A Study of Immunological and Clinical Effects of allergen immunotherapy on patients with allergic rhinitis in Babylon Province.

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الخلاصة

استهدفت هذه الدراسة تقييم تأثيرات اللقاح المناعي على مرضى حساسية الأنف في محافظة بابل تقييم تأثيرات اللقاح في بداية الدراسة ومرور ثلاثة أشهر، وكذلك بعد مرور ستة أشهر على 45 مريضاً حساسية الأنف يمتلكون استجابة موجبة في الاختبار الجلدي لحشرة العث (house dust mite) وحبوب الطلع (pollen) وتمت مقارنة تأثيرات على 30 من الذين اخذوا كمجموعة سيطرة (control group) لم يستلموا اللقاح المناعي لكن بقوا على الأدوية المضادة لحساسية الأنف.

وتم تقييم التأثيرات التي يسببها اللقاح المناعي وذلك بواسطة تسجيل الأعراض السريرية للمرضى وادراج الأدوية المستعملة، قياس الكلوبيولينات المناعية IgE and IgG، وكذلك تسجيل التاثيرات الجانبية للقاح المناعي.

بينت الدراسة الحساسية لحشرة العث (house dust mite) وحبوب الطلع والحساسية المزدوجة (رة العث وحبوب الطلع) فقد بلغت 67%، 13%، و20% من الحالات على التوالي.

من ناحية أخرى بينت الدراسة انخفاض مستوى الكلوبيولين المناعي (IgE) وكذلك زيادة مستوى الكلوبيولين المناعي (IgG) بشكل معنوي في مجموعة اللقاح المناعي مقارنة بمجموعة السيطرة.

كما بينت الدراسة وجود انخفاض في الأعراض السريرية للمرضى في مجموعة اللقاح المناعي مع وجود في مجموعة السيطرة وانخفاض كبير في استعمال الأدوية في المجموعة الأولى أكثر منه في المجموعة الثانية.

Abstract

This study aimed to assess the effects of allergen immunotherapy (AI) on patients with allergic rhinitis (AR) in Babylon Province. Allergen immunotherapy involved exposing a patient to gradually increasing doses of specific allergens with the intention of decreasing allergic and inflammatory response, ultimately leading to a sustained decrease in allergic symptoms. A build-up phase (once weekly injections for three months) was followed by a maintenance phase (once monthly injections) that generally continued for 3-5 years.

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The effects of allergen immunotherapy were assessed at 0 time, 3 months, and 6 months on 45 the patients with positive skin test to house dust mite and pollen as immunotherapy group (IT group) and the effects were compared to 30 patients as control group who remained on pharmacotherapy.

The changes caused by AI were assessed by symptoms and medications (drugs) use scores, measurement of total immunoglobulin E (IgE) and immunoglobulin G (IgG), and side effects score .

The study showed that the percentage of sensitivity to house dust mite, pollen, and mixed sensitivity (house dust mite and pollen) were 67% , 20%, and 13% from cases respectively.

The mean levels of total IgE was significantly decreased in the IT group as compared to the control group. Also, there was a significant increase in the mean levels of total IgG between the IT and control group ($p \leq 0.05$).In addition, the study revealed marked but nonsignificant reduction in symptoms and medications use score in the IT group with the progression of treatment while less reduction in the control group. The study also demonstrated that the IT is a safe procedure and the complications in this study was not significant. The mean score of side-effects was 0.3.

Introduction

Allergic rhinitis (AR) is the most common of the allergic diseases and is the most common cause of rhinitis. It affects approximately 20% of the population. Although it is not a life-threatening condition, complications can occur and the condition can significantly impair quality of life. It occurs in persons of all races. In childhood, allergic rhinitis is more common in boys than in girls, but in adulthood, the prevalence is approximately equal between men and women. Onset of allergic rhinitis is common in childhood, adolescence, and early adult years, with a range of onset between 8-11 years, but allergic rhinitis may occur in persons of any age (1).

