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Review

Interactions of allergic rhinitis and bronchial asthma at mucosal immunology level

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Abstract: Allergic rhinitis (AR) and bronchial asthma (BA) could be described as different aspects of one systemic disorder, where a mutual relationship is suggested founded on the well-known link between distinct mucosal sites in the organism. Moreover, several studies discuss the intimate association between AR and BA, including the observation that AR occurs usually as the first manifestation of the allergic respiratory (atopic) march. This review focuses on the various aspects of nose and lungs interaction during the course of the allergic disease. The dysfunction of the upper and lower airways is observed often simultaneously. It is thought that AR and BA share common pathogenic features and embryological, histological, anatomical and physiological characteristics. Furthermore, the data on the common nasal-bronchial reflex, inflammatory mechanisms, similar triggers, and genetic factors, clinical and epidemiological observations, the effect from the administered therapy, all confirm the suggested relation between AR and BA. The nasal-bronchial cross-talk rely on three different pathways: the immunological in the respiratory mucosa, the neural, and the circulatory pathway. In conclusion, AR and BA often occur simultaneously and share similar pathophysiological mechanisms. Nevertheless, the observation that the similar treatment is effective in both patients, gives hope for the management and prognosis of these patients.

Keywords: allergic rhinitis; bronchial asthma; mucosal inflammation; allergy; Th2 cells; cytokines

1. Introduction

Allergic rhinitis (AR) and bronchial asthma (BA) could be considered as different aspects of

one systemic allergic disorder. Since the allergy can affect the nose, lungs, eyes, skin, and gastrointestinal tract, simultaneously or consecutively, it was suggested that there is a mutual relationship between both diseases. This association was supported also by the data on well-known relation between the distinct mucosal sites in the organism, i.e., in the respiratory, gastrointestinal, genitourinal tract, etc. This review focuses on the various aspects of the nose and lungs interaction during the course of the allergic disease.

First to note the relationship between grass pollen exposure and the subsequent development of nasal and bronchial symptoms was Charles Blackley in 1873 [1]. Nowadays, a renewed interest in the interaction between AR and BA is observed due to the increasing health burden of both diseases in the industrialized world [2]. The accumulating evidence for that mucosal inflammation is not restricted to the mucosa of upper or lower airways of patients alone, but it was suggested common mucosal inflammation of the airways. Moreover, AR is considered a risk factor for the development of BA, due to its ability to aggravate ongoing bronchial inflammation [2].

It is well-known that AR patients present with symptoms caused by IgE-mediated inflammatory response. These symptoms are manifested mainly in the nasal mucosa after allergen exposure. Clinically, patients with AR complaints of sneezing, rhinorrhea, itching and nasal congestion due to the edema of the mucosa. However, atopic patients with AR may exhibit also conjunctival symptoms such as redness of the eye, excessive tearing, itching, caused by the same allergens due to the nasal-ocular axonal reflexes.

2. Relationship between allergic rhinitis and bronchial asthma

Several studies discuss the intimate bond between AR and BA [3–7], including the suggestion that AR is usually the first manifestation of allergic respiratory disease [7–10]. One of the studies involving 738 participants revealed that 66% of the AR cases occurred prior to or simultaneously with BA, where 69% of the recruited patients were diagnosed with asthma initially.

Often, AR is demonstrated as a first indication of the progression of any respiratory allergy to asthma. In 1999, on a meeting of the World Health Organization (WHO) a decision to form evidence-based guidelines for the treatment of rhinitis was taken. It was suggested also these guidelines to highlight the impact of rhinitis on asthma. The ARIA (Allergic rhinitis and its impact on asthma) guideline comprises clinical recommendations for treatment and prophylaxis of AR, and for better assessment of the two respiratory diseases when occurring together. The goal of the ARIA was to increase the awareness of rhinitis and to conduct an effective treatment worldwide. In the ARIA document [11], the AR as a risk factor the development of BA is clearly emphasized. The ARIA classification categorizes AR as intermittent or persistent according to the duration and mild or moderate to severe in accordance to the severity [11,12]. An analogy with the GINA (The Global Initiative for Asthma) can be made, where the classification includes intermittent or persistent asthma on one hand and mild, moderate or severe according to the severity of clinical symptoms and lung function, on the other hand [13].

