



Allergen vaccine for moderate and severe allergic asthmatics

Guoping Li[†] and Bin Liao

Evaluation of : Blumberga G, Groes L, Haugaard L, Dahl R. Steroid-sparing effect of subcutaneous SQ-standardised specific immunotherapy in moderate and severe house dust mite allergic asthmatics. *Allergy* 61(7), 843–848 (2006).

The prevalence of allergic disorders, such as asthma, has increased worldwide. Indoor allergen exposures were positively associated with persistent respiratory symptoms. Allergen vaccine is recommended as a therapeutic vaccine for allergic diseases. Asthmatics need inhaled corticosteroids to reduce symptoms, but this increases the risk of side effects. The paper under evaluation offers a steroid-sparing effect of subcutaneous standardized quality-standardized specific immunotherapy in house dust mite allergic asthmatics. This study was finished in allergic asthmatics with a double-blind, placebo-controlled study.

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Allergic asthma is considered currently as a chronic airway inflammatory disorder associated with the presence of activated CD4⁺ T helper (Th)2-type lymphocytes, eosinophils and mast cells. Inhaled corticosteroids (ICSs) are regarded as an important anti-inflammatory treatment for asthma and are recommended for persistent asthma. Despite the guidelines and extensive clinical experience of the safe use of ICSs, there are concerns regarding their side effects. Local side effects may lead to the discontinuation of therapy. In particular, higher doses can lead to systemic side effects, such as growth retardation, in children, and osteoporosis [1]. Several studies suggest that ICS do not alter the natural history of the disease and that the risk of wheezing will persist beyond the first years of life. High exposure to allergen can lead to asthma exacerbations and prolong the need for ICSs [2].

The paper under evaluation discusses the steroid-sparing effect of subcutaneous standardized quality (SQ)-standardized specific immunotherapy in house dust mite (HDM) allergic asthmatics. The use of ICS was reduced significantly without loss of asthma control in patients with moderate persistent

asthma receiving specific immunotherapy (SIT) [3]. SIT could induce immune deviation towards a regulatory T cell response and lead to a down-regulation in the cytokine production of Th2 cells. Regulatory T cells secrete interleukin (IL)-10 and transforming growth factor (TGF)- β , which induce immunoglobulin (Ig)G₄ and IgA production in B cells and suppress IgE production [4]. SIT is the only treatment that is able to modify the natural history of the allergic subjects. Allergen immunotherapy involves the administration of repeated doses of allergen to the patient with the goal of altering the immune system's responses and reducing symptoms triggered by subsequent exposures [5].

Methods & results

Study design & allergen immunotherapy

A group of 18–60 year-old HDM allergic patients with asthma were recruited for the randomized, double-blind, placebo-controlled study. These patients require long-term treatment with ICSs (500–2000 μ g/day, fluticasone propionate) to relieve their symptoms. Patients were randomized to subcutaneous SIT with allergen vaccine or placebo. Patients received 3-year allergen immunotherapy.

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Affiliations

[†]Author for correspondence
Department of Respiratory Disease,
Affiliated Hospital of Luzhou
Medical College, 646000, China
Tel.: +86 830 316 5324
Fax: +86 830 316 5324
lzlqp@163.com

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Allergen immunotherapy was divided into an up-dosing and maintenance phase. The up-dosing was performed during an 8-week period. In the maintenance phase, patients received the individual maximum tolerated allergen dose.

Patients were excluded if:

- They were polysensitized
- They had received previous HDM immunotherapy
- They were using inhaled long-acting β 2-agonists or β -blockers during the study

Asthma severity & treatment with ICS

Moderate asthmatics inhaled fluticasone propionate 500–1000 μ g/day at baseline, whereas severe asthmatics inhaled fluticasone propionate to more than 1000 μ g/day at baseline. During allergen immunotherapy, ICSs are adjusted in a stepwise fashion to define the lowest dose that could maintain asthma control (FIGURE 1).