The types of allergic rhinitis may differ depending on whether the symptoms are seasonal or perennial. Perennial allergic rhinitis is typically caused by allergens within the home but can also be caused by outdoor allergens that are present year-round.Seasonal allergic rhinitis, also known as hay fever, is an allergic response to pollen (the male component of the plant reproductive system) or other microscopic substances that are present only at certain times of the year (2).

Typical symptoms include sneezing, itching, tearing, and watery rhinorrhea. Significant complaints of congestion, particularly if unilateral, might suggest the possibility of structural obstruction, such as a polyp, foreign body, or deviated septum. Irritant triggers such as smoke, pollution, and strong smells can aggravate symptoms in a patient with allergic rhinitis (3).

AR can usually be diagnosed depending on compatible clinical history and physical examination, in addition to the skin test and measurement of total IgE in the blood (4).

Treatment of AR includes avoidance of trigger factors, use of medications and allergen immunotherapy. These measures can prevent or reduce the frequency and severity of symptoms. The common types of medications include: Antihistamines that are used for treating allergic symptoms, corticosteroids like nasal corticosteroid sprays are the most effective medications for allergic rhinitis, decongestants that help in reducing symptoms such as nasal congestion, saline nasal washes used alone or with medications may also be helpful .Surgery play a part in the treatment, it includes correction of any anatomical abnormality like nasal septal defect and enlarged turbinate (5).

Allergen immunotherapy is an optimal therapy for many patients and it can reduce the symptoms and the use of drugs. Allergen immunotherapy (AI) is also known as hyposensitization or allergy shots. It involves repeated administration of gradually increasing quantities of specific allergens to patients with IgE-mediated conditions until a dose is reached that is effective in reducing disease severity from natural exposure. It is effective in the treatment of allergic rhinitis, allergic conjunctivitis, stinging-insects (wasp and bee) hypersensitivity, and allergic asthma (6).

The clinical indications of AI include: Diagnosis of patients with history of allergy, inability to avoid allergens, inadequacy of drug treatment, side effects of drugs, and desire to avoid long-term medication use. The absolute contraindications include: concurrent significant illness, fever, or fatigue while the relative contraindications include: pregnancy (maintenance injections can be continued during pregnancy), small children (less than five years old), and elderly patients. It is usually a safe procedure without complications but immediate severe side effects in form of anaphylaxis can happen so fully equipped facilities with well trained medical staff should be available (3) .

The study aims to: 1. Evaluate IgE and IgG levels before initiation of allergen immunotherapy and after three and six

months, 2. Evaluation of symptoms and medication use scores before and after the use of immunotherapy, 3.Establishment for the efficacy and 4.The side-effects of allergen immunotherapy use.

Patients and Methods

A. Patients:

This study was conducted in Allergy and Asthma Centre (AAC) in Babylon Province in the period from October 2007 to May 2008,it included 75 patients with allergic rhinitis who were divided into two groups: the first group consisted of patients receiving AI (45 patients) (as IT group) while the second group consisted of patients receiving pharmacotherapy (30 patients) (as control group). The study was carried out on chronic patients with a history of AR for at least three years. The ages ranged from 20-60 years. Those patients were attended to the AAC and were diagnosed by specialized physicians depending on history and clinical criteria. Patients who were smokers, pregnants, and patients with history or current parasitic infections depending on general stool examinations were excluded. The control group included patients with AR not taking allergen immunotherapy (AI) but received pharmacotherapy.

B. Methods :

Blood samples:

About 5 ml of venous blood were obtained from antecubital vein and were put in plain tubes. The blood was allowed to clot, then the serum was separated by centrifugation for 15 minutes at 3000 round per minutes (RPM) and was put in another disposable sterile plain tubes and stored in deep freeze for immunological tests (7).

