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Review Article

Advances in the clinical and mechanism research of pollen induced seasonal allergic asthma

Zhi-Juan Xie[1,2], Kai Guan[1,2], Jia Yin[1,2]

[1]Department of Allergy, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, P.R. China; [2]Beijing Key Laboratory of Precision Medicine for Diagnosis and Treatment on Allergic Diseases, Beijing 100730, P.R. China

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Abstract: Seasonal allergic asthma prevalence has been increasing over the last decades and is one of global health concerns now. Pollen is one of the main reasons to cause seasonal allergic asthma and influenced by multiple risk factors. Thunderstorm-related asthma is a typical type of seasonal allergic asthma that thunderstorms occurring can induce severe asthma attacks during pollen season. The diagnosis of seasonal allergic asthma relies on precise medical history, skin prick tests (SPT) and specific IgE detection. Component resolved diagnosis is greatly significant in determining the complex situation. Allergen specific immunotherapy (AIT) is the only disease-modifying therapy that can change the natural course from seasonal allergic rhinitis to seasonal allergic asthma.

Keywords: Seasonal allergic asthma, pollen allergy, allergen specific immunotherapy, thunderstorm-asthma

Introduction

Asthma is a chronic airway inflammation defined by a series of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough, together with reversible expiratory airflow limitation, affecting 1-18% of the population in different countries [1]. The increasing morbidity of asthma over the years seriously affects patient quality of life and causes a heavy financial burden [2]. Seasonal allergic asthma is one of the most common phenotypes of asthma, and partly related to pollen induced respiratory allergic diseases [3]. In this review, we summarize the update of clinical and mechanism of seasonal allergic asthma and its treatment.

Etiology

Pollen allergen

Pollen allergy was first described by John Bostock, who was a physician at Guy's Hospital in London in 1819 [4]. Millions of individuals were diagnosed as seasonal allergic rhinitis and allergic asthma in the 20th century [5]. For now, it is recognized that more than 150 pollen allergens play a significant role in an allergic process originating from grasses, trees and weeds. (www.allergen.org) [6] Birch pollen is one of the most important spring pollens all over the world, while Artemisia and Humulus scandens pollens are the major causes of autumnal season allergic rhinitis and asthma in north of China [7, 8]. In Europe, 70% of birch pollen allergic rhinitis or allergic asthma patients have accompanying food allergy [9]. Pollen-related food allergy has become the most frequent form of food allergy in Europe [10].

Natural course of seasonal allergy

Although pollen is a well-known cause for seasonal allergic rhinitis and allergic rhino-conjunctivitis [11, 12], its role in developing seasonal allergic asthma is not fully clear. Epidemiological and pathophysiological studies have suggested that allergic rhinitis increases the risk of asthma development [13, 14]. Autumnal pollens (mainly refer to mugwort pollen and humulus pollen) may induce allergic asthma during autumnal season in northern China [15]. Among a total of 1096 Chinese patients with autumnal respiratory allergic diseases, almost half of allergic rhinitis patients develop to seasonal aller-

gic asthma within 9 years [16]. It is suggested that the natural course from allergic rhinitis to allergic asthma in the patients with autumnal pollen allergy, based on the theme of "one airway, one disease". Allergic rhinitis and allergic asthma are two major manifestations of one common allergic respiratory syndrome [11].

Risk factors

Many factors, such as climate change (especially for extreme weather events, temperature and change of weather patterns), urbanization, loss of biodiversity contribute to the rise morbidity of pollen-induced allergic asthma [17]. Based on the external exposome study, pollen aeroallergens, air pollutants and environmental factors are the key factors affecting the concentration of allergens and the severity of asthma [18, 19]. Taking thunderstorm-related asthma as an example, a combination of extreme environment factors has contributed to allergic exacerbation. There were several thunderstorm-related asthma outbreaks throughout the world, the worst one was happened in Melbourne (Australia) [20-22]. To our knowledge, storms can induce the release of pollens from their cytoplasm of airborne allergenic components into the atmosphere, where they act as trigger factors of allergic rhinitis and asthma during pollen seasons [23]. One explanation about the phenomenon is the rapidly increased exposure concentration of allergenic pollens, highly related to the degree of symptoms. During the period of 2006-2008, Jia Yin et al observed that the concentration of Artemisia pollen and Humulus scandens pollen in the air is strongly associated with severity of seasonal allergic asthma, as measured by the pulmonary ventilation function and the peak expiratory flow (PEF) through whole year [24]. Another explanation lays on pollen flies and encounters a high-humidity zone and then breaks into smaller pollen particles, which makes it easier to get to the lower respiratory tract and induce asthma [21]. Above all, the thunderstorm-asthma outbreaks are characterized, at the beginning of thunderstorms by a rapid increase of visits for asthma in general practitioner or hospital emergency departments [20]. As for the air pollutants, the increase of air temperature and CO_2 also directly or/and indirectly affects the plant growth, pollen distribution and production, which has been studied in ragweed pollen for the past 20 years [25, 26]. This finding is likely to attract clinical attention for these extreme events that may be an important cause of severe exacerbation of asthma. Even though thunderstorms can induce severe asthma exacerbations, there is no direct evidence for asthma exacerbation [27]. According to Yin's observation, it is the sunny and windy dry autumn that the morbidity of artemisia pollen allergy gets to the peak point in north of China. Among the 1096 patients, more than 16% asthma patients experienced severe allergic exacerbation that needs emergency intravenous steroid therapy while 42% patients feel difficult to lie down at night and require inhalant corticosteroid or oral amchamine.

