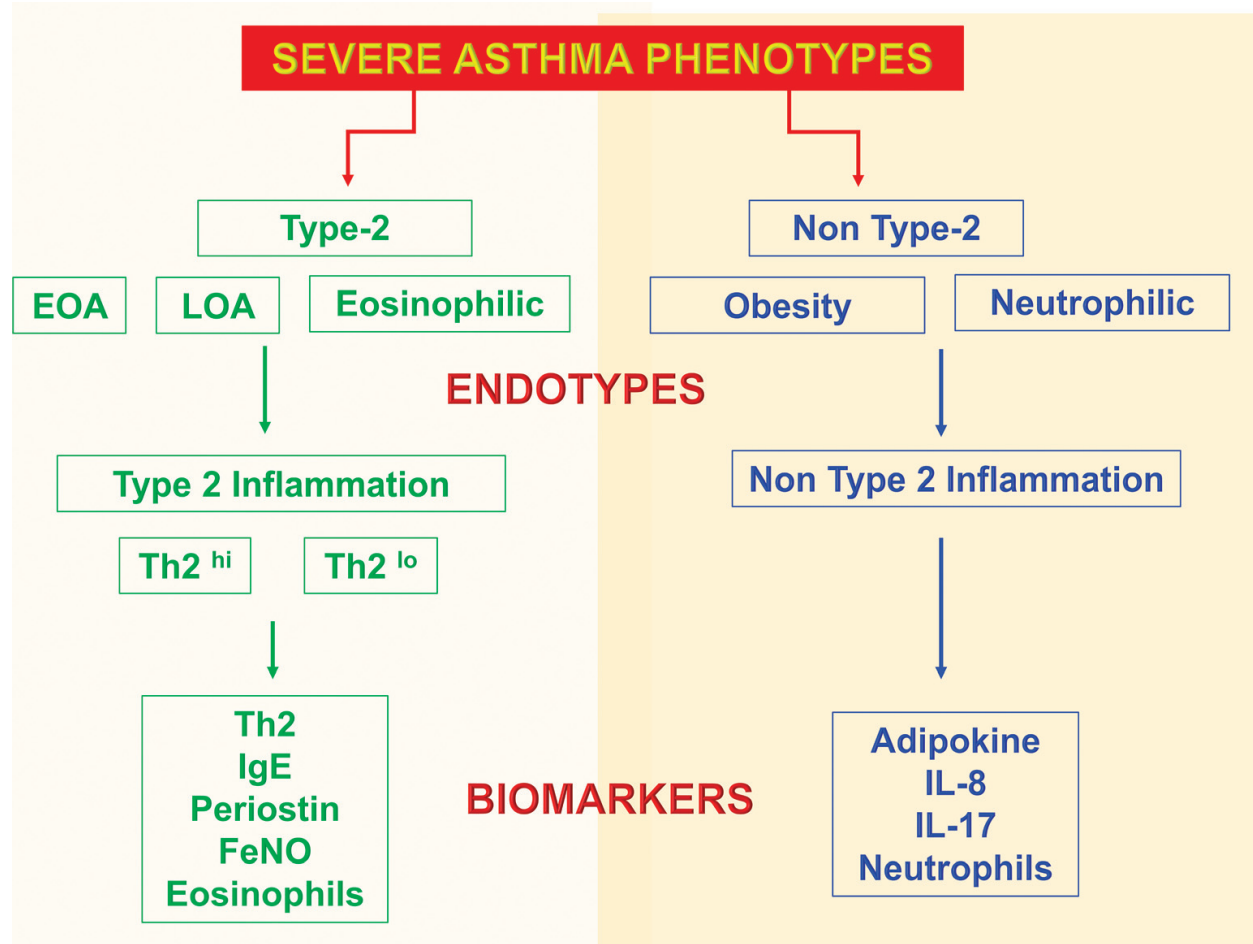

Figure 1. Phenotypes, endotypes, and biomarkers in severe asthma. Asthma is divided into phenotypes: type 2 inflammation and non-type 2 inflammation. Type 2 phenotype: early onset asthma (EOA), late onset asthma (LOA), and eosinophilic asthma; biomarkers: Th2 cytokines, IgE, Periostin, FeNO (fraction of nitric oxide expired), and eosinophilia. Non-type 2 phenotypes: asthma associated with obesity and neutrophilic asthma; biomarkers: adipokine, IL-8 or IL-17, and neutrophilia.

