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REVIEW ARTICLE

House dust mite-specific immunotherapy alters the natural course of atopic march

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Abstract: Allergen immunotherapy (AIT) is an effective treatment for patients with allergic diseases; it has been shown to modify the underlying cause of the disease. The house dust mite (HDM) is a major perennial allergen source and a significant cause of allergic-related diseases such as allergic rhinitis, asthma, and atopic dermatitis. HDM allergen is an important factor in the pathogenesis of allergic diseases. Sensitization to HDM allergen often occurs early in life and appears to play an important role in the progression from allergic rhinitis to asthma in children. The role of HDM AIT results in immunologic tolerance, provides an alternative option for treating HDM allergy through targeting the mechanisms of allergic reaction, and creates a long-term benefit. There are two forms of testing for aeroallergen, either detect by skin testing or by in vitro IgE assays. Both subcutaneous immunotherapy and sublingual immunotherapy are effective in the treatment of allergic diseases. In the future, new forms of allergen extracts can help improve safety and efficacy of AIT. Novel approaches to immunotherapy currently being explored include the use of adjuvants, allergen-derived peptides, modified recombinant allergen vaccines, and gene-specific immunotherapy.

Keywords: Allergic diseases; Allergen immunotherapy; House dust mite; Subcutaneous immunotherapy; Sublingual immunotherapy

1. INTRODUCTION

Allergen immunotherapy (AIT) is done using injected aeroallergen extracts for IgE-mediated allergic diseases, such as rhinoconjunctivitis, allergic asthma, venom allergy, and in some regions included atopic dermatitis. It has a history of more than a century and has been widely used as a treatment for respiratory allergies,[1–3] especially allergic rhinitis and asthma.[3,4] The efficacy of AIT has been demonstrated rapidly during the past 30 years; numerous controlled trials have shown that immunotherapy, using high-quality extracts in sufficient doses, relieves the symptoms of allergic rhinoconjunctivitis with minimal side effects.[4,5] Studies on immunotherapy for allergic asthma have shown that specific immunotherapy reduces airway sensitivity to allergens, decreases symptoms and signs, and improves basal pulmonary function.[6,7] The house dust mite (HDM) AIT has been used in allergic asthmatic children and adults demonstrating clinical improvement.[8,9] AIT is effective when appropriate doses of allergens are administered, sharing clinical improvement in allergic rhinitis and asthma, such as reduced symptoms, decreased medication use, and improvement on quality of life, with a long-lasting effect even after cessation of treatment. Effective subcutaneous AIT appears to correlate with administration of an optimal maintenance dose of major allergen for inhalant allergens.[10]

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2. THE PREVALENCE OF HDM ALLERGY

Over the past few decades, allergic diseases have become increasingly prevalent worldwide. The HDM is a major perennial allergen source and a significant cause of allergic diseases, such as allergic rhinitis, asthma, and atopic dermatitis.[11,12] Environmental factors induced by industrialization and climate change in temperature, humidity, air pollution, or other environmental conditions could modify natural HDM growth, survival, and allergen production. This can partially explain the increase in prevalence and severity of allergic disease. HDMs has increased in some regions of the world, especially in the subtropical and tropical areas.[13] Asthma has become the most prevalent chronic disease, especially in children.[14,15] In Taiwan, the prevalence of asthma and other allergic diseases has been increasing, with surveys documenting an asthma prevalence of 1.3% in 1974, 5.3% in 1987, and 11.9% in 2007.[16–19] Trends towards an increasing occurrence of asthma are not limited to Taiwan. Indeed, such trends seem to be global, the increase is associated with urbanization and the recent United States investigations have revealed rural pediatric asthma prevalence to be very similar to urban area and to be more closely correlated with socioeconomic and environmental factors than geographic location or population density.[13,14] Parallel with increased urbanization, the increase in asthma prevalence in most areas of the world will also continue. However, studies performed in Australia and North-West Europe, particularly among children and adolescents, indicate that the increase in asthma prevalence may now be leveling off.[15]

