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Eosinophils and T2 inflammation in severe asthma

Agamemnon Bakakos, Nektarios Anagnostopoulos, Petros Bakakos*

1st Department of Respiratory Medicine, National and Kapodistrian University of Athens, 11527 Athens, Greece

***Correspondence:** Petros Bakakos, 1st Department of Respiratory Medicine, National and Kapodistrian University of Athens, 152 Mesogeion Ave, 11527 Athens, Greece. petros44@hotmail.com

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Abstract

Asthma is a common chronic inflammatory disease of the airways that affects more than 330 million people globally. Severe asthma, despite being 5–10% of the total asthmatic population presents significant morbidity and high cost due to health care utilization. The management of severe asthma has dramatically changed with the use of biologics. However, biologics have been approved only for patients with severe asthma with type-2 mediated inflammation. Eosinophils are central in the T2 inflammatory process in asthma and this stands true for the severe form of the disease as well. In this review, we discuss basic insights into the pathogenesis of severe asthma related to eosinophilic inflammation and the pivotal role of T2 cytokines which have also become along with eosinophils the target of biologics. Novel biologics such as tezepelumab have demonstrated efficacy regardless of the blood eosinophil count and have shown promise for T2 low asthma, although to a lesser degree.

Keywords

Asthma, severe asthma, eosinophils, T2 inflammation

Introduction

Asthma affects globally more than 330 million people, accounting for a significant burden on public health [1]. Severe asthma is less than 10% of the total asthmatic population but its cost, both direct and indirect, is huge [2, 3]. The use of biologics has dramatically changed the management of severe asthma but still, an unmet need exists for some patients who suffer from it. Phenotyping and endotyping of severe asthma have become the cornerstone for its management and also for the choice of the proper biologic to be used [1, 4, 5]. Up to this moment, six biologics have been approved for severe asthma while there has been active research for more not only in asthma but also in chronic obstructive pulmonary disease (COPD). As the arsenal of our tools to control severe asthma is becoming bigger and more effective, a deeper insight into the pathophysiology of the severe disease is growing in parallel and thus gives us the opportunity to understand the mechanisms of action and the potential future interventions that may arise.

Severe asthma

Despite the existence of precise definitions, there has been a complexity in recognizing severe asthma in clinical practice. Traditionally, severe asthma was defined as one that requires treatment Global Initiative for Asthma (GINA) step 4 or 5 in order to be controlled or that remains uncontrolled despite this treatment [1, 2]. However, and this occurs quite often, other factors such as poor adherence to medication and inhaler technique and/or presence of comorbidities are the reason that asthma is not controlled despite step 4–5 treatment and that is called difficult-to-treat asthma [5]. After taking care of these factors properly, a significant proportion of asthmatics gain control and those who still remain uncontrolled are defined as severe asthma [6]. Patients with eventually severe asthma present frequent and bothersome symptoms, asthma exacerbations, and medication side effects, especially those who receive daily or frequent bursts of oral corticosteroids (OCS) [7]. Reducing the use of OCS has always been a priority in the management of asthma [8]. Side effects from OCS along with other medication costs, physician visits, and hospitalizations account for the huge healthcare cost that severe asthma imposes [7–9].

Severe asthma is quite heterogeneous in terms of age onset, underlying inflammation, symptom burden, exacerbation rate, and response to treatment [10]. The latest is the main reason for phenotyping severe asthma whereas in mild-to-moderate asthma response to inhaled corticosteroids (ICS) is remarkable and achieves disease control. In contrast, the "one size fits all" does not exist in severe asthma, and here is where the difficulties begin to be encountered.