high-serum titer of allergen-specific IgE as biomarkers [34]. The presence or absence of these cytokines, allergen-specific IgE and eosinophilia, is a feature of Th2^{hi} and Th2^{lo} endotype clusters, respectively [35, 36]. The type 2 asthma phenotype is divided into early-onset asthma (EOA), late-onset asthma, and eosinophilic asthma [37].

4.1.1.1. Early-onset asthma (EOA)

EOA phenotype originates in early childhood, is characterized by an allergic component, and might be observed on the most asthmatic patients. However, the lack of responsiveness to corticosteroids and the lower concentrations of IgE in some children with asthma suggest that not all EOA is type 2-associated phenotype, and this may be important in the development of SA [38].

Recent researches have shown the importance of age at the onset to the SA phenotype [7, 13, 39]. Early onset better identifies "allergic asthma" than clinically available tests of atopy/allergy. Classification of adult asthma into EOA is widely used in the literature. A recent review included 12 studies comparing early- and late-onset current asthma in adults. The most common age used to delineate the 2 age-of-onset phenotypes was 12 years [40, 41]. EOA can be present with mild-to-severe disease, but it is unclear whether mild allergic asthma progresses to a severe disease or whether severe allergic asthma arises in childhood and remains severe [32].

The Severe Asthma Research Program (SARP) cluster analysis showed that people with the most severe EOA had greater numbers of skin-test reactions and poorer lung functions than individuals with mild asthma and that they were more likely to be of African descent. It also linked SA to a longer duration of disease and a history of pneumonia [42]. These data suggest that both genetic and environmental factors are important in asthma pathogenesis [13]. It is likely that as the severity of allergic early-onset type 2 asthma increases, non-Th2 immune pathways including those related to Th17 and Th1 are also engaged, as is innate immunity [43, 44].

The prognosis for children with initial severe atopic phenotypes is worse than for other phenotypes and this poor prognosis of allergic asthma with early onset has also been described in numerous prospective birth cohorts [23, 40]. In adults, mold sensitization in allergic asthma is associated with severe exacerbations requiring hospitalization and uncontrolled asthma despite high doses of ICS usage [13, 42].

4.1.1.2. Late-onset asthma

LOA is prevalent in adults over 65 and is also denominated as adult-onset asthma. The rate of morbidity and mortality of patients directly attributable to LOA is 4–15% higher than young patients with asthma [45, 46]. In addition, these numbers are underestimated due to the presence of comorbid diseases that complicate the diagnosis, as wheezing, breathlessness, and cough can also be caused by cardiovascular diseases [47]. The prevalence of asthma in the elderly is higher than was previously thought and considering the rapid aging of the global population the burden of asthma in the elderly is expected to rise significantly [15, 37]. In addition, older adults are more likely to be diagnosed with COPD without consideration of asthma, especially if they have a history of smoking [30]. Taking together these factors, the

differential diagnosis of asthma in adults is potentially more challenging than in children, and asthma costs may be higher among older patients due to increase of hospitalization.

The role of genetic predisposition in LOA is less clear than in atopic childhood-onset asthma. In LOA, a family history of asthma is often lacking and atopy is not more common than in the general population. Occupational asthma has become the most common type of LOA in many industrialized countries [48]. Forward, female sex hormones are associated with non-atopic LOA [49] whereas no sex difference was observed for the incidence of allergic asthma. Alternatively, asthma prevalence decreases with the number of years of oral contraceptive pill use [50]. In addition to that, there is evidence that the incidence of asthma decreases after menopause [51], whereas hormone replacement therapy in post-menopausal females is associated with an increased risk of asthma onset [52, 53].

