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Asthma, COPD, the "asthma-COPD" syndrome and severe asthma - relatives or "incidental strangers"?

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Abstract

Objective: Airways obstructive diseases (asthma, COPD, asthma-COPD overlap (ACO) and severe asthma) are different entities characterized by airflow obstruction. They may share common pathogenetic mechanisms allowing new therapeutic options for patients.

Methods: A review of the current literature is performed to investigate the common pathogenetic mechanisms among these medical conditions.

Results: Different specific cytokones are involved in both asthma and COPD pathogenesis, while ACO shares some of these cytokines placing the condition between the two entities. The cytokines regulate accumulations and contraction of airways smooth muscle cells which leads to different expression of airflow obstruction. A special cytokine, TSLP, is highlighted as playing a key role in the pathogenesis of asthma, COPD, ACO, and severe asthma which opens the opportunity for new treatment options for patients suffering from these conditions.

Conclusion: COPD, asthma, ACO and severe asthma share some common elements in their pathogenesis which opens the gate for new therapeutic options for the patients

Keywords: Pathogenesis; Biomarkers; Inflammation; Biologics

1. Introduction

Obstructive pulmonary diseases affect a significant number of people worldwide. The hypothesis of a single obstructive airway disease with varying pathogenic mechanisms is still a point of debate within the pulmonary community. Some patients exhibit hallmarks typical of both asthma and COPD, as seen in conditions like asthma-COPD overlap (ACO) syndrome and severe asthma. The article emphasizes the similarities in the pathogenesis of these conditions. The presence of common elements in the development of asthma, ACO, COPD, and severe asthma provides a foundation for implementing new therapeutic options, such as biologics, which are also discussed in the article.

2. COPD and asthma – pulmonary Janus?

Since the 1960s, two hypotheses regarding asthma and chronic obstructive pulmonary disease (COPD) exist in pulmonary medicine. According to the first one, the so-called Dutch hypothesis put forward by Prof. Dick Ory and colleagues, both asthma and COPD (then called bronchitis) share the same causes but are essentially different manifestations of a single disease, which they call "chronic non-specific lung disease" [1[. According to the so-called British hypothesis both asthma and COPD represent two different nosological entities with different aetiologies and

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different therapeutic approaches [2]. For instance, both asthma and COPD are small airways diseases characterized by airflow limitation [3]. In COPD this limitation is constant and progresses over time, so patients have constant symptoms, while in asthma it is variable as patients can often be in a long period of remission characterized by absence of symptoms and normal lung function. Furthermore, they may not even need inhalation therapy [4,5]. Advances in science have shed additional light on the intimate processes underlying the two socially significant small airways diseases. The mechanisms leading to the development of specific for both diseases types of inflammation - predominantly neutrophilic in COPD and predominantly eosinophilic in asthma, have become clear. In addition, the diseases themselves have been found not to be homogeneous, but heterogeneous entities, consisting of multiple pathogenetically and clinically defined phenotypes [6-8].

3. ACO

In 2014 one new term is added to the picture - the syndrome of co-occurrence of asthma and COPD in one organism, the so-called Asthma-COPD Overlap Syndrome (ACOS), currently called ACO [9,10]. According to the original definition, ACO is characterized by a persistent airflow limitation accompanied by a number of features associated with both asthma and COPD [9]. It is known that untreated and/or uncontrolled bronchial asthma, as well as that in active smoking patients, leads to airways remodelling resulting in fixed bronchial obstruction. Thus, a patient with asthma can acquire clinical, biochemical and functional characteristics of COPD [8,11]. Hence, in 2014 ACO is considered as the asthma-COPD transition, i.e. as the connecting unit between the two nosological entities. A question arises - which hypothesis is the correct one - the Dutch or the British one? The therapeutic approach for ACOS is a combination of asthma and COPD therapies. It is interesting that after 2015 the ACO concept has somehow disappeared from GOLD. The diagnosis of ACO gave each pulmonologist the right to choose whatever therapeutic combination of inhaled bronchodilators and inhaled corticosteroids (ICS) he/she preferred, but apart from this fact ACOS presented nothing new to the pulmonology community.

