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REVIEW

Immunotherapy of house dust mite allergy

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ABSTRACT

House dust mite (HDM) is a predominant source of indoor aeroallergen worldwide, which induces allergic diseases including allergic rhinoconjunctivitis, allergic asthma, atopic eczema and other allergic skin diseases. Allergen specific immunotherapy (AIT) is the only potential disease-modifying treatment of HDM allergic subjects. However, AIT remains underused due to no universally accepted allergen standardization and a shortage of rigorous clinical studies to confirm safety and efficacy. With the effort of doctors and researchers in allergy field, efficacy, safety, standardization and strategy of AIT are being continuously developed. This review presents the updated research based on recently published trials and meta-analyses.

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Introduction

House dust mite (HDM), a predominant source of indoor aeroallergen worldwide,[1] has been associated with allergic diseases from 1920.[2] HDM induced allergic diseases include allergic rhinoconjunctivitis, allergic asthma, atopic eczema and other allergic skin diseases. The World Health Orgnization (WHO) estimates that allergic rhinitis (AR) affects 600 million people worldwide, with 200 million associated with asthma.[3] Half of all adults with asthma and at least 2 thirds of children with asthma have allergies.[4] Up to 85% of asthma patients in North and South America, Europe, south-east Asia and Australiaare typically HDM allergic in spite of differences in geography, temperature and humidity.[1] For AR patients, the sensitization rate could be up to 91.1% in Central China.[5] In children with atopic dermatitis (AD), 74.5% of patients showed positive skin prick test reactions to either *D. pteronyssinus* or *D. farinae* extracts and usually both.[6]

According to a WHO position paper, the optimal treatment strategy for allergic rhinitis consists in allergen avoidance, pharmacotherapy, allergen immunotherapy (AIT) and patient education with varied combination of these methods in different cases.[7] HDM avoidance is the first recommended method to reduce the symptoms in clinic now. However in Cochrane meta-analyses on mite avoidance, the use of environmental control measures has been found to be of little benefit in reducing rhinitis symptoms and with no effect on alleviating asthma symptoms.[8,9] Apart from allergen avoidance, pharmacotherapy is also part of the treatment, especially antihistamines, leukotriene receptor antagonist and inhaled/intranasal corticosteroids, which aim at regulating inflammation of the upper and lower airways.[10] Although these treatments are effective and, in most cases, safe, they have been proved difficult to change the course of HDM-related allergic diseases.

AIT has been in use for the past century, which intends to achieve clinical tolerance to the causative allergens through the administration of allergen extracts to patients with allergic disease. It has been defined by a WHO leading paperas "the only form of treatment able to modify the natural course of allergic diseases.[7] It is effective in the treatment of the type I allergic diseases induced by IgE, in term of alleviating the symptoms of allergic rhinitis and/or asthma, reducing the use of symptom relieving medication, and improving the quality of life. AIT also shows long-lasting benefits, even after cessation of the treatment,[11] In addition, AIT has also been shown to be able to reduce new allergen sensitization risk and prevent development of bronchial asthma in allergic individuals.[12]

House dust mite allergenic extracts

House Dust Mite Allergen. HDMs are found mainly in mattresses, sofas and carpets throughout the year. They have a fast reproductive turnover and their life expectancy varies from 7 to 10 weeks, during which females could deliver 40 to 80 eggs.[13] The main species of HDM includes *Dermatophagoides pteronyssius, Dermatophagoides farinae and Blomia tropicalis* which coexist in most geographical regions.[14]

Research on HDM already progressed into the molecular level. To date, 82 mite allergens derived from 10 species have been identified. Group1, 2 and 23 are considered as dominant allergens. Trombone et al[15] showed that 95% of patients bound one and usually both of group1 and group 2. Group1 (Der p1, Der f1) allergens have the protease activity to potentially destroy the epithelial tight junctions; group2 (Der p2, Der f2) allergens might mimic the effect of Toll-like receptor 4 coreceptor MD-2.[16] Group 23 (Der p23) represents a new major *D. pteronyssinus* allergen, which reacted with IgE Abs from 74% of *D. pteronyssinus* allergic patients.[17]

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The current diagnosis and immunotherapy treatment of HDM allergy are conducted with HDM extracts made from the bodies, excrement and other emanations of mites.