Adult-onset asthma with highly elevated numbers of eosinophils often is related to sinusitis and nasal polyps. This phenotype indicates an association to type 2 cytokines and inflammatory cells such mast cells and basophils [54]. However, the lack of allergy clinical symptoms in this phenotype suggests that the Th2 process differs from and is probably more complex than the one associated with the early-onset asthma phenotype. As type 2 cytokines are also upregulated in cancer, inflammatory bowel disease, and interstitial fibrosis, a Th2 inflammatory process in the lung without mucosal-allergen-specific IgE and associated clinical allergic reactions is clearly possible [55, 56].

Also, some asthmatics present a mix of sputum neutrophilia and eosinophilia which might imply that there are interactions of additional immune pathways (endotypes) with Th2 immunity, including activation of pathways related to IL-33 and IL-17 by Th17 cells [57–59].

The phenotype named late-onset non-allergic asthma of the elderly [54] occurs in individuals beyond 65 years with a frequency of 8–10%. This phenotype can be grouped into two sub-phenotypes: (i) the persistent asthma and (ii) the newly diagnosed asthma [13, 20, 60] where atopy and elevated IgE levels are less frequent.

The physiologic and histopathologic findings in the airways of aging subjects are driven by important cellular age-associated changes. The immune system is complex and with increasing age, there are alterations in both the innate and adaptive immune responses, termed "immunosenescence." Research on this subject has focused primarily on cancer and autoimmunity but not in asthma. However, immunosenescence likely has important consequences in elderly asthmatics and increases susceptibility to airway infections, which in turn may exacerbate underlying SA or potentially play a role in the inception of LOA patients [22]. Another important issue in the airway of aging individuals is the increase in the number of sputum neutrophils [22, 26] and neutrophil mediators including MMP-9, neutrophil elastase, and IL-8, biomarkers for this phenotype, resembling changes seen in a phenotype of SA noted in some younger adults [1].

4.1.1.3. Eosinophilic severe asthma

Eosinophils are granulocytic effector cells that produce and store biologically active molecules, including cytotoxic proteins, that is, major basic protein (MBP), eosinophil peroxidase (EPX),

eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN), lipid mediators, chemotactic peptides, as well as cytokines [61] against pathogens. However, the eosinophil-derived granule proteins are not only toxic to pathogens but also to other cells within immune responses, causing tissue damage and consequently organ dysfunction. In addition, eosinophils can contribute to inflammatory pathways through their capacity to synthesize and secrete a remarkable number of pro-inflammatory cytokines and chemokines [61–63].

Indeed, eosinophils produce type-2 cytokines (IL-4, IL-5, IL-13, and IL-25) and chemokines (CCL5/RANTES, CCL11/eotaxin, and CCL3) and are able to recruit leukocytes to the inflamed site [64, 44]. Alternately, following the allergen challenge, airway eosinophils have been shown to express GM-CSF and CXCL8/IL-8 [65, 66], thereby inducing neutrophil recruitment.

Therefore, eosinophils may contribute to airway remodeling in SA through release of transforming growth factor (TGFβ-1) [64]. It has also been reported that interferon-gamma (IFN-γ) might also potently activate eosinophils [67] and is elevated in the serum of some acute severe asthmatic patients [68], underscoring the importance of these pathways in SA.

Recently, a multiple-biomarker approach has been described to predict eosinophilic SA. These ones are represented by high-exhaled nitric oxide (FeNO) and elevated serum levels of periostin which correlate with increased eosinophil numbers in sputum, poor asthma control, and severe disease phenotype [69, 70]. FeNO is secreted by epithelial cells, macrophages, and other inflammatory cells in response to different stimuli into the asthmatic lung; however, the mechanisms involved in FeNO enhances still remain poorly unknown. On the other hand, periostin is mainly secreted by airway fibroblasts and epithelial cells in response to type 2 cytokines IL-4/IL-13 and TGF-β. Elevated levels of this biomarker have also been reported to correlate with eosinophil adhesion, recruitment and activation, airway remodeling, as well as chronic eosinophilic rhinosinusitis [70].