Unlike GOLD, in GINA the interest in ACOS does not disappear. In GINA 2017 report, the concept is renamed as asthma-COPD overlap (ACO), but applying the 2014 definition [9,10]. According to GINA, ACO does not represent a uniform nosological entity, but rather a heterogeneous group. As a main argument for the presence of ACO in GINA, the difference in the therapeutic approach is highlighted – in COPD the initial single or combined treatment with inhaled β-agonists and/or anticholinergics is fundamental, but not recommended, as it could be harmful for patients with asthma, in whom ICS plays the main role in the therapy and who are not recommended for initial treatment of COPD [10].

4. Severe asthma

Bronchial asthma is not a uniform nosological entity, but represents a collection of different phenotypes [8]. In the recent years, one of them – known as severe asthma, has gained particular popularity because of the widespread introduction of biological therapy in pulmonology practice [12,13]. By definition, severe asthma may group patients with different phenotypes that require treatment defined in steps 4 and 5 of the GINA guidelines, i.e. with a high-dose ICS/long-acting β2-agonist (LABA) to prevent it from becoming uncontrolled, or asthma that remains uncontrolled despite this treatment [12]. As severe asthma is practically unresponsive or responds hardly to ICS treatment, and is characterized by frequent episodes of exacerbations and progressive loss of lung function, it closely resembles COPD, but differs from it in pathogenesis.

The presented brief literature review shows that there are many similarities, but also differences, between asthma, severe asthma, ACO and COPD. This reasonably raises the question if there are any similar or common pathogenetic mechanisms underlying these conditions.

5. Pathogenesis – similarities and differences

5.1. Biomarkers

Both diseases, asthma and COPD, are characterized by airflow obstruction and systemic inflammation underlying airways remodelling and patient symptoms. In asthma, the obstruction and patients' symptoms are variable over time, whereas in COPD, the obstruction is constant and progressive, the severity of symptoms is increasing along with the increasing loss of lung function [14]. In asthma, the systemic inflammation is mainly due to the T-helper (Th) type 2 cells. In addition, a major role is played by the eosinophils (Eo) and type 2 innate lymphoid cells producing interleukins IL-4, IL-5, IL-6, IL-9, IL-13 and IL-17E. This results in significant production of immunoglobulin E (IgE), accumulation of Eo and suppression of phagocyte-dependent inflammation [15-17]. In COPD, the systemic inflammation is

predominantly neutrophilic with a main involvement of CD4/CD8 lymphocytes and macrophages. The immune response in COPD is a Th1 cell-mediated type and phagocyte-dependent inflammation involves the interleukins IL-2, IL6, IL-8, IL-9 and IL-17A, interferon-γ and tumour necrosis factor-α (TNF-α) [15,18].

According to the 2014 definition ACO is characterized by persistent airflow limitation and features common to both asthma and COPD [9]. Thus, the two different inflammatory mechanisms in asthma and COPD may overlap in ACO [14]. Studies with patients diagnosed with ACO show high levels of markers typical for asthma such as nitric oxide fraction in exhaled air (FeNO), peripheral blood Eo (absolute count and percentage) and markers of Th2 inflammation compared to patients with COPD [19-22]. Another study comparing patients with COPD, asthma and ACO found low, high and medium levels of IL-13 and IL-5 respectively [23]. The main risk factor for the development of COPD is smoking, and for the development of asthma – exposure to allergens [4,5]. It can be easily assumed that in asthmatics who smoke or are exposed to other COPD risk factors (e.g. air pollution) the airflow obstruction may become fixed and they may develop COPD as a consequence of the increased oxidative stress, the release of cytokines and chemokines, the altered activity of innate immune cells, dysfunction of regulatory T cells, changes in DNA methylation [2,3]. This is supported by studies with asthmatic patients who smoke, showing high levels of neutrophils in sputum and the airways, which is mediated by the secretion of interleukins IL-6, IL-8 and IL-17A [24-26]. Of particular importance is IL-17, which regulates neutrophilic inflammation in asthma, while in COPD it stimulates the secretion of matrix metallopeptidase-9 (MMP-9) by the macrophages [26,27]. In another study conducted among 2 groups of asthmatic patients - smokers and nonsmokers, bronchial infiltration with CD8+ T cells, macrophages and epithelial remodelling was found in the first group, similar to that in COPD in contrast to the second group, and therefore CD8+ T cells and macrophages can be considered the dominant inflammatory cells in smokers with asthma [28].