It is beyond doubt that AR and BA are common allergic diseases which association and simultaneous presence were demonstrated by a number of epidemiological studies [8,14–16]. Valero et al. [12] in a large study of 3225 AR patients examined the relationship between dermal sensitization, rhinitis, and asthma. Authors concluded that respiratory allergic disease is a systemic disease. They further propose that AR and BA could be manifestations of the same illness. Besides, some characteristics of

AR may affect the development of asthma, including their type [12].

Since both AR and BA could present together, it is assumed that the dysfunction of the upper and lower airways run simultaneously embracing common features of the inflammatory pathogenesis. Data from epidemiological studies showed that nasal symptoms were observed in 78% of patients with BA, whereas asthma symptoms were determined in 38–40% of patients with AR [10,17]. Surveys also demonstrated that AR may precede the development of BA [9,18]. Moreover, AR patients with no clinical symptoms of asthma may exhibit non-specific bronchial hyperreactivity [15,19]. Nevertheless, it was shown that the treatment of patients with concomitant AR and BA alleviates the symptoms of the latter, as well as reduces the risk of severe asthma exacerbations and hospitalization [9]. This consolidates the relationship between the two diseases once again [20,21].

Inflammation arisen in the upper airways could propagate to the lower and vice versa. Braunstahl et al. [22] showed that the bronchial provocation might affect also the nasal mucosa, including to alter the mucosal function in these allergic patients. These findings explain why the allergic inflammation of lower airways and the related respiratory symptoms (i.e., dyspnea and wheezing) may facilitate the onset of AR. Furthermore, the prevalence of AR in BA patients was significantly higher than that in the control subjects. When non-asthmatic patients with AR underwent bronchial allergen challenge, a reduction in nasal inspiratory flow with a simultaneous flare of the nasal symptoms was observed. The number of eosinophils, eotaxin-positive cells and IL-5 expression in a biopsy from the nasal mucosa were increased [23], whereas the number of mast cells was decreased due to the higher degree of degranulation [24].

The assessment of the occurrence of rhinitis and asthma in series, especially in adult patients, is complex. Subclinical forms of BA, as well as mild bronchial inflammation and bronchial hyperresponsiveness, may be observed before the onset of dyspnea and wheezing [15]. Additionally, some adult patients did not remember having mild symptoms of asthma in childhood [25]. Interestingly, despite some patients denied pre-existing asthma in their medical history, about 22.4% of newly diagnosed patients reported “respiratory problems” in childhood. These respiratory symptoms could be a manifestation of asthma that has begun during the childhood but not have been intensely expressed to establish the diagnosis of asthma [26].

3. Similarities between allergic rhinitis and bronchial asthma

AR and BA share some similarities regarding embryological, histological, anatomical, and physiological features, common triggers and genetic factors, mutual clinical and epidemiological observations, an overall effect from the administered therapy. Moreover, both nasal-bronchial reflex and mucosal immune system create a base for the common pathophysiological mechanisms underlying in AR and BA. Post-nasal drip of mucus containing inflammatory cells and mediators from the nose to the lower airways, as well as the crossing of inflammatory cells and mediators into the systemic circulation and in the lungs, lead to the common inflammation of the whole airways. In line with this, the disruption of the filtered role of the upper airways (i.e., warming and purifying of the airflow) reflects in disruption of the homeostasis of the lower airways. Thus, three related pathways could be described: the immunological in the respiratory mucosa, the neural, and the circulatory pathway on which depends the so-called nasal-bronchial cross-talk [24]. However, one could suggest that during the onset or acute phase of the allergic disease the three pathways may contribute equally, although we believe that in the phase of chronic inflammation, the immunological

pathway plays the major role for maintaining the inflammation.