T2 inflammation in severe asthma

Asthma has been traditionally characterized by eosinophilic inflammation of the airways but this is not true for all asthmatics, especially those towards the most severe end of the disease. T2 high asthma is defined as asthma where type 2 inflammation predominates with eosinophilic infiltration of the airways [11]. It is accompanied by elevated blood eosinophil count and elevated fractional exhaled nitric oxide (FeNO) which are the main biomarkers used in order to characterize T2 high asthma in clinical practice. On the other hand, T2 low asthma is the one with neutrophilic inflammation or paucigranulocytic asthma where in both cases markers of eosinophilic inflammation are lacking [12]. There is a broad range of percentages when trying to estimate the frequency of T2 high and T2 low asthma among severe asthmatics mainly due to the different criteria and cut-off levels for biomarkers used for definition. It seems that more than 60–70% belongs to the T2 high phenotype of severe asthma [13–15].

The main T2 high cytokines involved in asthmatic inflammation are interleukin (IL)-4, IL-5 and IL-13 [16]. IL-4 plays a key role in the differentiation of CD4 T helper lymphocytes and in the isotype switching of immunoglobulin E (IgE) in B-lymphocytes [4]. IL-5 is the key cytokine for the differentiation, mobilization, and survival of eosinophils [17]. IL-13 is important for the constriction of smooth muscle cells and also in the production of mucus [4]. Targeting IgE at first and these T2 cytokines became today the holy grail of the biological treatment of severe asthma.

Thymic stromal lymphopoietin (TSLP), an epithelial cytokine that regulates upstream airway inflammation has been a recent target of biologics [18]. TSLP expression has been found to increase in patients with asthma [19]. Moreover, TSLP can induce T2 airway inflammation as has been demonstrated in animal studies [20, 21]. It is important to note that TSLP may trigger non-T2 inflammatory responses in asthmatics as well, thus making it a more interesting target for type 2 low asthma [22].

In allergic response, naive T cells are polarized into activated T2 cells through allergen presentation by antigen-presenting cells, thus leading to the release of T2 cytokines IL-4, IL-5, and IL-13 [18]. In a non-allergic response, the epithelial cells are triggered by pollutants, viruses, and bacteria to release alarmins (IL-25, IL-33, and TSLP) that activate the type 2 innate lymphoid cells (ILC2) resulting again in the production of T2 cytokines IL-5 and IL-13 [23].

On the other hand, T2 low asthma has a poorly understood pathophysiology. It is predominantly late-onset and non-atopic [24]. In some asthmatics, it is associated with neutrophilic inflammation in which T17

cells are involved with the production of IL-17A and IL-17F that lead to the production of cytokines that are neutrophil chemoattractants such as CXCL-10 and CXCL-8 [25]. Alternatively, the activation of type 3 innate lymphoid cells may lead to neutrophilic inflammation through the production of cytokines by macrophages [26]. TSLP activates dendritic cells that consequently polarize naive T cells towards Th17 cells that release IL-17 thus promoting neutrophilic inflammation [27, 28].

Paucigranulocytic asthma is also considered as T2 low asthma despite the fact that in some cases it is believed to represent a well-controlled underlying T2 inflammation [29]. It is true that some patients with this asthma phenotype present significant symptoms and frequent exacerbations [29, 30].

Biologics are recommended by GINA for T2 high severe asthma [1]. GINA defines refractory T2 high inflammation in an asthmatic patient who receives high-dose ICS and presents blood eosinophils > 150 cells/μL and/or FeNO > 20 ppb and/or sputum eosinophils > 2% and/or asthma that is clinically allergen driven. They have inaugurated a new era in severe asthma treatment that was mainly biomarker-driven instead of symptom-driven [4]. They also have the advantage of improving comorbidities such as atopic dermatitis, chronic rhinosinusitis with nasal polyps, and chronic urticaria [31–35].