4.1.2. Non-type 2 asthma

Absence of type 2 profile in asthmatics represents half of all asthmatic patients and the lack of described biomarkers makes difficult phenotype-based therapy [71–73]. Some patients might lack type 2 inflammation profiles simply because corticosteroids have substantially reduced that pathway. Non-type 2 patients generally have LOA often in association with obesity, post-infectious, neutrophilia, smoking-related factors and are less likely to be atopic or allergic [7, 74].

4.1.2.1. Obesity-related asthma

Obesity and asthma are important public health problems [75], and the symptoms of asthma in obese individuals are more severe once these patients present development of steroid resistance, destabilization or lack of asthma control, and the worst quality of life [76]. Obese asthmatics are characterized in two phenotypes based in the Th2 profile: (i) an early-onset atopic asthma (EOA)—this phenotype presents Th2^{hi} profile, where allergic asthma is complicated by the presence of obesity and (ii) late-onset non-atopic asthma (LOA)—this phenotype presents the Th2^{lo} profile, occurring preferably in women and where the development of asthma is a consequence of obesity [77].

In the EOA phenotype, obese asthmatics have a history of atopy, increased airway obstruction, greater bronchial hyper-reactivity, higher IgE serum level, and a greater likelihood of allergic sensitization and reactions compared with late-onset obese asthmatics [78]. In contrast, late-onset obese asthmatics had less atopy, less bronchial hyper-reactivity, less airway obstruction, and fewer exacerbations [77]. There is a clear association between obesity and asthma and probably childhood obesity precedes the onset of asthma. However, more studies that clarify the characteristics of the two described phenotypes are needed [78].