The embryonic development of upper and lower respiratory tract is also similar. Their development begins during the fourth week of pregnancy and lasts several years after birth. The nose develops by invagination of the nasal placoid, whereas the larynx, trachea, bronchi, and lungs develop from the laryngotracheal diverticulum which arises from endoderm on the ventral wall of the primitive pharynx [10]. Anatomical and physiological similarities include the mucosal layers covering the upper and lower airways consisting of the same pseudostratified ciliated columnar epithelium on a basal membrane [8,27,28]. Based on this anatomical characteristic, the respiratory mucosa is sensitive to inhaled allergens. The lymphoid system, part of the mucosal-associated lymphoid tissue (MALT), is widely represented in the nose and the bronchial tree [4,30]. However, some anatomical differences could also be mentioned, such as the presence of smooth muscle layers in the lower airways in contrast with the presence of venous sinuous and prominent submucosal glands in the upper airways [4,5,21,27,29–31]. These differences define the differences in the pathophysiological responses to the same triggers factors–mainly rhinorrhea and congestion in the nose, whereas secretion and bronchoconstriction in the lungs.

Nasal-bronchial reflex connects the upper with lower airways. Receptors are located in the nose, sinuses, larynx, pharynx, trachea and the bronchial tree. The trigeminal nerve is responsible for the afferent sensory innervation of the nose. The nerve impulse is transported by n. trigeminus, n. facialis, n. glossopharyngeus to the medulla oblongata. There is a connection with fibers of n. vagus which performs the afferent and efferent innervation of the lower airways resulting in constriction of the bronchi [3,29,32].

However, it was shown that the nasal and bronchial tissues share common gene expression patterns regarding molecules involved in inflammation, apoptosis, innate immunity and cancer development [33].

4. Immunology of allergic rhinitis and bronchial asthma

The above-mentioned common pathogenic mechanisms observed in AR and BA includes also the participation of inflammatory cells and mediators (cysteinyl leukotrienes, prostaglandins, cytokines). The early and late phases of the allergic response, triggered by common allergens (causative agents) are similar. It is well-known that the allergic response begins with the antigen presentation of the antigen-presenting cell (i.e., dendritic cell) [34,35] to T-lymphocytes in regional lymphatic nodes [8,10] followed by specific recognition and activation of the naïve Th cells (Th0 cells) [36]. The latter differentiate into Th1 or Th2 subtype depending on the surrounding cytokine milieu. Activation of Th1 results in the release of IL-2 and IFN-γ, while the Th2 cytokine profile includes the release of IL-2, IL-3, IL-4, IL-5, IL-9, IL-10, IL-13, and GM-CSF [19,34]. Th2 cytokines are crucial for the synthesis of IgE antibody (especially IL-4) [19,34,35]. In addition, neural growth factor (NGF) and its receptors are expressed in the nasal mucosa. In patients with AR and allergic bronchial asthma, NGF levels in serum, nasal and bronchial fluid are increased [19,32,34]. Typical for patients with AR is nasal hyperreactivity to specific allergens, as well as to non-specific stimuli. Activated inflammatory cells and secreted mediators facilitate mucosal penetration of the allergens, thus, providing additional antigen-specific stimulation. Neurotrophins, such as NGF, are one of the major mediators of neurogenic hyperactivity.