3. ALLERGIC MARCH AND THE HYGIENE HYPOTHESIS

The allergic march refers to the natural history progression of atopic disorders. The allergic march is concerned with the development of atopic dermatitis and concomitant sensitization

to food and HDM allergens in early childhood, progressing to asthma, and allergic rhinitis in later childhood or adult life.[20,21] The hygiene hypothesis suggests that childhood asthma develops as a result of decreased exposure to infectious disease and other stimuli. As Westernization develops, the environment becomes cleaner, and people lack the immunologic and infectious stimuli needed for the immune systems to shift from the T-helper cell type (TH) 2 to TH1 response. The microbiota hypothesis, implicating non-pathogenic commensal microorganisms as the source of immunomodulatory signals necessary to prevent immune-mediated chronic disorders.[22] Diversity in the mucosal microbiome probably reflects an undisturbed balance of beneficial microorganisms and pathogens such as *Moraxella catarrhalis*, which has been associated with subsequent development of asthma and pneumonia. In addition, specific fermenters of plant fibers, such as the genera Ruminococcus and Bacteroides, have been implied in creating asthma protection through production of short-chain fatty acids, reducing TH2-mediated allergic airway inflammation. Nonetheless, current available epidemiologic evidence does not support a mechanism of early life immune deviation. The principal environmental influences on atopic disease are likely to occur throughout life and involve interactions between microbes and non-infective and lifestyle factors.[23,24]

Exposure to indoor allergens during early life may play a role in the development of the immune system and inception of asthma.[25] Current evidence suggests a combination of strategies, including natural childbirth, breast feeding, increased social exposure through sport and other outdoor activities, less time spent indoors, proper diet, and appropriate antibiotic use, may help restore the microbiome and perhaps reduce risk of allergic disease. Preventive efforts must focus on early life style change.[26,27]

4. ALLERGY TESTING

The selection on allergens for immunotherapy is based on clinical history, specific IgE antibodies, and allergen exposure. HDM, especially *Dermatophagoides pteronyssinus* (*Dp*) and *Dermatophagoides farinae* (*Df*), have been shown to comprise the most important allergens in airway hypersensitivity,[28] AIT in its subcutaneous and sublingual forms is currently a well-established and experimentally supported treatment for respiratory allergy disorders, such as allergic rhinitis and asthma.[29] Currently, there are two main testing for IgE-mediated allergy diseases, including the in vivo skin prick test and the in vitro serum-specific antibody tests. It can precisely detect reactions to *Dp* and *Df* in allergic children. Compared with aeroallergen or medication provocation challenges test, both are less time consuming procedure and have lower risk of adverse reactions.[30–32]

5. MECHANISM OF AIT

Immunologic changes associated with immunotherapy are complex, and the exact mechanisms responsible for its clinical efficacy are continually being explored.[33] The role of HDM allergen in allergic inflammation through innate immune system with toll-like receptors, protease-activated receptors, and local dendritic cells can be activated by different HDM major allergens and proinflammatory cytokines can also be upregulated. Immunotherapy provides an alternative option for treating HDM allergy by targeting the mechanisms of allergic reaction and presenting a long-term symptoms relief.[12]

Immunotherapy creates in immunologic tolerance. AIT is effective when appropriate doses of allergens are administered. There were no significant changes in serum-specific IgE antibody titer for a short course immunotherapy, lasting 1 year or less in mite-sensitive asthmatic children. But, significant reduction of specific IgE HDM in the immunotherapy group are shown after receiving long-term immunotherapy; namely 2–3 years.[34] Till now, there are no current available validated biomarkers that can predict AIT success.[3] Immunotherapy inhibits both early and late responses to allergen exposure. Immunotherapy is accompanied by increases in allergen-specific IgG, particularly the IgG4-blocking antibody, which blocks not only IgE-dependent histamine release from basophils but also IgE-mediated antigen presentation to T cells. The mean level of anti-mite-specific IgG4 tended to increase during immunotherapy with clinical improvement in asthmatic children during immunotherapy. It is suggested that the anti-mite-specific IgG4 antibody titer may serve as an indicator for clinical outcome of mite allergy during immunotherapy.[35–37] Immunotherapy acts on T cells to modify peripheral and mucosal system from a TH2 to a TH1 cytokine profile. Regulatory T (Treg) cells and their cytokines, primarily interleukin (IL)-10, transforming growth factor beta, IL-2, and IL-2R suppress TH2 immune responses and control allergic diseases.[38–40] Regulatory B (Breg) cells, which produce IL-10 and IgG4 and expressing CD25 on their surface, are also generated. Both Treg and Breg cells suppress allergen-specific effector TH2 cells and appear to be identified by the $CD4^+CD8^+CD25^+CD137$ phenotype.[41]

6. PRACTICE GUIDELINES

AIT may be an option if allergy plays a prominent role in the disease, for example, asthma with allergic rhinoconjunctivitis. AIT may also reduce the risk of progression from allergic rhinitis to asthma in children and prevent the onset of new sensitizations, thus representing a potentially preventive method of treatment. There are significant variations in the way of allergen-specific immunotherapy, including differences in schedules for injections, safety precautions, and training requirements. Since 1988, numerous AIT guidelines have been developed by national and international organizations to guide physicians in AIT. Even so, AIT is still severely underused, both in children and in adults.[1–3]

In North America; AIT: a practice parameter established in 2003 with standardized terminology for describing AIT extract dilutions, which is update in 2011.[33] These parameters also provided specific recommendations for immunotherapy maintenance doses for some standardized allergens and is recommended as an adjunct to standard pharmacotherapy.