Adiponectin is an important adipokine secreted by the adipocytes and its levels have been reported to be lower in obese patients [78]. In the asthma context, it appears that adiponectin does not protect against the development of inflammation and may in fact exacerbate the
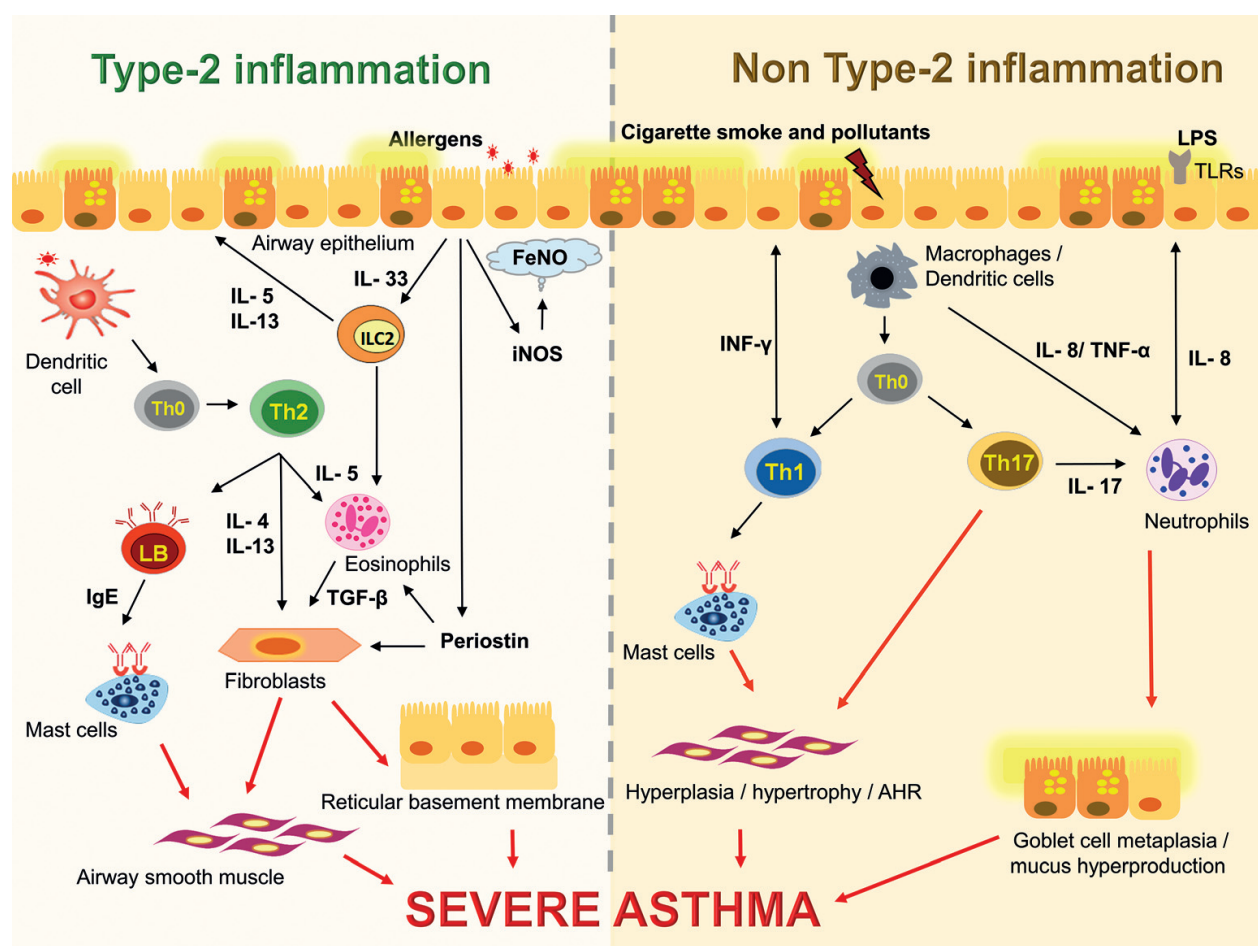

Figure 2. Type 2 inflammation and non-type 2 inflammation and its relation to structural changes in severe asthma. In type 2 inflammation, self-maintenance of the inflammatory process occurs through the following mechanism: Type 2 cytokines are generated by Th2. Lymphocytes and ILC2 cells, which activate several cells downstream, inducing remodeling of the airways through the thickening of the MBR, metaplasia/hyperplasia of goblet cells, mucus overproduction, and airway smooth muscle hyperplasia/hypertrophy. Factors involved in the development of non-type 2 inflammation in asthma include pollutants, cigarette smoke and microorganisms. These factors can activate innate immunity as well as Th1 and Th17 inflammatory processes. *Abbreviations*: AHR, hyper reactivity of the airways; FeNO, fraction of nitric oxide expired; IL, interleukin; ILC2, innate lymphoid cell; iNOS, nitric inducible oxide synthase; RBM, reticular basilar membrane; TGF-β, transforming growth factor-β; LPS, lipopolysaccharide; TLRs, toll-like receptors; TNF-α, tumor necrosis factor-α; IFN-γ, interferon-γ.

disease via anti-Th1 inflammatory effects, allowing type 2 differentiation and a more severe allergic response [75]. Another pro-inflammatory adipokine is resistin [29] whose levels of resistin: adiponectin ratio have been found to be higher in asthmatic uncontrolled subjects than in control subjects [78].

4.1.2.2. Neutrophilic asthma

Neutrophilia has been inconsistently associated with SA for several years although it is generally seen in corticosteroid-treated patients [79–81]. In affected individuals, lung neutrophilia has been associated with lower lung function, more trapping of air, thicker airway walls, and greater expression of matrix metalloproteinases compared to people with non-neutrophilic asthma; however, neutrophilia has not been associated with airway hyper reactivity [82, 83].