During the early phase of the mucosal inflammation, specific adhesion molecules are expressed

on the surface of the endothelium and the epithelium (i.e., selectins), leading to the extravasation of inflammatory cells and tissue infiltration [19]. Adhesion molecules promote leukocyte-endothelial interaction. Oligosaccharide-binding proteins, selectins (L-, P-, E - selectin) are expressed on the surface of the leukocytes (L-selectins) and endothelial cells (P- and E-selectins). These molecules allow leukocytes to roll and move along the vessel. The surface of leukocytes also expresses another type of adhesion molecule called integrins (Mac-1, LFA-1) which bind strongly to the corresponding endothelial cell surface protein (ICAM-1, ICAM-2, VCAM). The interactions of integrins facilitate neutrophil migration through the vascular wall to the adjacent tissues [35]. Furthermore, epithelial cells of allergic patients express ICAM-1 relatively early during the allergic response. Thus, the expression of this adhesion molecule could be employed as an inflammatory marker [23,37]. Typical for allergic inflammation in patients with AR and BA is the accumulation of eosinophils in mucous membranes, which are important effector cells in both diseases [23,38]. In addition, chemotactic molecules along with the adhesion molecules play a crucial role in the extravasation of eosinophils in the tissues at the sites of inflammation by the mechanisms described above [23]. When activated in the nasal mucosa, eosinophils degranulate and secrete various inflammatory mediators, leading to edema of the nasal mucous membrane and increased reactivity [38]. These processes describe the late phase of an allergic response.

To establish and confirm the nasal-bronchial relationship, Braunstahl et al. [2] examined the expression of adhesion molecules in the nasal and bronchial mucosa after a nasal provocation test with an allergen. At a 24th hour after the nasal exposure, an increase in eosinophil counts in the nasal mucosa and lamina propria was found, as well as in lung mucosa and lamina propria in patients with AR. Increased expression of adhesion molecule: ICAM-1, VCAM-1, E-selectins in the nasal and bronchial tissue of AR patients was also observed [2]. The number of eosinophils in mucous membranes of both nose and bronchi correlated with the local expression of adhesion molecules [8]. In conclusion, the results of this study emphasize that the nasal provocation in patients with AR leads to generalized airway inflammation (i.e., both upper and lower airways) by increasing expression of adhesion molecules.

The similarity between the early and late phases of the allergic response is supported by the infiltration by mast cells along with secretion of mediators such as histamine, leukotrienes, prostaglandins, platelet activating factor, during the early allergic reaction. Clinical symptoms vary from sneezing, itching, rhinorrhea [39]. The late-phase of the allergic reaction results in infiltration of the mucosa not only with mast cells but also Th2 lymphocytes, eosinophils, and basophils. Additional symptoms arise such as nose obstruction, loss of sense of smell, nasal hyperreactivity. An early-stage or immediate type allergic reaction (type I) occurs in hypersensitive individuals, seconds or minutes after allergen exposure. As a result of mast cell degranulation, a number of mediators are released, such as histamine, leukotrienes, and prostaglandins [40]. The early-phase response is usually followed by a late phase that occurs 4–6 hours after antigen stimulation, characterized by persistent symptoms: sneezing, rhinorrhea, especially nasal obstruction which could last 18–24 hours [40]. Various cytokines and chemokines such as IL-4, IL-13 are released by T cells and mast cells, followed by increased expression of adhesion molecules on endothelial cells (i.e., VCAM) infiltration of cells in the nasal mucosa [34]. Chemokines RANTES, eotaxin, monocyte chemoattractant protein 4 (MCP-4) and thymus and activation-regulated chemokine (TARC/CCL17), released from epithelial cells, serve as chemoattractants for additional recruiting of eosinophils, basophils, and T lymphocytes. The model of both phases of the allergic response in the lower

respiratory tract is similar. However, the allergic response in the lower respiratory tract is clinically manifested with obstruction of the bronchi and increased secretion of mucus [34].

There are some publications, however, which revealed that nasal cells produce different patterns of cytokines in response to viral infection than other cells. Furthermore, some authors concluded that the inducible response of nasal cells do not mimic that of bronchial cells including differences in IL8 IL6 and others, whereas ICAM1 is similar [41]. Mcdougall et al. demonstrated no differences in constitutive expression of markers such as CD44, intercellular adhesion molecule-1, etc., although similar nasal and bronchial cell secretion of IL-6, RANTES, vascular endothelial growth factor, monocyte chemoattractant protein-1, MMP-9, and tissue inhibitor of metalloproteinase-1. The authors concluded that on the bases of these findings nasal epithelial inflammation represents that in the lower airways [41].