In Europe; a clinical practice guideline provides evidence-based recommendations for the use of HDM AIT as add-on treatment for HDM-driven allergic asthma. This guideline was developed by a multidisciplinary working group using the Grading of Recommendations Assessment, Development and Evaluation approach. HDM AIT was evaluated separately by route of administration in children and adults.[1–3]

7. SUBCUTANEOUS OR SUBLINGUAL IMMUNOTHERAPY

AIT should be reserved for patients with moderate/severe rhinitis or for those with moderate asthma, despite appropriate pharmacotherapy and adherence, continue to exhibit exacerbations that appear to be related to allergen exposure.[3] Several systemic reviews and meta-analysis indicate that both subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) are effective in the treatment of allergic rhinitis and asthma for HDM sensitivity.[1–3,42–44]

SCIT has been the gold standard. It is effective for both seasonal and perennial allergic rhinitis. Sustained effectiveness will require several years of treatment. SCIT may prevent the

development of allergic asthma in children with allergic rhinitis. In people with asthma and allergic sensitization, SCIT is associated with a reduction in symptom scores and medication requirements, and improved allergen-specific and nonspecific airway hyperresponsiveness. SCIT reduces the use of long-term control medications. It may also improve quality of life and reduces the use of quick-relief medications and systemic corticosteroids. Adverse effects include risk of both local and systemic adverse reactions, and uncommon systemic anaphylactic reactions which may be life-threatening. However, in most cases, symptoms are readily reversible if they are recognized early and treated promptly.

SLIT is currently considered an alternative treatment to the subcutaneous route. SLIT involves the regular self-administration and retention of allergen extract under the tongue for 1–2 minutes before the extract is swallowed. The allergen crosses the mucosa in 15–30 minutes and are then captured by tolerogenic dendritic cells and processed as small peptides. Next, via the lymphatic system, causes a systemic immune response to produce an early decrease in mast cell and basophil degranulation. The use of SLIT has been included in international guidelines for the treatment of allergic rhinitis with or without conjunctivitis. A study on SLIT for HDM in patients with asthma and allergic rhinitis demonstrated a modest reduction of ICS.[42] In patients sensitized to HDM with allergic rhinitis and persistent asthma requiring ICS, SLIT for HDM showed improvement in asthma symptoms, quality of life, and reduces the use of long-term control medications. It may also reduce the use of quick-relief medications, showing benefit in decreasing mild to moderate asthma exacerbations.[43] Adverse effects include mild oral and gastrointestinal symptoms. The safety profile of SLIT is generally good; therefore, SLIT can be self-administered by patients in their homes.

8. FUTURE APPROACHES FOR IMMUNOTHERAPY

AIT provided an alternative option for treating HDM allergy and represented a long-term symptoms relief. Immunotherapy is the only current disease-modifying treatment option besides allergen avoidance.[45] The allergenic potency of HD extracts was examined by comparing with a standardized HDM allergen extracts which have been used to provide efficacy and safer AIT preparations to lower or even totally overcome this risk.[46] There are differences in clinical approach to SCIT for polysensitized patients. In the United States, mixed extracts containing multiple aeroallergens are used, whereas European allergists preferably administer separate injections of single allergen source or homologous group deemed to be clinically relevant. More product options are available, including adsorbed allergens, chemically modified allergens, or both.[47] In the near future, novel approach to immunotherapy currently being explored include the use of adjuvants, such as monophosphoryl lipid A or nucleotide immunostimulatory sequences derived from bacteria that potentiate TH1 responses. New routes of administration (intralymphatic and epicutaneous) and new allergen preparations, including allergoids, peptides, and recombinant allergens, are used in subcutaneous as well as in mucosal immunotherapies (using bronchial, nasal, oral, and sublingual application) with sublingual being the established mucosal application route. Immune-modifying agents like virus-like particles and toll-like receptor ligands, also depot-forming adjuvants further enhances activation of innate as well as adaptive immune responses and direct the immunological response toward immunological tolerance.[29,47] Gene-specific immunotherapy are currently being developed, and it can decrease allergic inflammation and improve the efficacy of treatment.[12]

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