Assessments

The patients were assessed on their day- and night-time asthma symptoms, patient subjective evaluation of the disease, morning and evening peak expiratory flow (PEF) and their use of emergency medication for the condition (TABLE 1). All adverse events were recorded. Systemic reactions were scored according to the European Academy of Allergy and Clinical Immunology (EAACI) guidelines. Local reactions were defined as those measuring more than 8 $\times$ 8 cm in diameter.

Results

Reduction in inhaled steroids

The study demonstrated that SIT was able to reduce the use of ICS in HDM allergic asthmatics. The difference was statistically significant at year 2, with a median reduction of 50% in the active group and 25% in the placebo group. The greatest effect of SIT was found in the moderate asthmatic subgroup,

Table 1. Abbreviated text used to make assessments during treatment.

Abbreviated text	Scale
Day time asthma symptoms	0–5 (from no symptoms to severe symptoms)
Night-time asthma symptoms	0–5 (from no symptoms to severe symptoms)
Patients' subjective evaluation	0–100 (from no symptoms to severe symptoms)
Morning and evening peak expiratory flow	Peak flow meter

where the treatment difference at 3 years reached statistical significance. This apparently reduced the efficacy in severe asthmatic patients (FIGURE 2).

Dosage of specific immunotherapy

In the maintenance phase, 55% of patients (11 out of 22) received the maximum tolerated dose, up to a maximum dose of 100,000 standardized quality units (SQ-U). A total of 45% of patients (nine out of 11) did not receive the maximum tolerated dose, up to a maximum dose of 100,000 SQ-U. A total of 20% (four out of 22) reached 80,000 SQ-U and the remaining 25% of patients (five out of 11) had a maintenance dose lower than 80,000 SQ-U. All patients in the placebo group reached the maximum dose.

Adverse events related to immunotherapy

Adverse events included systemic reactions and local reactions. There were no life-threatening reactions during the trial. The rate of systemic side effects was 4.7%. One patient in the SIT group was withdrawn as a result of an asthma attack induced by the allergen immunotherapy. A total of ten out of the 26 patients (38%) in the active group experienced at least one systemic side effect (ten patients had grade 2 reactions and one patient also had a grade 3 reaction). Most of the systemic side effects occurred during the up-dosing phase.

Discussion & significance

The present study demonstrates that SIT with SQ-standardized HDM extract is well tolerated in HDM allergic asthmatic patients dependent on moderate-to-high doses of ICS. The use of ICS was reduced significantly without loss of asthma control in patients with moderate, persistent asthma. An ICS sparing effect was evident in patients with moderate, persistent asthma. SIT with a SQ-standardized HDM extract is safe. The rate of systemic side effects was 4.7%.

Expert commentary & conclusion

Allergic diseases, such as asthma, are an increasing health problem. Allergic diseases are caused by environmental antigens, such as cockroaches and mite dust. Allergic patients are often associated with allergen-specific IgE production. ICS are used

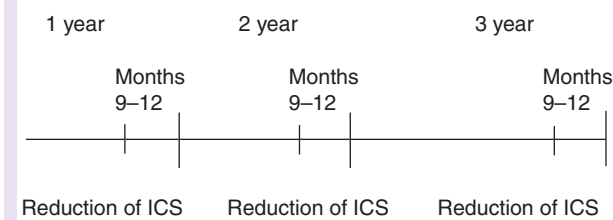


Figure 1. Flow chart of the trial. Patients received 3-year allergen immunotherapy. Stepwise reduction of the dose of ICS was repeated (September–December) after 1, 2 and 3 years of SIT. The daily dose of ICS was reduced in a stepwise fashion every 3 weeks until asthma was no longer controlled. Treatment was then continued with a dose one step higher. The dose steps of fluticasone propionate were 100, 250, 500, 750, 1000, 1500 and 2000 μ g daily.

ICS: Inhaled corticosteroids; SIT: Specific immunotherapy.