Standardization of Mite Allergenic Extracts for Diagnosis and Treatment. HDM extracts are conventionally standardized by their ability to produce skin prick test reactions in allergic volunteers rather than by the allergen content.[18] Unfortunately, no standards for HDM extracts are universally accepted till now.[19,20]

In Europe, biologic standardization of mite allergen extracts is based on the wheal size of skin prick testing. The consistency is ensured mainly by using in-house standards and international references. For ALK Company (Denmark), unit is based on SPT in 30 allergic patients. STU and SQ-U: based on therapeutic response. For Stallergènes Company (France), Quadruple SPT with 3 serial 1/10 dilutions in 30 allergic patients is used and control is 9% codeine phosphate (7 mm).[21] The extracts produced by different European manufacturers are not usually interchangeable.[22] In United States, ID50EAL (intradermal dilution for 50 mm sum of erythema), is used to determine the potency of mite extracts as reference preparations. The Center for Biologics Evaluations and Research (CBER) of the FDA provides the reference extracts to the manufacturers and authorized products are compared with the references using the relative potency value obtained by a parallel-line bioassay analysis.[23] In China, the standards for manufacturers are also not unified. Different in-house standards are used by different manufacturers and there are still no standards for HDM extracts.

Casset and colleagues[24] analyzed commercially available *Dermatophagoides pteronyssinus* extracts from 10 different manufacturers and found great variability regarding the allergen composition that lacks of important allergens and showed different IgE reactivity profiles to the individual mite allergens. Although, HDM extracts are difficult to standardize and still not comparable due to small number of patients tested, different sensitivity of the chosen patient population, different HDM material, and the method to extract,[25,26] no progress will occur if each manufacturer uses its own in-house standard. Therefore, the use of standardized assays (provided by WHO), should be implemented.

Efficiency of AIT on HDM-related allergic diseases

Mechanisms of subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). AIT is applied worldwide mainly based on evidence of its clinical efficacy.[27] Nowadays, itsmechanisms are becoming better understood these years. Effective AIT activates multiple mechanisms. Firstly, SCIT reduces allergen-specific IgE production and increases the production of specific IgG (which acts as a "blocking" antibody).[28] IL-10-producing Breg cells play an essential role in suppression of IgE and induction of IgG_4.[29] Secondly, AIT induces a major change in allergen-specific T-cell subsets, including immunologic deviation (stimulation of Th0/Th1 lymphocytes, with increased IFN-γ and IL-2 production), specific T-lymphocyte anergy (a decrease in Th2/Th0 lymphocyte counts) and induction of regulatory T-lymphocytes, which produce cytokines such as IL-10 and TGF-β. Thirdly, suppression of peripheral ILCs, especially ILC2s, might contribute to Th2 suppression and immunologic tolerance.[30] Lastly, AIT decreases inflammatory cells recruitment, activation, and mediator release (histamine, prostaglandin D2, and eosinophil cationic protein).[28] All these effects contribute to immune tolerance and the long-lasting changes in the immune system even after treatment is discontinued. The mechanisms of SLIT are not fully understood but they seem to be similar to those of SCIT, except that in SLIT, mucosal dendritic cells are particularly involved in this process.[31]

Efficiency Research of SCIT for allergic rhinitis and asthma. SCIT has been in use for 100 y and numerous studies have demonstrated the efficacy of SCIT using HDM allergen for both asthma and AR.[32,33] Recent systematic reviews also confirmed the presence of moderate to strong evidence for the effectiveness of SCIT.[34]

In a recently published meta-analysis, a total of 796 subjects from 19 different randomized controlled trials (RCTs) of SCIT on asthma were analyzed. The results suggest that SCIT is helpful in alleviating symptoms and in reducing medication used in mite-sensitive asthma subjects, but with no improvement in lung function. The safety of SCIT is acceptable.[35] Another Cochrane review meta-analysis specifically designed to evaluate the effect of SCIT on asthma has reviewed 42 HDM-SCIT randomized control trials published between 1968 and 2004. It identified that SCIT reduces asthma symptoms and use of asthma medications and improves bronchial hyper-reactivity.[36]