Pathogenesis

Traditional view believes that allergic asthma is associated with allergen-specific IgE dependent activation. Pollen allergen cross-linking of the IgE that is bound to FcεRI on sensitized mast cells and basophils, leading to the release of histamine, tryptase and the formation of sulphidopeptide leukotrienes, platelet-activating factor and prostaglandin D2 [28-30]. To our knowledge, Type-2 driven inflammation contribute to the pathology of allergic asthma by producing Th 2-related cytokines (IL4, IL5, IL9, IL13) and influencing the formation of IgE [31, 32]. Type 2 immune response involves Th2 cells, group 2 innate lymphoid cells (ILC2), B cells, IL-4-secreting NK-T cells, basophils, eosinophils, mast cells and related cytokines [33, 34]. Apart of Type 2 inflammation, newly emerging cytokines IL-33, IL17 and its producing cells Th17 contribute to the pathogenic immune responses of allergic asthma [35]. In the early age of human, the mutations of FOXP3 may lead to X-Linked Syndrome named as the immunodeficiency polyendocrinopathy and enteropathy (IPEX), which is a combination of autoimmunity and severe allergic disorders [36]. Unlike Th17, it is suggested that Foxp3+CD4+ CD25+ regulatory T (Treg) cells suppress the allergic inflammation mainly via cell contact or secretion of soluble cytokines, such as interleukin-10 (IL-10) and transforming growth factor-β (TGF-β) [33, 37]. Treg cells alleviate allergic asthma patients' symptoms by not only inhibit mast cell and the production of pollen specific IgE, but also inhibit DCs maturation [38].

Diagnosis

Appropriate allergy diagnosis is directly influencing decisions for therapeutic interventions, and thus reliable biomarkers are pivotal when diagnosing seasonal allergic asthma. The diag-

nosis of pollen-induced seasonal allergic asthma is based on asthma manifestations and etiologic biomarkers. Asthma diagnosis is strictly based on guideline of the global strategy for asthma management and prevention (GINA), while traditional etiologic diagnostic approaches in seasonal allergic asthma include precise medical history, routine clinical asthma diagnosis methods as well as skin prick tests (SPT), specific IgE detection and pollen provocation test, which is rarely used in clinic for its substantial risk to patients. The key point of etiologic diagnosis is to distinguish dust mites and mold induced seasonal allergic asthma. Nowadays, more and more new technologies have been implied in etiologic diagnosis. Component resolved diagnosis (CRD), also known as molecular diagnosis, is an allergen detection method developed over the past 20 years [39]. Since the 1990s, purified recombinant pollen allergens was investigated to detect serum specific IgE level. CRD is currently performed to distinguish between genuine sensitization and clinical mostly irrelevant IgE cross-reactivity due to panallergens or carbohydrate determinants [6]. Basophil activation test (BAT), a flow cytometry-based functional assay, to assess the change of specific markers such as CD63 and CD203c expressed upon basophils after challenge. It is generally believed that BAT is more suitable for the diagnosis of complex allergy situations than simple pollen allergy [40]. Multiple omics technologies also showed a great potential in the diagnosis of seasonal allergic asthma [41, 42].

Treatment

In clinical trials, avoidance measure is the most important part of treatment. To cut down the amounts of pollen into the respiratory system, pollen allergic patients are usually suggested to stay indoors or wear masks outdoors to keep away from pollen allergens during pollen season. For worse, it is suggested to move to live in a non-pollen area.

Symptomatic drug treatment

For treatment, first- and second-generation H1-antihistamines and leukotriene receptor antagonists are of great clinical evidence existence. Inhaled corticosteroid acting beta-agonist is used for allergic asthma patients strictly based on the severity of asthma according to the GINA guidelines during pollen season. Interestingly, some researchers suggested that seasonal omalizumab treatment from four to six weeks before the peak period of pollen could reduce autumn asthma exacerbation [43].

Allergen specific immunotherapy (AIT)

However, the European Academy of Allergy and Clinical Immunology (EAACI) recommended that allergen specific immunotherapy (AIT) is the only way to effectively control allergy symptoms, induce tolerance and change the natural courses from allergic rhinitis to allergic asthma [44]. Allergen-specific immunotherapy (AIT) was reported first to treat grass pollen allergy patients for one year by Leonard Noon in 1911 [45]. AIT is defined as the repeated administration of specific pollen allergens to provide protection against the same pollen induced allergic inflammation in seasonal allergic asthma patients [46]. EAACI guidelines on allergen immunotherapy suggest a more efficient and safe use of AIT for personalized health care [47]. AIT is widely used for numerous advantages. Firstly, AIT uses the immune system of patients to establish a tolerant immune response and keep a long-lasting effects even after discontinuation of treatment [48]. Secondly, AIT is a cost-saving method especially compared with anti-cytokine antibodies and can reduce the usage of symptomatic drug treatment. A review examined 27 publications of seasonal allergic conditions that conducted across Southern, Europe, Scandinavia, Northern Europe, North America, and the Czech Republic spanning 18 years. It suggests that cost saving conferred by AIT over symptomatic drug treatment [49]. Thirdly, AIT is the only disease-modifying therapy and can prevent the development of new sensitivities to allergens [50, 51].