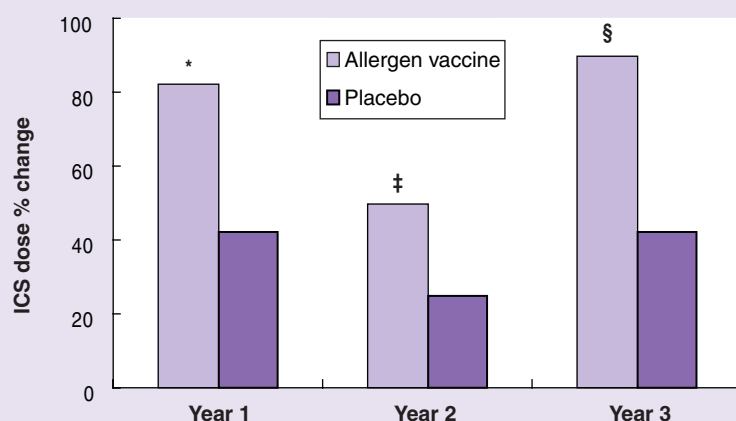


Figure 2. Median percentage reduction of inhaled steroids in patients with moderate, persistent, treated asthma.

* $p = 0.17$ compared with placebo groups.

‡ $p = 0.03$ compared with placebo groups.

§ $p = 0.04$ compared with placebo groups.

ICS: Inhaled corticosteroids.

most widely as anti-inflammatory drugs in mild-to-severe asthma but this has not been shown to have an impact on the basic pathological mechanisms. Meanwhile, higher dose corticosteroids provide little further benefits of asthma control and subsequently increase the risk of side effects. Many studies show that allergen immunotherapy could alter the natural course of allergic disorders. Allergen immunotherapy, known as desensitization or hyposensitization, is defined by the WHO as therapeutic vaccines for allergic diseases [6]. The paper confirmed the steroid-sparing effect of subcutaneous SQ-standardized specific immunotherapy in moderately allergic asthmatics. The use of ICS was reduced significantly in patients with moderate, persistent asthma.

Immunotherapy with protein allergens is effective in reducing symptoms in patients with allergic rhinitis and asthma. Unfortunately, its safety is still being questioned owing to possible severe systemic reactions [7]. The dose of allergen that can be administered to allergic asthmatic patients is frequently limited because of reduced forced expiratory volume in 1 s (FEV₁) and safety concerns. In the paper, 45% could not receive a maximum tolerated dose up to a maximum dose of 100,000 SQ-U (FIGURE 3).

It was confirmed that there are several types of reactions, such as local and systemic reactions. Local reactions occur at the injection site, which can be divided into reactions that occur within 20–30 min and those that occur more than 30 min after an injection. Systemic reactions are those characterized by generalized signs and/or symptoms occurring at a distance from the injection site. Systemic reactions usually begin within a few minutes of the injection and more rarely after 30 min [8]. Systemic reactions include nonspecific reactions, mild systemic

reactions, nonlife-threatening systemic reactions and anaphylactic shock. Asthma patients have an increased risk of developing acute systemic side effects after SIT. The rate of systemic reactions in asthma ranges from 5 to 35% but the main causes of systemic reactions were not clear. In the present study, 38% of patients in the immunotherapy group experienced at least one systemic side effect (ten patients had mild systemic reactions and one patient also had a nonlife-threatening systemic reaction). Reyes Moreno reported that 126 allergic patients with asthma received allergen-specific immunotherapy [9]. Specific immunotherapy with allergens failed in 32 (23%) patients. The main causes of failure were as a result of abandoning treatment and high serum levels of IgE, as well as the existence of other conditions, such as obesity, gastroesophagl reflux and chronic rhinosinusitis [9]. In the paper, Blumberga and colleagues thought that the side effects could be reduced by carefully individualized dosing, that is, by evaluating the patients' reactions after each injection and paying meticulous attention to their health status before each injection. Rossi observed 220 patients suffering from rhinoconjunctivitis and/or asthma who were administered sublingual immunotherapy. The results showed that for sublingual immunotherapy, not only the dose of allergen but also the biochemical characteristic of the major allergen, may be important factors in determining possible systemic reactions [10]. Frew and colleagues performed a double-blind, randomized, placebo-controlled study of 410 subjects