Induced sputum has been used in order to phenotype severe asthma according to the predominant cell type and four phenotypes have been described: eosinophilic, neutrophilic, mixed (both eosinophilic and neutrophilic), and paucigranulocytic [36–38]. It is essential to note that this definition of phenotype may be influenced by the received treatment as it is evident that corticosteroid treatment reduces sputum eosinophil counts and may also increase neutrophil counts [39]. Accordingly, the observed phenotype might not accurately reflect the underlying asthma pathophysiology. Moreover, airway remodeling that is not directly related to inflammation may differ among severe asthmatics [40].

Eosinophils and severe asthma

Eosinophils are myeloid cells that differentiate in the bone marrow and migrate into tissues [41]. In the lungs of asthmatics, these cells are pivotal for the inflammatory response but also for the other pathophysiologic feature of asthma, so-called airway remodeling [42]. The degranulation of eosinophils results in the release of proteins that cause damage to the bronchial wall [43].

The trafficking of eosinophils in the airways results from attraction by IL-5 and eotaxin-1 [44]. IL-5 is produced either by T-helper 2 cells or ILC2. In the first situation production of IgE by IL-4 is important and leads to the development of more Th2 cells. IL-4 drives the IgE isotype switching in B lymphocytes and is the key cytokine for the differentiation of Th2 lymphocytes [4]. Alternatively, ILC2 cells secrete both IL-5 and IL-13 induced eotaxin that leads to eosinophil accumulation [45]. ILC2 cells produce these Th2-type cytokines in response to epithelium-derived cytokines IL-25 and IL-33 that mediate the response to pathogens, viruses, and particles attacking the airway epithelium [46]. ILC2 cells express the cysteinyl leukotriene receptor 1 (CysLT1R) which upon ligation with its ligand leukotriene D4 (LTD4) may stimulate the production of type-2 cytokines such as IL-4, IL-5, and IL-13 [47]. Based on the above, it is obvious that eosinophilic asthmatic inflammation may arise through allergic or non-allergic pathways. Translating this into clinical practice it means that the treatment of the eosinophilic phenotype in asthma with anti-IL-5 antibodies might be for patients with differing underlying inflammatory pathophysiology.

The assessment of eosinophils in different samples of patients with asthma and mainly severe asthma such as biopsies, bronchoalveolar lavage fluid (BAL), sputum, and peripheral blood has been used to characterize the disease from many clinical aspects. Asthma severity has been related to the number of eosinophils in peripheral blood, BAL, and bronchial biopsy [48]. Moreover, eosinophils have been associated with an increased rate of asthma exacerbations [1]. A percentage of sputum eosinophils > 3% has been correlated with airway eosinophilia [49]. A strategy aiming at reducing sputum eosinophils resulted in a reduction in the rate of exacerbations, especially in severe asthmatics [50].

Blood eosinophil count is an easy-to-use biomarker but it has its advantages and limitations. It has been used as a biomarker for airway eosinophilia due to the correlation between blood and sputum

eosinophil counts [51]. Although high blood eosinophil counts demonstrate good specificity for airway eosinophilia low blood eosinophil counts are not always indicative of a lack of airway eosinophilia [52–55]. This was obvious in a study with children having severe asthma, where 84% presented airway eosinophilia despite 86% of them having normal blood eosinophil counts [56]. Another significant factor is the stability of numbers and/or percentages of blood eosinophils in time. There is inherent variability in peripheral blood eosinophil counts over time and moreover eosinophils are very sensitive to factors such as treatment with corticosteroids (systemic and/or inhaled) [57]. In severe asthmatics who receive maintenance OCS the number of blood eosinophils is suppressed. It has been suggested that OCS should be stopped or at least the blood eosinophil measurement should be performed at the lowest possible OCS dose [6]. It should also be noted that high-dose ICS may influence the blood eosinophil count but to a lesser degree compared to OCS. It has been shown that a single measurement of at least 150 cells/L was predictive of subsequent measurements on average of at least 150 cells/L in 85% of patients [57].