Efficiency Research of SLIT for allergic rhinitis and asthma. Systematic reviews and meta-analyses of SLIT have reported variable clinical effects for HDM allergy in both rhinitis and asthma.[37-39] But trials on SLIT with positive results continue to be published recently. For rhinitis, in a randomized, double-blind, single-site trial, dose-dependent and time-dependent treatment improves with HDM sublingual immunotherapy tablet MK-8237 (Merck/ALK-Abello) compared with the placebo groupand the onset of action for 12 developmental units (DU) of MK-8237 was week 8.[40] Another RCT result identified that 12 months of treatment with 500IR and 300IR sublingual tablets of HDM allergen extracts were efficacious and well tolerated. Efficacy was maintained during the treatment-free follow-up year.[41] Efficacy in mild-to-moderate asthma of 6 SQ-HDM relative to placebo was demonstrated by a moderate but statistically significant reduction in the ICS dose required to maintain asthma control. All active doses were well tolerated.[42] A meta-analysis indicated that SLIT provided significant symptom relief and reduced the need for medications in persistent allergic rhinitis (PAR).[43]

The heterogeneity of the studies is partly due to the use of different standards in various studies. A review of AIT studies using extracts of HDMs for AR and asthma found no consensus on basic treatment parameters (eg, dose and duration).[44] The authors suggested that there is an urgent need for rigorous, long-term, double-blind, placebo-controlled randomized clinical trials with an efficacy criterion that reflects the particular features of HDM-induced allergic disease.

In 2016, 2 high profile large multicenter trials on HDM-SLIT on asthma and rhinitis were published. Virchow JC, et al[45] reported a double-blind, randomized, placebo-controlled trial that included 834 adults with HDM sensitization whose asthma was not well controlled with inhaled corticosteroids or combination products. 693 completed the study. The 6 SQ-HDM and 12

SQ-HDM doses both significantly reduced the risk of a moderate or severe asthma exacerbation compared with placebo. Compared with placebo, there was a reduced risk of an exacerbation with deterioration in asthma symptoms and a significant increase in allergen-specific IgG_4. The observation period was 6 months but those trial subjects received up to 18 months of AIT.

Demoly and colleagues conducted[46] a randomized, double-blind, placebo-controlled phase III trial conducted in 12 European countries including 992 adults with moderate-to-severe HDM-induced AR despite treatment with pharmacotherapy. The trial confirmed the efficacy and a favorable safety profile of both 2 doses of 6 SQ-HDM and 12 SQ-HDM by SLIT in adults with HDM-induced AR. The treatment effect was present from 14 weeks of treatment onward.

Comparisons of HDM-SCIT and HDM-SLIT for allergic rhinitis and asthma. There are several randomized controlled trials that prospectively compared the clinical effectiveness and mechanisms of HDM-SCIT and HDM-SLIT patients bearing asthma and rhinitis.[47-50] Overall, SLIT appears to be somewhat less effective than SCIT. However, these studies give low quality evidence and more adequately powered comparisons are needed. Furthermore, SLIT is associated with fewer adverse reactions, especially in patients with asthma, than SCIT.[51] More rigorous studies of SLIT are clearly needed to refine in the practice of SLIT.

AIT for atopic dermatitis. AIT for atopic dermatitis (AD) usage throughout the world remains limited because of variability in results and the lack of evidence from large randomized controlled trials. In one study, a total of 217 AD patients who were treated with AIT for at least 3 y were retrospectively assessed. They emphasize the usefulness of long-term HDM AIT as a disease-modifying therapy for AD.[52] A meta-analysis provides moderate-level evidence for the efficacy of AIT against atopic dermatitis and AIT also showed significant efficacy in long-term treatment of patients with severe atopic dermatitis.[53] In another study, although SCIT showed no statistically significant difference in the overall population of patients with AD, statistically significant reduction of the total SCORAD could be achieved in a subgroup of patients with severe AD.[54] Hence, although the efficacy of AIT for extrinsic AD patients with positive reactions to HDM was believed to have controversial results for patients in the past, now there is a growing trend of thought that AIT is indeed an efficient and safe treatment modality for AD patients through many double-blind placebo-controlled trials and meta-analysis.[55]