The term minimal persistent inflammation, an emerging concept in the nature and treatment of allergic rhinitis, was coined in 2000 [37,42] to describe a phenomenon observed at the mucosal level. Minimal persistent inflammation represents an inflammatory cell infiltration in the mucosa after suboptimal exposure of allergens and in the absence of symptoms (Figure 1). This condition may lead to hyperreactivity and a predisposition to full disease occurrence. Thus, at low allergen exposure, symptoms may not be observed despite the persistent allergic inflammation.

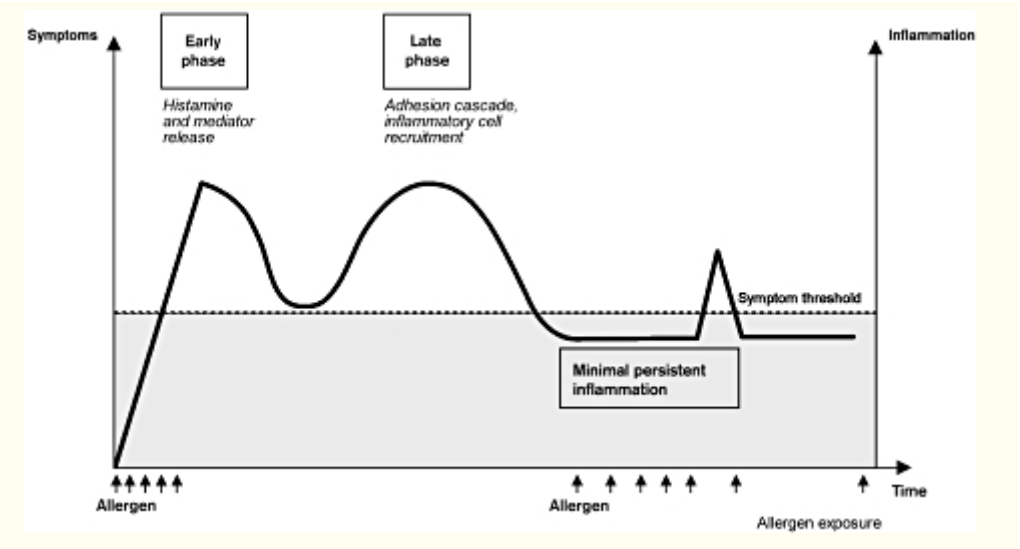

Figure 1. Early and late phase of an allergic response along with minimal persistent inflammation (Courtesy on Canonica et al. Clin Exp Immunol, 2009 [42]).

In the nasal mucosa, the minimal persistent inflammation is characterized by the presence of inflammatory cells (eosinophils and neutrophils) and increased ICAM-1 expression on the epithelial cells. These changes were found in patients with seasonal or perennial AR in the absence of clinical symptoms. Some authors suggest that clinically manifested symptoms form “the tip of the iceberg”, whereas the allergic reactions, inflammation, and hypersensitivity which persist for a long time, represent the underwater part of the iceberg [37]. As a result, it could be suggested that the therapeutic strategy must aim at reducing inflammation along with the symptoms during the entire period of exposure to allergens, even though suboptimal [29,31].