Biologic treatment choices for T2 high eosinophilic severe asthma

Omalizumab

The first biologic treatment for severe asthma was omalizumab. Its mechanism of action is the binding of free IgE, thus reducing its levels and preventing it from binding to the high-affinity receptor on basophils and mast cells which leads to receptor downregulation [23]. The indication of omalizumab is moderate-severe atopic asthma with at least one positive skin prick test or RAST to a perennial allergen, that is not controlled by ICS. Its dosage relies on body weight and initial level of IgE, however, this level is not predictive of a response to the treatment [58, 59]. Omalizumab is being administered subcutaneously every two to four weeks. The data regarding the reduction of exacerbations are more robust compared to the data regarding a steroid-sparing effect [60, 61]. In a study by Hanania et al. [62], omalizumab was more effective in reducing exacerbations in patients with blood eosinophils ≥ 260 cells/μL or FeNO ≥ 20 ppb, while in the STELLAIR study omalizumab was effective in reducing exacerbations irrespective of the number of eosinophils [62, 63]. In the studies POLYP 1 and POLYP 2, omalizumab significantly improved endoscopic, clinical, and patient-reported outcomes in patients with severe chronic rhinosinusitis with nasal polyps who presented inadequate response to intranasal corticosteroids, and it was well tolerated [31].

Mepolizumab, reslizumab, benralizumab

Mepolizumab and reslizumab which target IL-5 and benralizumab which targets IL-5R are the three monoclonal antibodies that have been approved for severe eosinophilic asthma. These treatments proved effective in reducing exacerbations and systemic steroids in severe asthmatics. Blood eosinophil count (> 150 cells/μL) was a pre-requisite for using them but also a predictive marker as it was demonstrated that the higher the blood eosinophil count is the more likely the patient to respond [64]. Mepolizumab proved to be effective in severe chronic rhinosinusitis with nasal polyps and has been licensed in patients with eosinophilic granulomatosis with polyangiitis (EGPA) and hypereosinophilic syndrome [32, 65, 66]. Real-world studies managed to confirm the findings of randomized controlled trials (RCTs) and also showed better lung function, improved symptom control, and quality of life. In a real-life study from Italy, benralizumab given in severe eosinophilic asthma showed long-term efficacy in all asthma outcomes after 96 weeks of treatment with a dramatic decrease of exacerbation rate by 95%, elimination of OCS in 60% of asthmatics and improvements in lung function and asthma control that progressed over time [67].

Dupilumab

Dupilumab binds to the IL-4Rα and inhibits the signaling of both IL-4 and IL-13 [68]. Dupilumab reduced exacerbation rate and use of systemic steroids in asthmatics with non-controlled moderate-to-severe asthma who presented with a high blood eosinophil count (> 150/μL) and/or high FeNO (25 ppb) [69, 70]. It has also been approved for the treatment of chronic rhinosinusitis with nasal polyps which is frequently encountered with asthma, either severe or not [33]. Dupilumab's main adverse effect is hypereosinophilia which occurs in almost 15% of those who receive this treatment [70]. Usually, it is asymptomatic and it may

lead to cessation of treatment in a lower percentage of receivers. FeNO and total IgE were reduced by dupilumab treatment [69]. Dupilumab proved to be effective in atopic dermatitis [71].

Tezepelumab

The "new kid on the block" is tezepelumab. It is a monoclonal antibody directed against TSLP which is an alarmin (along with IL-25 and IL-33) that are all released by epithelial cells. The mechanism of action of tezepelumab arises from binding to TSLP, thus preventing its interaction with the TSLP receptor [72]. Tezepelumab, apart from reducing the rate of exacerbations in severe asthmatics was able to reduce all T2-high biomarkers, thus blood eosinophils, FeNO, and IgE [73, 74]. At the same time, it demonstrated efficacy in patients with T2-low severe asthma, being the only biologic having this property, but still to a lesser degree compared to T2-high asthma. Although strangely it did not prove to be effective in reducing OCS, ongoing studies re-evaluate this outcome [75]. The DESTINATION study demonstrated that treatment with tezepelumab was safe and the improvements in exacerbation rate, lung function, and asthma control were sustained for up to 2 years [76]. Tezepelumab showed an effect in improving airway hyperresponsiveness, a hallmark of asthma not being evaluated in other studies involving monoclonal antibodies [77–79].