High serum IgE levels are characteristic of asthma, but they are also found in COPD patients with allergic sensitization [29]. The use of tobacco products also leads to an increase of total serum IgE levels. In patients with ACO high levels of IgE and signs of Th2-type inflammation with its characteristic tissue and peripheral eosinophilia, bronchial hyperreactivity and good response to ICS treatment are found [30-32]. Thus, ACO is characterized as a complex tangle of pathogenetic pathways characteristic of both asthma and COPD, rather than a mechanistic sum of the two diseases. (**Fig. 1, table 1.**)

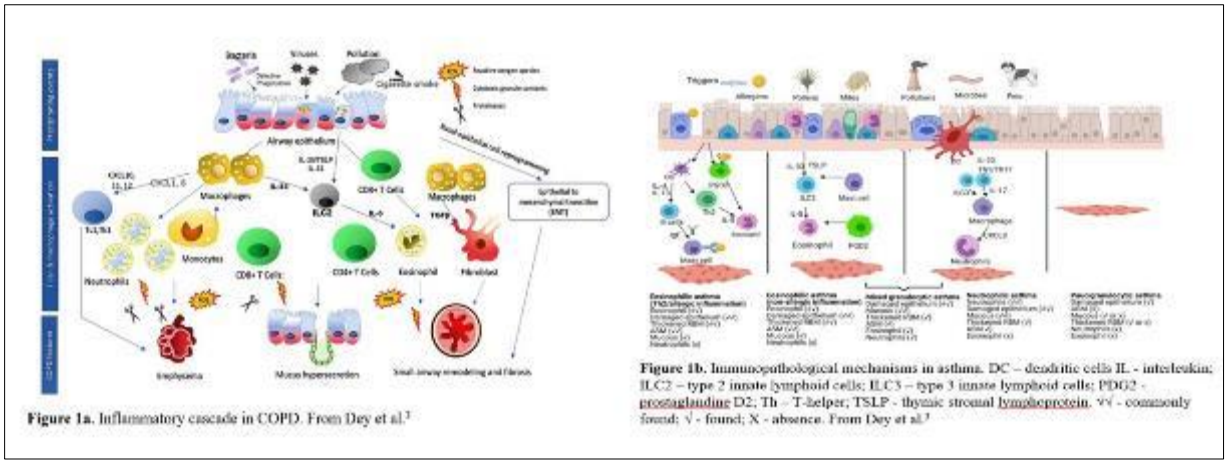

Figure 1 Comparison of the inflammatory mechanisms of asthma and COPD.

Severe asthma represents a particular phenotypic manifestation of the disease that remains uncontrolled despite adherence to optimal high-dose ICS/LABA therapy and control of contributing factors, or that becomes uncontrolled when high-dose therapy is reduced [5]. This definition is more general than the one used since 2018 according to which severe asthma is a condition requiring treatment as defined in steps 4 and 5 of the GINA guidelines, i.e. with a high-dose ICS/LABA to prevent it from becoming uncontrolled, or asthma that remains uncontrolled despite this treatment [12]. Severe asthma closely resembles ACO in terms of clinical course and therapeutic approach – patients are symptomatic, with low lung function (fixed airflow obstruction), with frequent episodes of exacerbations, with partial response to ICS treatment, their treatment includes the main inhaler groups of medications used both for the treatment of asthma and COPD – ICS, LABA, anticholinergics [5]. In pathogenetic terms, similarities with ACO are also found.

Table 1. Pathogenetic comparison among COPD, asthma, ACO, and severe asthma. Legend: Il – inteleukin; IFN-γ – interferon gamma; TNF-α – tumour necrosis factor alpha; Th - T-helper cell; + - present; ++ - moderate presence; +++ - pronounced presence

	Asthma	**COPD**	**ACO**	**Severe asthma**
Inflammation	Type 2	Type 1	Type 1 predominantly; Type 2 in eosinophilic patients	Type 2
Cells	Eosinophils, Th2	CD4/CD8, Th1, macrophages	both	Eosinophils, Th2
IgE	+++	+ in exacerbators	++	+++
Cytokins	Il-4,5,6,9,13,17	Il-1β,2,6,9,17a, IFN-γ, TNF-α	Il-5,6,8,13,17A	Il-4,5,13,17
TSLP	+++	+	++	+++

