Allergen Immunotherapy for Asthma

Subjects: Allergy

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For asthma, allergen immunotherapy using house dust mite (HDM) improves clinical symptoms and airway hyperresponsiveness and decreases drug requirements. Furthermore, it has been suggested that allergen immunotherapy also has the following effects: (1) the effect can be maintained for more than a year even if the treatment is terminated, (2) the remission rate of childhood asthma can be increased, (3) new allergen sensitization can be suppressed, and (4) asthma development can be prevented if allergen immunotherapy was performed in the case of pollinosis. Allergen immunotherapy differs from conventional drug therapy, in particular the effect of modifying the natural course of allergic diseases and the effect of controlling complicated allergic diseases such as rhinoconjunctivitis.

Keywords: Asthma,subcutaneous immunotherapy (SCIT),sublingual immunotherapy (SLIT)

1. Introduction

Bronchial asthma has become a well-controlled disease in general because of advances in drug therapy centered on inhaled corticosteroid (ICS). However, ICS does not modify the natural course of asthma and is being positioned as a so-called symptomatic treatment [1][2]. Furthermore, ICS does not provide therapeutic benefits for allergic rhinoconjunctivitis, which is often complicated in asthmatic patients. Allergen immunotherapy is the only existing treatment that can be expected to induce immunological remission, that is, a possible cure of allergic diseases [3]. Moreover, allergen immunotherapy has therapeutic potency for a variety of allergic diseases simultaneously observed.

In asthma, meta-analyses have demonstrated that SCIT improves clinical symptoms and airway hyperresponsiveness and decreases drug requirements [4][5]. For example, Abramson et al. reported that the odds ratio for symptom improvement by SCIT with any allergen was 3.2 (95% CI 2.2–4.9), the odds ratio for drug reduction in SCIT using house dust mite (HDM) was 4.2 (95% CI 2.2–7.9), and the odds ratio for improvement of airway hypersensitivity was 6.8 (95% CI 3.8–12.0) [4].

The effect of the addition of SCIT with HDM (HDM-SCIT) to the guideline treatment was reported in patients with mild or moderate HDM-sensitized asthma [6]. In the immunotherapy group, a decrease in the frequency of inhalational β2-agonists and a significant improvement in peak flow were observed. Furthermore, in pediatric asthma, adding HDM-SCIT to the guideline treatment reduces the requirement for ICS and improves the morning peak flow [7]. Therefore, HDM-SCIT has an additional effect even after the standard treatment is already performed. Furthermore, as described below, allergen immunotherapy has a controlling effect on other allergic diseases such as rhinoconjunctivitis, which is often complicated in asthma, a maintenance effect for more than a year even after discontinuation of treatment, and may have an inhibitory effect on sensitization to new allergens. Therefore, allergen immunotherapy has shown significantly different clinical meaning from drug therapy represented by ICS.

However, the efficacy and effectiveness of SCIT in asthma remain controversial. Current evidence is derived from several small randomized controlled trials (RCTs), not only registration trials. Additionally, even in registration RCT, the effect of SCIT seems to be small to moderate. Furthermore, several biases including potential publication bias are also suggested in the meta-analyses [5].

Nonetheless, the United States adult asthma management guideline (EPR3) states that SCIT should be considered for allergic asthma in steps two to four (mild persistent-moderate persistent equivalent) of the six treatment steps [8]. The European Academy of Allergy and Clinical Immunology (EAACI) guideline states that HDM-SCIT is recommended as an add-on to regular asthma therapy for adults with controlled or partially controlled HDM-driven allergic asthma [9].

2. Allergen Immunotherapy in Japan

The standardized HDM allergen for SCIT was not available in Japan until 2015. Before 2015, SCIT using house dust (HD), collected from the general house, was utilized as an alternative therapeutic agent. The main component of HD is mites, but there were problems with product quality, and it was necessary to improve the effect and safety by standardizing allergens. The standardized purified HDM allergen for SCIT was prepared in 2015 and is currently used for the treatment of asthma.

For sublingual immunotherapy (SLIT), two HDM-SLIT tablets were approved for allergic rhinitis, but not for asthma, in 2015. The tablet developed by Torii Pharmaceutical Co., Ltd., Tokyo, Japan (MITICURE®) is the same as the tablet manufactured by ALK, in which the effect on asthma has been fully proven in Europe as described (10,000 Japanese allergy unit (JAU); the maintenance dose in Japan is equivalent to 6SQ in Europe).

Recently, the effect of the HDM-SLIT tablet on asthma has also been determined in Japan. In HDM-sensitized atopic asthma with rhinitis, the addition of MITICURE® to the standard treatment improved the symptom scores of asthma, fractional exhaled nitric oxide, FEV_1, and airway wall thickening in chest CT [10], suggesting that HDM-SLIT can suppress not only airway inflammation but also airway remodeling of asthma. Furthermore, a study of the effect of MITICURE® on asthma exacerbation associated with ICS reduction demonstrated that this treatment suppresses asthma exacerbation in patients who used short-acting β2-agonists during the observation period [11], which is consistent with the previous study in Europe [12].

Japanese cedar pollen (JCP) is widely scattered in the spring in Japan. Pollinosis by JCP is a representative seasonal rhinitis in Japan. People living in urban areas also suffer from pollinosis because JCP is scattered over tens of thousands of kilometers. One epidemiological study reported that the prevalence of Japanese cedar pollinosis was 26.5% [13]. Furthermore, its prevalence increased by about 10% in 10 years. This situation in Japan is unique in that Japanese cedars are planted forests and not natural ones. Similar to other pollens, JCP has been reported to exacerbate asthma. For example, Hojo et al. reported that the asthma control level, measured by the visual analog scale of Self-Assessment of Allergic Rhinitis and Asthma Questionnaire and Asthma Control Test score, worsened during the JCP-scattering season in asthmatic patients with allergic rhinitis by JCP, although 84% received treatment for rhinitis [14]. Asthma control during the pollen season was impaired in 18–38% of asthmatics with seasonal rhinitis with JCP [14]. Although the mechanisms for asthma exacerbation by JCP have not been fully clarified, several possible mechanisms are proposed. For example, fine orbicules (about 1 μm) adhering to the surface of JCP can reach the lower respiratory tract and directly induce asthma exacerbation. In addition, the effects of nasal obstruction, mediator released locally in the nose, and increased systemic cytokine production may be involved in JCP-related asthma exacerbation.

Regarding JCP-related asthma, we have confirmed that treatment with JCP-SLIT almost completely abrogates the appearance of asthma exacerbation during the JCP-scattering season [15], supporting the certain prevention effect of SLIT on asthma exacerbation. Collectively, these findings indicate that HDM- or JCP-SLIT should be considered for asthmatic patients with rhinitis.

3. Conclusions

In HDM-sensitized asthma, HDM-SCIT improves clinical symptoms and airway hyperresponsiveness and decreases drug requirements. Furthermore, HDM- or JCP-SLIT can decrease asthma exacerbation and drug requirements. Current pharmacotherapy, such as ICS, provides powerful anti-symptomatic benefits in asthma; however, it does not modify the natural course of allergic diseases. In contrast, allergen immunotherapy targets the immunological background including the pathological activation of Th2 cells. Thus, it is expected to lead to long-term amelioration of asthma and allergic diseases. It is hoped that allergen immunotherapy is more widely applied in the treatment of asthma as a strategy for comprehensive management of allergy symptoms and modification of disease course.

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