In SA, the number of neutrophils, in bronchi, is elevated compared to healthy subjects [58]. These cells were characterized by a high expression of the high affinity receptor for IgE (FcεRI) and released IL-8 (CXCL8) [84]. The expression of FcεRI on neutrophils seems to depend on the presence of type 2 cytokines [85]. The number of neutrophils in the airways of asthmatic individuals depends on IL-8 and TNF-α concentrations, both being chemotactic cytokines released from macrophages, epithelial cells, and neutrophils [86, 87].

Transcripts for IL17A were found to be elevated in the sputum of patients with asthma and were correlated with IL-8 transcripts and sputum neutrophils as well as with asthma severity [88]. Although, type 2 cells are predominant in the course of atopic diseases, the recruitment of neutrophils in the course of non-atopic asthma is driven by Th17—a subset of T helper cells releasing IL-17 [89, 90]. Neutrophilia can also coexist with eosinophilia, and this characteristic identifies people with disease severity and emphasizes the complexity of the immunobiology of SA in respect of the multiple different innate and adaptive immune pathways and cell functions involved in asthma phenotypes and endotypes [57, 91] (**Figure 2**).

5. Severe asthma management: classical and biological therapies

Several endotypes are targeted to control SA symptoms by reducing future asthma attacks. The most classical strategy to approach such outcomes in asthma pharmacological therapy is linked to regulation of the smooth muscle cell contraction/relaxation machinery. These targets are represented by an array of cell receptors reported as β2 adrenergic, muscarinic, and glucocorticoid receptors, phosphodiesterases enzymes, leukotrienes receptors, and leukotriene synthase enzyme [20]. These receptor functions are largely regulated by the classical pharmacological therapies used to treat asthma and they have been mentioned to cause a satisfactory disease control when administrated as monotherapy or in combination in different dosages for children, adolescents, adults, or special population which are the ones with comorbidities, that is, obesity, food allergy, anxiety, and depression and others [3].

Medications used for SA control and risk reduction so far represent the main strategy to attenuate the illness symptoms. In case of SA the combination of higher dose ICS and LABA

is recommended. These medications are pharmacologically classified as gold-standard steroid/bronchodilator drugs. Their effects occur by linking on nuclear cell receptors leading to strong inhibition of several inflammatory asthma parameters such as type-2 cytokine production, eosinophil activation, and mucus-secreting goblet cells, which are key components to asthma symptoms initiation, maintenance, and exacerbation [92, 93]. Also, the long-acting muscarinic agonist—LAMA named tiotropium—has been used as an add-on pharmacotherapy for SA control [94]. See below the main SA management medication/procedures in **Table 1**.

Adapted from [3].

However, classical pharmacological therapy causes side-effects and adverse drug events affecting for instance adrenal, growth suppression, and other organ malfunction [95]. Additionally, it has been reported that ≥40% of asthmatic patients are not well controlled which may require escalated treatment [96]. Therefore, new asthma targets/biomarkers have been searched in the perspective of improving asthma therapy considering the different disease endotype such as type 2, non-type 2, and bronchial epithelium-derived factors [28].

5.1. Endotypes/biomarkers-based asthma therapy

Anti-IgE therapy was previously described to treat SA patients that do not respond to classical therapy. High allergen-specific-IgE serum level has been reported as the type 2 asthma biomarker. Its secretion is crucial to eosinophil and basophil sensitization that is defined as a previous step to mast cell degranulation, and posterior pro-inflammatory and spasmogenic molecules stimulate smooth muscle cells, blood vessels, sensory nerves, and mucus-secreting goblet cells which are altogether pivotal to induce hyper-reactivity and lung inflammation [97]. Therefore, inhibiting IgE response is an important approach to control SA symptoms and in this perspective the anti-IgE medication omalizumab has provided good outcomes [98].