Severe asthma is characterized by the development of Th2-type inflammation with the typical high levels of serum IgE, peripheral and tissue Eo, IL-4 IL-5 and IL-13 [33-36]. However, similar to ACO, Th1-type inflammation mediated by IL-17 can be observed in severe asthma, especially in patients with late-onset asthma [37-40]. On its turn, IL-17 induces bronchial smooth muscle cells (SMCs) contraction, thereby inducing bronchial hyperresponsiveness in the absence of neutrophilic inflammation [41]. On the other hand, Th17 cytokine production is resistant to inhibition by steroids, which explains why neutrophilic inflammation driven by Th17 cells is the pathomorphological correlation to steroid-resistant asthma [37]. Some studies have found an association between Th17 cell-dominated asthma and tumour TNF-α - its pulmonary and systemic levels are increased in patients with steroid-resistant asthma [40,42].

The sharing of some pathogenetic mechanisms between asthma, COPD, ACO and severe asthma raises the question are there connecting or distinctive elements between these conditions?

In 2018 Wang et al. published a study with 423 patients (147 with COPD, 124 with asthma, 102 with ACO, and 50 healthy nonsmokers) in which they investigated associations between plasma levels of biomarkers characteristic of asthma (periostin, thymic stromal lipoprotein (TSLP), and YKL- 40), COPD (neutrophil gelatinase-associated lipocalin (NGAL)), lung function, bronchodilator response and imaging changes. They have found that patients with ACO could be distinguished from patients with COPD by high levels of YKL-40 and from patients with asthma by high levels of NGAL. No statistically significant differences are found between the different groups regarding the levels of periostin and TSLP. A negative correlation between YKL-40 levels and lung function and a positive correlation between emphysema prevalence and NGAL levels are also noted. The level of peripheral Eo correlates positively with the level of TSLP, and that of peripheral neutrophils with NGAL. According to Wang et al. the results obtained in their study defined ACO as an intermediate condition between COPD and asthma [43].

In 2016 Korosec et al. publish a study involving 362 patients with asthma, 184 with COPD, 39 with ACO and 14 healthy controls. They have found that the level of TSLP in the peripheral blood of patients with asthma and ACO is significantly higher than that of patients with COPD, the results are marked with high specificity and sensitivity. According to Korosec et al. TSLP deficiency in COPD patients is a marker of epithelial dysfunction [44]. This result suggests a role for TSLP as a link between the pathogenesis of asthma and COPD in ACO.

In another study published in 2022 examining the genetic associations and architecture of ACO, John et al. have highlighted a strong genetic correlation between ACO and COPD/pulmonary function and between ACO and asthma, particularly moderate-severe asthma. The genetic correlation between peripheral blood Eo level and ACO is similar in strength to that between Eo and asthma compared to that between Eo and FEV1/FVC and COPD [45]. As known from the literature, increased Eo counts in peripheral blood are associated with exacerbations of asthma and COPD as well as with a decline in lung function in non-asthmatic patients [46-49].

6. Role of airways smooth muscle cells

A main feature of the airways obstructive chronic diseases like COPD, asthma, ACO and severe asthma is the differently expressed obstruction of the airflow due to spasm of the airways SMCs [4,5]. Thus, airways SMCs emerge as the main

participants in the regulation of airways tissue homeostasis and in their remodelling which in turn develops in chronic obstructive inflammatory diseases. Accumulation of SMCs as a result of hypertrophy and hyperplasia is an important hallmark of asthma and COPD [50]. Airways SMCs react directly to various inhaled factors from the environment (allergens, tobacco smoke, gases, dusts, pollutants) in an immune-dependent and immune-independent manner [51-54]. Chronic immune inflammation underlying the pathogenesis of asthma and COPD triggers and maintains a vicious cycle of tissue damage and repair leading to tissue remodelling [50].