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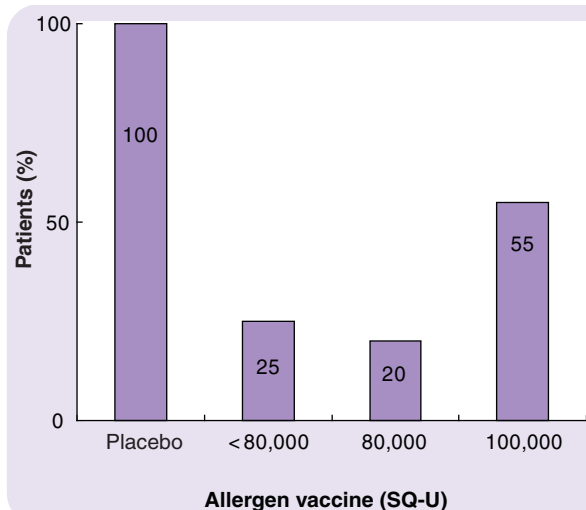


Figure 3. Percentage of patients receiving the individual maximum tolerated dose.

SQ-U: Standardized quality units.

(203 randomized to 100,000 SQ-U maintenance, 104 to 10,000 SQ-U and 103 to placebo). A total of 347 (85%) patients completed the treatment. The data showed that local and delayed side effects were common but generally mild, but no life-threatening reactions occurred [11].

Several of these modified allergen preparations are being developed, which aim to increase safety and improve efficacy of SIT. Recombinant production of allergens offers new perspectives for the increasing problems of immunotherapy. Recombinant-based approaches are focused mostly on genetic modification of allergens to produce hypoallergens, which reduce allergenic activity and conserved antigenicity. An alternative to genetic engineering is the chemical modification of allergens. So far, clinical trials have shown the efficacy and safety of immunotherapy with an Amb a 1-immunostimulatory sequence (ISS) DNA conjugate for ragweed pollen-allergic patients [12]. Colas reported that a depigmented and glutaraldehyde-polymerized therapeutic vaccine is safe and efficacious to patients who are clinically sensitive to this pollen. No moderate or severe systemic reactions were registered [13]. Korematsu developed a mutant protein of the major mite allergen *dermatophagoides farinae* (Derf)-2, C8/119S, which could reduce binding to IgE. The mutant exhibited a more efficient hyposensitizing effect than Derf-2 in the animal model of allergic bronchial asthma. These results indicated that the allergen mutant increased T cell-immunogenicity and induced exclusive Th1-cell differentiation in atopic patients. The results demonstrated that the

recombinant C8/119S protein can provide an effective allergen with the least risk of anaphylaxis for allergen immunotherapy against the HDM in humans [14].

In conclusion, Blumberga and colleagues confirmed the steroid-sparing effect of subcutaneous SQ-standardized specific immunotherapy in moderate allergic asthmatics. The use of ICS was reduced significantly in patients with moderate persistent asthma. SIT with SQ-standardized HDM extract is well tolerated in HDM allergic asthma patients dependent on moderate-to-high doses of ICS. Local and systemic reactions could be reduced by the carefully individualized dosing, that is, evaluation of patients' reactions after each injection and meticulous attention to health status before each injection, however, local and delayed side effects were common. It is important to improve the safety and efficacy of future allergen vaccines for specific immunotherapy.

Key issues

- Exposure to allergens can lead to asthma exacerbations, thus increasing the need for inhaled corticosteroid use.
- Specific immunotherapy is effective in reducing symptoms in patients with allergic rhinitis and asthma.
- The steroid-sparing effect of allergen-specific immunotherapy has been demonstrated in moderate allergic asthmatics.

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Affiliations

- Guoping Li
Department of Respiratory Disease,
Affiliated Hospital of Luzhou Medical College,
646000, China
Tel.: +86 830 316 5324
Fax: +86 830 316 5324
lzlqg@163.com
- Bin Liao
Inflammation & Allergic Diseases Research Unit,
Affiliated Hospital of Luzhou Medical College,
646000, China
Tel.: +86 830 316 5001
Fax: +86 830 239 2753
liaobindr@tom.com