Other benefits of AIT

Long term effect of AIT. A prolonged duration of treatment is required for long-term efficacy after discontinuation of immunotherapy. Prospective studies of HDM extract for respiratory allergy patients suggest that 3 y of AIT sufficiently produces prolonged remission of symptoms after discontinuation.[56] SLIT with HDM extract in AR patients demonstrated a remission lasting for 7 and 8 y after 3 or 4 y of AIT.[57]

Prevention of development of allergy. AIT may prevent the development of new sensitizations in HDM monosensitized children.[58] Prophylactic HDM oral immunotherapy is well tolerated in children with high heredity risk. The results met the trial's prespecified criteria for proof of concept in reducing sensitization to any allergen; however, no significant preventive effect was observed regarding HDM sensitization or allergy-related symptoms.[59] This may lead to a new indication of AIT with the potential of reducing increasing prevalence of allergic disease. However, more randomized controlled trials are required.

Safety of AIT

Local Reactions (LRs). In general, both SCIT and SLIT can cause local or systemic reactions. Swelling and redness at the injection site in SCIT and oral itching and tingling in SLIT are common local adverse effects. A 3 grade classification system for SLIT LRs was developed by a World Allergy Organization (WAO) task force[60] and a grading system for SCIT also proposed by WAO.[61] LRs are not supposed to predict of subsequent systemic reactions (SRs) with either AIT route,[62] however, in Zhu's study, SR rate was higher when an LR or a large local reaction (LLR) proceeded immediately during the injection.[63] Further studies are needed to evaluate the predictive relationship.

Systemic Reactions (SRs). In SCIT, mild-to-moderate SRs occur in approximately 0.1% of the patients, while severe reactions are rare (1 in 1 million injections).[64] SRs in SLIT are extremely rare.[65] Only one SRs of anaphylaxis have been reported.[66]

In a recent prospective, multi-center non-interventional study, AEs were observed in 4/117 adults (3.4%) and in 7/103 children (6.8%). Serious AEs were reported in 3 adults and one child.[67] In Devillier's study, they concluded that HDM SCIT was safe and well tolerated in adult patients with mild-to-moderate, persistent asthma.[68] Zhu and colleagues also identified that the incidence of SRs to dust mite SCIT was low. Children, asthmatics and patients with concomitant LR may be prone to develop SRs.[63] From the above, Symptomatic or poorly controlled asthma was identified as a contributing factor in most fatal and near-fatal SCIT-related SRs. Asthma assessment before SCIT injections is suggested.

In a comprehensive review of 104 SLIT studies published in 2006, the SLIT-related SR rate was 0.056% of doses administered.[69] In recent trials, the safety of HDM SLIT is all confirmed,[46,70,71] which allows for administration outside of a medically supervised setting.

AIT with multi-sensitizations, mix or no mix

Allergic patients are often sensitized to several allergens. The selection, total number, and proportions of allergen components that are included in therapeutic mixtures are critical aspects of formulating allergen immunotherapy. When preparing mixtures of allergen extracts, the prescribing physician must take into account the cross-reactivity of allergen extracts and the potential for allergen degradation caused by proteolytic enzymes.[72] In previous researches, mite allergens are resistant to insect and fungal proteases if stored in $\geq$ 10% glycerin. No detectable loss of allergen reactivity was observed after mixing grass pollen with the various manufacturers' mite extracts at concentrations equivalent to current immunotherapy practice parameter recommendations.[73]

Moreover, most studies demonstrating the efficacy of immunotherapy have used single allergen, with few data to support the multi-allergens AIT. In Virchow JC's[45] study, 66% of the cases were multi-sensitizations in addition to HDM, however no difference in outcomes was detected between those patients and monosensitized to HDM. The recent approvals by regulatory authorities of sublingual tablets containing mixtures of mite extracts (2 species) and grass (5 species) will provide data on the topic later.[74]

Quality of life for AIT

Multiple studies have demonstrated the superior clinical efficacy of AIT compared with symptomatic drug treatment (SDT) in clinic. However, improved quality of life and cost-effectiveness, are becoming more important to patients and healthcare decision-makers.[75]