Treatment and strategies	Medication/procedure	Dosage
Higher-dose ICS/LABA combination	Prednisolone, formoterol	ICS: Max 2000 mcg/day LABA: Max. 72 mcg/day
Oral corticosteroids	Prednisone or prednisolone	Adults: 1 mg/kg/day Children: 1–2 mg/kg/day
Add-on therapy without phenotyping	Tiotropium (LAMA)	5 μg, 2.5 μg or 1.25 μg once daily during 4–week period
Add-on therapy with phenotyping	Omalizumab (anti-IgE), mepolizumab and reslizumab (anti-IL-5)	Omalizumab: 150–1200 mg once every 2 or 4 weeks Mepolizumab: 750 mg once every 4 weeks Reslizumab: 3 mg/kg every 4 weeks up to 24 months
Non-pharmacological therapy	Bronchial thermoplasty, high-altitude treatment and psychological interventions	

Table 1. Severe asthma management.

Therapy based on anti-IL-5 administration, mepolizumab, has been shown effective to reduce severe eosinophilic asthma symptoms by inhibiting IL-5 actions highly on eosinophils but also in basophil cells [61]. It is well documented that IL-5 is a key cytokine implicated in maturation, activation, proliferation, and survival of eosinophils. Then, part of difficult-to-treat eosinophilic asthma patients does not respond to both ICS and systemic glucocorticoids, which points to IL-5 as an important biomarker to be targeted in SA therapy. Also, a placebo-controlled trial in patients with eosinophilic severe asthma has revealed the safety and efficacy of the anti-IL-5 therapy named reslizumab which reduces asthma exacerbation and improves lung function as asthma control [99].

Another endotype-based therapy for SA has emerged and the use of anti-IL-4 and anti-IL-13 therapies indicates satisfactory outcomes [41]. Both cytokines present a crucial role in IgE synthesis, eosinophil activation, mucus secretion, and airway remodeling indicating that neutralizing these biomarkers might collaborate to SA control. Additionally, prostaglandin D (PGD) 2 receptor expressed by type 2 cells named CRTH2 has been implicated in SA symptoms which might be controlled by the use of a CRTH2 antagonist. PGD2 is an arachidonic acid derivative mainly secreted by mast cells and activates several cells. In response to activation, these cells secrete an array of pro-inflammatory cytokines present into the asthmatic lung [100].

Besides classical pharmacological and/or biological asthma therapy, other therapies (i.e., allergen immunotherapy, vaccinations, bronchial thermoplasty, and vitamin D), non-pharmacological treatments (i.e., avoidance of allergens, air pollutants, some foods and medicines, healthy diet, physical activity, weight reduction, dealing with emotional stress, and others), and complementary and alternative medicine have been reported in the literature. However, the last one has been not recommended for use by severe adult asthmatic patients due its limited evidence of effectiveness [101].

Individualized management protocol should be taken into account for asthmatic special population, for instance, exercise-induced bronchoconstriction in adolescents, elderly, pregnant, and aspirin-exacerbated respiratory disease; however, the management of SA is importantly challenging and the endotype-based therapies might be the better strategy to approach the illness control.

6. Conclusion

Human severe asthma is a heterogeneous disease and an emerging health public issue affecting hundreds of million people worldwide and such a complex inflammatory condition which has led this to be classified as a syndrome. Recent cluster analyses on severe asthma based on phenotypes, endotypes, and biomarkers have hardly classified this illness to better improving its management. Updated asthma phenotypes known as type 2, non-type 2, eosinophilic, or neutrophilic raise the necessity of new biomarker identification, mainly a single one, for diagnosis and therapy purposes. In this chapter, we reviewed the advances on severe asthma phenotypes/endotypes, diagnoses, and management based on classical medication composed of high doses of inhaled corticosteroids and long-acting β2 agonist combination as well as

those add-on therapies represented by long-acting muscarinic agonists, biological/monoclonal antibodies, and non-pharmacological approaches routinely used to control difficult-to-treat asthma. Finally, taking all these new concepts and management strategies on severe asthma, it has been agreed by international consensus on the urgent need for the development of a new phenotype/endotype-based therapy to treat severe asthma.

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