During the minimal persistent inflammation, the expression of CD54 (ICAM-1) is increased. It is important to note that CD54 is the main human rhinovirus receptor employed in the exacerbation of asthma as a result of viral infection of upper airways in children [29]. Taking into account the connection between the upper and lower airways, the impact of minimal persistent inflammation is extended on the mucosa of the whole respiratory tract. Allergen provocation of the nose or bronchi leads to generalized inflammation of the respiratory tract. It could be observed an increase in the number of eosinophils in the blood, as well as bronchial and nasal mucus 24 hours after bronchial provocation simultaneously with an increased expression of IL-5 and presence of eotaxin-positive cells in the lamina propria of the nasal mucosa. Another study revealed that 24 hours after nasal allergen challenge eosinophils were released in the epithelium and lamina propria of the nasal and bronchial mucosa [22]. Nasal allergen provocation induced a decrease in the forced expiratory volume for 1 second (FEV1) with a peak at 5th–6th and 22nd hour in 25–30% of the cases [41]. In patients with AR, the number of eosinophils in the mucosa correlated with the local expression of some adhesion molecules such as ICAM-1, E-selectin, and VCAM-1 [9,11,22,23,38].

Despite the similar inflammatory infiltrate in AR and BA, the degree of inflammation may vary. In patients with moderate to severe asthma, eosinophilic infiltration is more pronounced in bronchi than in the nose while patients with mild asthma have a similar degree of inflammation at both places [11]. However, eosinophilic inflammation in the nasal mucosa is observed in asthmatic patients with or without concomitant AR. Remodeling of the airways is more pronounced in the bronchial than in the nasal mucosa. In BA patients, it is observed a reticular basement membrane thickening along with hypertrophy of the smooth muscles and pronounced epithelial desquamation, a pathognomonic model of remodeling for BA, whereas the nasal epithelium in patients with AR is significantly less impaired [8,28].

5. Functional testing and therapy of allergic rhinitis and bronchial asthma

Some of the allergens (such as pollen, arthropods, molds, animal and food antigens) as well as pollutants, infections, and drugs, are common causative agents for both AR and BA patients. Furthermore, AR and BA often arise in patients with a genetic predisposition for the increased production of IgE antibodies to proteins from the environment: dust mites, pollen, dietary allergens, a condition known as atopy. Atopic diseases include various diseases such as urticaria, atopic dermatitis, conjunctivitis, food allergy, AR and asthma.

Both AR and BA could have changes in the functional respiratory testing. A large group of patients with moderate to severe persistent AR showed a positive bronchodilator test with an increase above 12% and 200 ml [43]. In this study, bronchial reversibility was associated with early restriction of the airflow, although the FEV1 values were borderline. Reversibility was also associated with a longer duration of rhinitis, which confirmed that bronchial damage was more common in patients with long-lasting rhinitis.

It is well-known that BA is characterized by reversible bronchial obstruction, where FEV1 being used as a gold standard for bronchial obstruction assessment [44]. Recently, the interest in the role of the small airways in the pathogenesis of asthma has increased [45]. Although there is no direct parameter for assessing the small airways, it is assumed that the forced expiratory flow of 25% and 75% (FEF25-75) may be considered as a more sensitive indicator for small airways obstruction than FEV1. FEF25-75 has been shown to be a reliable marker for early respiratory tract involvement

in AR [43,45–47]. This suggests that AR could be considered as the first step in the progression of respiratory allergy to asthma. Moreover, there are accumulating evidence that AR could be a precursor of BA. Ciprandi et al. in an 8-year follow-up study showed that reducing FEF25-75 with more than 70% may be considered as a marker for early bronchial pathology in patients suffering from AR [46]. The long duration of rhinitis was a risk factor for spirometric abnormalities itself, for bronchial hyperreactivity and a positive response to a bronchodilator test. Furthermore, this study provides evidence of some risk factors influencing FEF alteration and bronchial hyperreactivity-birch sensitization, home dust mites, Parietaria and grass pollen, as well as the duration of rhinitis. These findings highlight the role of minimal persistent inflammation in the contribution to structural bronchial remodeling. The progression of allergic inflammation of the nose to the bronchi may be called ‘asthmatic march’ [46].