7. Role of TSLP

Airways SMCs secrete, react with, and are regulated by various cytokines, especially TSLP [50]. It is an IL-7-like cytokine (alarmin) secreted by the epithelial cells of the lungs, intestines, skin, as well as by fibroblasts, airways SMCs, mast cells, macrophages, granulocytes, synovial fibroblasts, intervertebral disc cells and dendritic cells [55-62]. Its expression is regulated by a number of factors such as mechanical damage, trauma, microorganisms, infection, pro-inflammatory and Th2-type cytokines [63,64]. An interesting fact is that 1-2% cigarette smoke extract increased the basal expression of TSLP by the airways SMCs, which proves the pathogenetic role of cigarette smoke in the development of inflammation in the airways [65]. TSLP fulfils a number of functions – activates myeloid dendritic cells and triggers pro-allergic CD4+ and CD8+ immune responses, interacts synergistically with IL-1β and TNF-α to induce Th2-type cytokine and chemokine expression in mast cells [56,66,67]. TSLP is expressed by airways SMCs in COPD, and the pro-inflammatory cytokines IL-1β and TNF-α stimulate this expression [59,68]. In addition, IgE also induces TSLP expression by the airways SMCs [69]. Thus, TSLP appears as a link in the interaction between mast cells and the airways SMCs [50]. The TSLP produced by the airways SMCs is involved in the regulation of the local immune response through its interaction with mast cells, Eo and dendritic cells located near the airways SMCs [56,66,70,71]. This is possible because airways SMCs are a rich source of IL-8, express its receptors, produce eotaxin-1 and the proinflammatory IL-6. Furthermore, IL-8 and eotaxin-1 are attractants for neutrophils and Eo respectively [72-75]. The activation of IL-8 receptors increases intracellular Ca^{++} concentration [76].

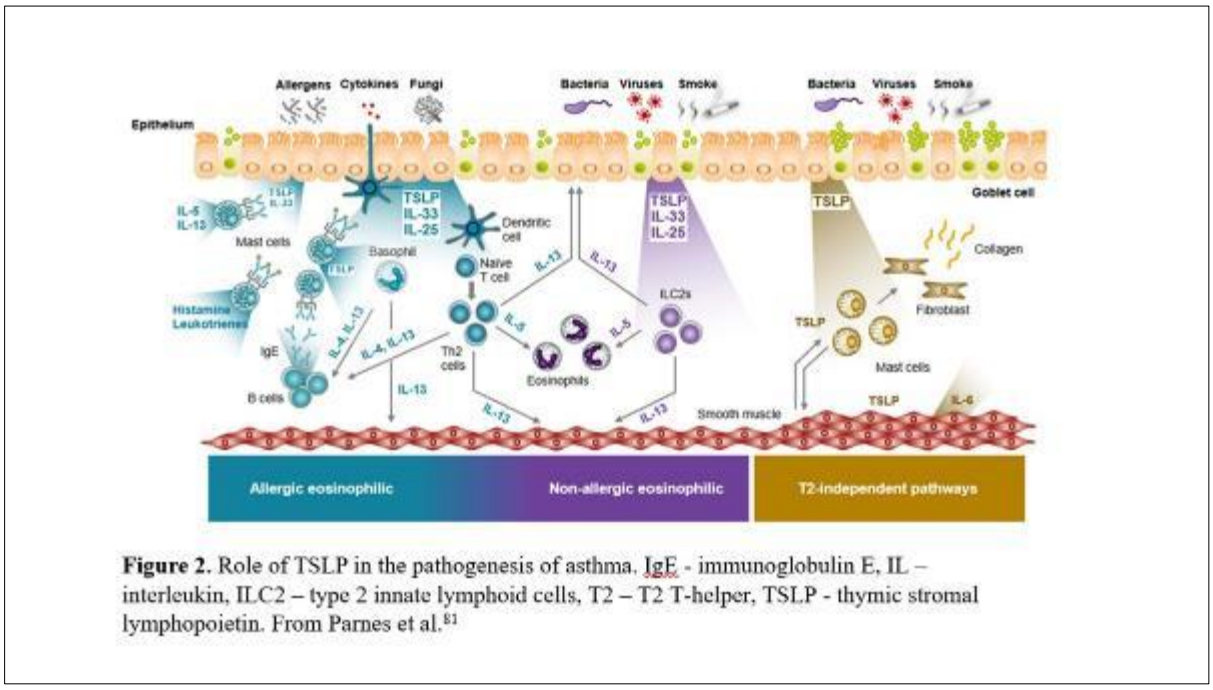

Figure 2. Role of TSLP in the pathogenesis of asthma. IgE - immunoglobulin E, IL – interleukin, ILC2 – type 2 innate lymphoid cells, T2 – T2 T-helper, TSLP - thymic stromal lymphopoietin. From Parnes et al.[81]

Figure 2 Asthma pathogenesis overview

As it has already been mentioned, the key inflammatory mediators in COPD are the cytokines IL-1β, TNF-α and chemokine IL-8, whereas airways SMCs express TSLP significantly [59,77]. Although Th1-type cytokines predominate in COPD, there is also a Th2-type immune response in the airways, especially in patients with chronic bronchitis [78]. This Th2 immune response is modulated by CD8+ T cells. TSLP stimulates dendritic cells to initiate activation of naïve CD8+ T cells by differentiating them into IL-5 producing cells [67]. In COPD, frequent bacterial/viral infections and oxidative stress contribute to the enhanced expression of TSLP by the airways SMCs [58].