Discussion

Eosinophils are key cells in the pathophysiology of asthma and more often in the severe form of the disease. T2 inflammation is most frequently the underlying inflammatory process that characterizes severe asthma but a T2 low phenotype also exists. T2 cytokines have become the primary target of new therapies for severe asthma with monoclonal antibodies, called biologics. Phenotyping severe asthma has been achieved with the use of biomarkers and among them, blood eosinophil count is the most commonly assessed biomarker. This has proved extremely important in the clinical decision for the choice of biologics. Eosinophils have become the target of biological therapies in both allergic and non-allergic severe asthma. Moreover, comorbidities are an integrated part of such an assessment, even more vividly now that many biologics have been approved for some of these co-existing conditions. Since there are no head-to-head studies to compare biologics the switch from one to another has been an attractive option although it should also be based on the phenotypic evaluation of the patient [80].

The era of biologics has definitely changed the landscape of severe asthma treatment and has made the quality of life of such patients better. At the same time, it has helped us to understand more deeply the pathophysiology of the disease in which we attempt to intervene with the biologics. Whether such an intervention may lead to permanent changes in the underlying endotype remains an unanswered question, especially in view of the fact that there are no guidelines on the duration of treatment with a biologic in a responsive severe asthmatic. For sure, the reduction of the exacerbation rate and the use of systemic corticosteroids have been the main outcomes that RCTs for biologics have focused on. However, with the elapse of time lung function improvement, asthma control and quality of life have also been examined, mainly in real-world studies.

T2 low asthma is not associated with eosinophils and despite the fact that there are gaps in the understanding of its pathophysiology there are no biologic therapies available for this phenotype. However, tezepelumab demonstrated effectiveness in reducing exacerbations regardless of the blood eosinophil count and FeNO, another T2 high biomarker.

The current biologics are monoclonal antibodies against IgE, type 2 cytokines, and alarmins but all three targets involve more or less eosinophils as a key operator in the respective pathophysiologic pathway. They have reduced the disease burden of severe asthma but there are no approved therapies for patients with eosinophil-low asthma. The exception of tezepelumab is unique in terms of being positioned at a central spot of the inflammatory cascade, thus mediating downstream pathways that lead to either eosinophilic or neutrophilic inflammation. It should be noted that tezepelumab is more efficacious in severe asthmatics with high T2 biomarkers.

Conclusions

Eosinophils are key cells in the T2 inflammatory process in asthma especially severe asthma. Biologics have been approved for patients with severe asthma with type-2 mediated inflammation while there are no biologic therapies for T2 low asthma. The future challenge may not only be the addition of new biologics but also of other pharmacological and non-pharmacological treatments while simultaneously the deeper understanding of asthma pathophysiology arising from the more extensive use of biologics will assist us in elaborating better therapies for severe asthma and possibly examine combinations of biologics or initiate them at a milder disease state.

Abbreviations

FeNO: fractional exhaled nitric oxide

GINA: Global Initiative for Asthma

ICS: inhaled corticosteroids

IgE: immunoglobulin E

IL: interleukin

ILC2: type 2 innate lymphoid cells

OCS: oral corticosteroids

TSLP: thymic stromal lymphopoietin

Declarations

Author contributions

AB, NA, and PB: Conceptualization, Writing—original draft, Writing—review & editing. All authors read and approved the submitted version.

Conflicts of interest

Prof. Petros Bakakos who is the Guest Editor of Exploration of Asthma & Allergy had no involvement in the decision-making or the review process of this manuscript. The other authors declare that they have no conflicts of interest.

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