In a previous study, we found an evolution of AR to BA at a relatively high percentage (50%), with asthma development time averaged about 6.5 years. We have recruited 20 patients with AR, examined in the ambulatory and diagnostic offices of the Clinic of Clinical Allergology. All of our patients were with atopic disease, most often seasonal (n = 12), year-round with seasonal exacerbation n = 6) and perennial (n = 2). The diagnosis of AR was made by detailed anamnesis, rhinoscopy, skin allergy tests, and BA as a consequence was confirmed with anamnesis, physical examination, pulmonary function testing including post-bronchodilator testing, where it was necessary. Despite the proposed high percentage of post nasal drip (65%), we rejected that asthma symptoms were due to this phenomenon through a number of objective methods [25]. Other studies also confirmed a correlation between the duration of AR and spirometric abnormalities. This was confirmed also by the established relationship of the duration of rhinitis and the decrease in FEV1 and FEF25-75, respectively, in patients with long-lasting rhinitis.

Patients with AR and BA have also a common therapeutic approach: the limitation of allergenic exposure and elimination of etiological factors, common drugs, allergen-specific hyposensitization. It is essential to follow-up the AR patients for developing asthma symptoms, to treat simultaneously upper and lower airways, to educate patients and their relatives. It is necessary to find and treat the associated with AR diseases such as rhinosinusitis, conjunctivitis, BA. Furthermore, there is evidence that the treatment of AR may influence the control of asthma in patients who possess both respiratory diseases [7,8,15]. The use of intranasal corticosteroids leads to a reduction in asthma symptoms and bronchial reactivity in people with seasonal and long-term respiratory allergy, regardless of the drug's depot in the lower respiratory tract. Corren et al. reported that nasal corticosteroids reduce the bronchial response associated with seasonal pollen exposure. This observation is common for both AR and BA [48]. Moreover, it is known that the use of leukotriene and anti-histamines in patients with AR improves the symptoms of asthma, and reduce the need for frequent use of beta-2 agonists [49]. Many studies showed reducing asthma exacerbations and the number of visits to emergency units for patients with concomitant AR when using anti-allergic therapy for rhinitis (i.e., montelukast and cetirizine) [50,51]. Greiff et al. treat patients with AR alone with inhaled budesonide during the pollen season. As a result of this therapeutic approach, a reduction in eosinophilia in blood and nasal mucosa and significantly lighter rhinitis symptoms was observed [52]. Allergen-specific immunotherapy (allergen-SIT) reduces the accumulation and activation of inflammatory cells and the secretion of mediators in patients with AR and BA. Allergen-SIT reduces also the hyperactivity in methacholine challenge test, improves the quality of life of patients and reduces seasonal exacerbations of BA. Reducing sensitivity to allergens not only leads to alleviates symptoms of

rhinitis but also helps to control asthma.

Anti-IgE (i.e., omalizumab) treatment has proven its importance for the management of BA by reducing airway hyperresponsiveness, obstruction and remodeling, ameliorating respiratory symptoms, asthma exacerbations, emergency room visits and the use of systemic corticosteroids, as well as improving the quality of life of the patients. Furthermore, it is thought that inhibition of IgE pathway may stop the propagation of the allergic inflammation cascade, including in AR patients. Anti-IgE treatment gives hope to the patients by remaining effective long after it has been discontinued [53,54].

Novel therapy including use of synthetic short immune-regulatory T cell epitope showed promising results from randomized, double-blind, placebo-controlled clinical trials. It was demonstrated that Treg induction contributes to successful outcomes, compared to conventional autoimmune therapy. Moreover, this therapy is safe and effective not only for BA but for other severe allergic diseases [55].

6. Conclusion

In conclusion, AR and BA often occur together and have similar pathophysiological mechanisms, including IgE-mast cell-dependent inflammation, T-lymphocyte activation with Th2-cytokine inflammation profile, eosinophil accumulation. Therefore, the effective response of both corticosteroids, anticholinergic drugs, and leukotriene antagonists is observed, which is the main and useful benefit of the relationship between both diseases.

Conflict of interest

All authors declare no conflicts of interest in this paper.

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