Individual studies have demonstrated HDM AIT quality of life and cost-savings compared with SDT.[76] For HDM SCIT, a study reveals that it is associated with initial resource investments and subsequent resource savings in the long-term compared with standard care and suggests that it also increases societal welfare.[77] For HDM SLIT, SQ HDM SLIT-tablet in addition to pharmacotherapy is cost-effective compared with allergy pharmacotherapy plus placebo for the treatment of persistent moderate-to-severe HDM allergic rhinitis that is not well controlled by allergy pharmacotherapy.[78] However, the cost-efficacy time-point varies according to different researches. Significant cost savings were reported as early as 3 months after AIT initiation. In some studies, cost-efficacy time-point was not established until after treatment discontinuation. The magnitude of cost-efficacy is likely to be underestimated in that few studies consider the cost savings due to AIT's long-term benefits or preventive effect.[79]

As AIT is a long and tedious treatment procedures and it is uncertain to what extent this statistical significance translates into clinically significant differences across the different types of outcome measures used.

Future perspective

In an effort to reduce systemic allergic reactions during immunotherapy and to maximize immunogenicity and clinical efficacy, several methods have been developed. Lee SP[80] assessed the clinical efficacy and adverse effects of Intralymphatic immunotherapy (ILIT) using aqueous Df, Dp, dog, and cat allergens or mixtures thereof in patients with allergic rhinitis. ILIT can rapidly improve allergy symptoms and quality of life, and this effect lasts for one year. However, ILIT can provoke severe systemic and/or local hypersensitivity reactions when performed using aqueous allergen extracts; Other than Lee's study,several novel immunotherapeutic approaches might also improve the immunogenicity of AIT without increasing its allergenicity. Such approaches have included adding therapy to standard AIT, altering the allergen extract, using novel adjuvants, or changing the mode of delivery of the allergen extract. Adding omalizumab (anti-IgE monoclonal antibody) to SCIT improves its safety and tolerability during build-up, the likelihood of the patient reaching the maintenance phase, and the therapy's overall effectiveness.[81,82] Other well-knownapproaches include modified HDM extract, such as using recombinant antigen technology to produce allergen extract against specific proteins to which the patient is allergic, rather than the whole allergen, or using DNA containing a CpG motif as immunostimulants.[83] Recently, a study compared Der p 23, and PreS-2XP4P5 (fusion proteins of nonallergenic peptides from the C-terminal IgE epitope-containing part of Der p 23 and hepatitis B virus-derived PreS domain) and finds that the latter induced lower T cell proliferation but higher levels of the tolerogenic cytokine IL-10 and the Th1 cytokine IFN-γ in PBMCs from HDM-allergic patients, which indicated an immunomodulatory capacity of the fusion protein.[84] In addition to the above-mentioned approaches, what is expected to take the field to the next step is molecular allergology, this means the component of treatment will be defined in greater precision in terms of quality and quantity.[85] Research is being conducted to individualize AIT, using recombinant antigen technology, to produce allergen extract against specific proteins to which the patient is allergic, rather than the whole allergen. The recent studies on grass pollen are promising. Two published studies have found that extracts containing recombinant allergens were effective in reducing the symptoms of AR.[86-88]

Conclusion

AIT is still the only potential disease-modifying treatment of HDM allergic subjects. Both SCIT and SLIT with HDM vaccine show safety and efficacy in reducing symptom and medication use, and in improving quality of life for treatment of AR and AS. AIT also has long-term remission effect after cessation of treatment and prevents new sensitization.

However, the quality of evidence for individual AIT products is very heterogeneous, and extensions of overall conclusions ("class effects") and the efficacy to all AIT products are unjustified. In contrast, each product needs to be evaluated individually, based on available study results, to justify efficacy per allergen and targeted patient group.[89]

High-quality evidence and further well-designed studies are still needed. Effectiveness of HDM-AIT on monosensitized compared with multisensitized individuals needs to be assessed. A better understanding of mechanisms of HDM-SCIT and HDM-SLIT might facilitate the development of biomarkers to monitor response of treatment.

Disclosure of potential conflicts of interest

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