Mechanism of AIT

Most studies show that the alleviation of allergy symptoms is related to the suppression of Th2 response, decrease the level of Th2-producing cytokines, such as IL-4, IL-5, IL13 or of Th17-producing cytokines [31, 52-56]. IgG4 are widely considered as blocking antibodies. AIT may induce the production of specific IgG4 (IgG2a in mice) to compete with specific IgE for binding to the allergens, thus inhibit mast cell activation [57, 58]. Conversely, suppressor cells or regulatory T cells can suppress allergic response and diseases [59-61]. For example, IL-10 producing regulatory T cell (Treg) and regulatory B cell (Breg) also play a vital role in SCIT [28, 62]. The

infusion of Treg holds a suppression effect on asthma and other allergic responses [63, 64]. One hypothesis is that pollen-specific Treg cell produce IL-10 and TGF-β, which may suppress mast cells, basophils, and eosinophils degranulation, release histamine and leukotriene [65]. In innate immune phase, Treg inhibit dendritic cell (DCs), B cells and seasonal increase of group 2 innate lymphoid cells (ILC2) [66-69]. The long-lasting clinical tolerance is associated with long-lived B cell or plasma cells secreting high-affinity antibodies induced by increasing pollen content [70].

Animal models of AIT

Using a mouse model to study seasonal allergic asthma, birch pollen mouse model is the most typical component for studying the mechanisms of seasonal allergic asthma and AIT. Many publications have demonstrated the innate immune and adaptive immune change after AIT [28, 71, 72]. Currently, some researchers have reported that birch pollen SCIT can alleviate food allergy symptoms and reduce the occurrence of anaphylaxis in mouse [71]. As for Chinese most important autumnal pollens (Mugwort pollen), there is a successful mouse model and SLIT treatment case published in 2012 [73].

Classification of AIT

Subcutaneous immunotherapy (SCIT) is the traditional form of allergen-specific injection immunotherapy in treating seasonal allergic disorders [74]. Seasonal asthma patients have shown long-term clinical and immunological tolerance after pollen subcutaneous immunotherapy (SCIT) [70, 75, 76]. Since injection immunotherapy must be supervised by allergists on a repeated basis, sublingual immunotherapy (SLIT) is generally gaining interest due to its more accessible and lower risk of anaphylaxis [77]. Although multiple studies have proven its safety and efficacy for allergic asthma patients, the desired schedule and the optimal dosage of SLIT remains unclear [78, 79]. SLIT requires daily self-dosing for at least 3 years, leading to considerable treatment costs and low treatment compliance [46]. To shorten the treatment period, rapid intradermal allergen injection raises allergist's attention. However, a randomized controlled trial showed no significant differences in evaluating the efficacy of intradermal grass pollen immunotherapy [80].

Limitations of AIT

Although patients take advantage of AIT, the concern about systemic side-effects and anaphylaxis keep their paces [81]. One of the safe and effective strategies is to combine AIT with immunomodulators. The latter is defined as substance that can augment or reduce the reaction between antibodies and pollen allergens, like Omalizumab and Toll-like receptor agonists [82]. Omalizumab can bind the circulating IgE molecule and decrease free IgE interacting with IgE receptors on effector cells. Toll-like receptor agonists works on activating innate immune system. Another concern is that crude pollen allergen extracts are used in AIT lacking standard reference based on potency and stability [66]. This means different manufactures can perform differently in patients and allergist feel hard to choose optimal dosage based on past studies [78]. This affects allergist awareness on the side-effect of AIT products [47]. New effective modification of allergens like recombinant should be adopted through genetic engineering. To our knowledge, recombinant wild-type allergen and recombinant hypoallergen have been used for clinical treatment [83-85]. The development of T cell epitope peptide-based vaccines aims to reduce allergic inflammation by inhibition of T cell responses [66]. The recombinant B cell epitope-based grass pollen has proved safe and effective in treating seasonal grass pollen allergy [86]. Allergen immunotherapy is time-wasting and involves weekly up-dosing treatments for at least 3 years, which needs further study [28].

Conclusion

Pollen induced seasonal allergic asthma is one of the most important subtypes of asthma and affects millions of population all over the world. Appropriate diagnosis methods and precision treatment are of crucial significance. With the development of omics technologies, more and more reliable biomarkers will be found for therapeutic interventions and the mechanisms of seasonal allergic asthma will be clarified.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Jia Yin, Department of Allergy, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, NO. 1 Shuai Fu Yuan, Wang Fu Jing street, Beijing 100730, P.R. China. Tel: +86-10-69156346; Fax: +86-10-69156346; E-mail: doctoryinjia@163.com

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