In asthma, TSLP is a necessary and sufficient factor for the development of Th2-type inflammation in the airways, its prolonged expression triggers allergic inflammation characterized by massive infiltration of inflammatory cells, goblet cell hyperplasia, subepithelial fibrosis and elevated serum IgE levels [79].

The role of TSLP in the pathogenesis of severe asthma is best studied. Exogenous and endogenous irritants (allergens, bacteria, viruses, fungi, cigarette smoke and other environmental pollutants, other cytokines) stimulate bronchial epithelial cells to secrete TSLP, IL-33 and IL-25, which in turn triggers Th2-type inflammation [80]. TSLP activates naïve T-cells through dendritic cells as they differentiate into Th2 cells, which in turn begin to produce IL-4, IL-5, IL-13. Both Eo and basophils are activated while production of specific antibodies and Th2-type inflammatory molecules begins. Allergic Eo inflammation is triggered in the airways. TSLP interacts directly with innate type 2 lymphoid cells, causing them to produce and secrete IL-13, thus allergic non-Eo inflammation develops in the airways. Direct interaction of TSLP with mast cells underlies Th2-independent inflammation in the airways of patients with severe asthma [37,81-84]. (**Fig. 2**)

8. Therapeutic options

The presence of common elements in the pathogenesis of asthma, COPD, ACO and severe asthma raises the question about common or similar therapeutic approach. The therapies for asthma, severe asthma and COPD are well specified in the relevant guidelines [4,5]. Although presented as a mechanical sum of asthma and COPD therapies, the therapeutic management in ACO is also clarified [9,10]. The detection of TSLP in the sera of patients with asthma, COPD, severe asthma and ACO points it out as a significant therapeutic target. The monoclonal antibody tezepelumab directed against TSLP, tested in several phase II and phase III clinical trials, has shown its effectiveness in patients with severe asthma - achieving clinically significant, rapid and stable relief of patients from asthma exacerbations, regardless of its phenotype. This includes patients with a low Eo level for whom there is no specific treatment [81]. Although about 40% of patients with COPD have peripheral eosinophilia as well as other hallmarks of Th2-inflammation, the studies conducted so far involving other biological drugs - mepolizumab, benrazlizumab, dupilomumab have not shown promising results in patients with COPD. A phase II study for the action of tezepelumab is still ongoing, the results of which are expected given the key role of the alarmin in the pathogenesis of obstructive pulmonary disease [85,86]. The presence of signs of Th2- and Th1-type inflammation in ACO is a reason to expect a positive effect from the application of biological medications used in severe asthma [14]. In 2024 new results from trials with biologics in COPD patients with eosinophilic inflammation were presented at the European Respiratory Society Annual Congress in Vienna, Austria [87]. According to the obtained data, the application of dupilomab, mepolizumab, tezepelumab and itipecimab leads to a reduction of exacerbations rate, and to an improvement of the quality of life and the pulmonary function of patients, which is dependent on the Eo level in the peripheral blood, especially at levels above 300 cells/μL blood. Officially, dupilomab is the first biologic medication approved for the treatment of COPD [88-91].

9. Conclusion

Asthma, COPD, severe asthma and ACO share common risk factors for impaired lung function like tobacco smoking and there are similar elements in their pathogenesis. Signes of both Th type 1 and 2 inflammation can be noticed in these entities together with interaction of proinflammatory molecules and interleukins like TSLP, Il-17, Il-6, Il-8. The role of SMCs for the bronchobstruction is emphasized. The similarity in the pathogenesis and the clinical course of these medical conditions is a basis for developing of new common treatments

Compliance with ethical standards

Disclosure of conflict of interest

Both authors disclose no conflict of interest.

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