Allergen immunotherapy (allergen vaccine):

Method of dilution:

The stock concentration was different for mite and pollen. The stock concentration of mite extract was (1/1000), while for pollen extract was (1/100) (Allergy vaccine lab., Iraq). Each stock vial contains informations including: type of allergen, concentration, volume, storage temperature (2-8 C^{o}),expiration date, company, and state of origin). Each stock of allergen was diluted in multi-vials of phenolated saline according to type of allergen. Series of dilutions for mite and pollen stocks was (1/10,000 ,1/100,000 ,and 1/1000,000) (1/1000, 1/10,000, 1/100,000, and 1/1000,000) respectively (8) .

Allergy intradermal skin test :

Procedure:

In this test, intradermal injections were done on one of the forearms of each patient. Two sites of injection were recognized by two circles one above the other and marked by pen with two letters to coincide the identity of allergen to be tested. These letters were (M) for mite and (P) for pollen. The sites of injections were cleaned with 70% alcohol, and intradermal injections were performed with syringes (G 29x1/2).The doses of allergy intradermal skin test were taken from the vial with 1/100,000 dilution and only 10 units (0.1ml) were withdrawn by the syringe from each type of allergens (house dust mite (HDM) and pollen), after completion of injections, patients must stay in the AAC for about 15-20 minutes to see the reactions in order to read the results of the test, to monitor for the local reactions, and to manage systemic reactions that may happen occasionally. Obtained results at sites of injection were cleaned with alcohol, also cortisone cream can be applied to relieve itching and local reactions (9).

The diameter of the local reactions was measured by a special ruler called phostal-staloral. This ruler consists of circles for measurement of wheal or erythema, each circle represents (5)mm. The skin test in this study was interpreted as recommended by the Rolland *etal.*,(2008) as the following: wheal greater than 5mm or erythema greater than 10mm is considered a positive reaction (10).

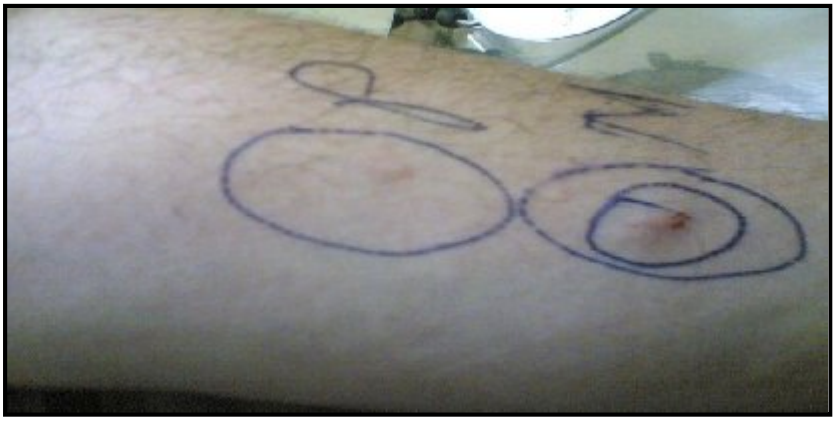

Figure (1): Results of allergy skin test.M (mite, positive :erythema and wheal larger than 10mm) and P (pollen, negative: no wheal or erythema).

Subcutaneous immunotherapy:

The patients included in this study with positive skin tests results were told to come every week to the AAC for a period of three months to complete the build-up phase, then come every month for 3-5 years to complete the maintenance phase. The injections were carried out subcutaneously on the outer aspect of the upper arm midway between the shoulder and elbow. The injections were performed according to (11).

Doses of injections :

The doses of injections were different according to the phase as follow:

A. Build –up phase:

This phase started by the lowest dose which was increased gradually every week. For each diluted vial, four doses were given to each patient, one dose was given weekly, starting from the vial with greatest dilution (1/1000,000).The doses given were calculated by units (U) by syringes which were graduated up to 100 U that equal to one ml. Project of injections started by 10 U, 20U,then 40 U, and lastly 60 U (12).

B. Maintenance phase:

In this phase, patients were given the same dose monthly. This dose represented the largest effective dose that can be tolerated and it was different according to the patient response (6).

Assessment of patients :

Patients were assessed at the end of the study by symptoms and drugs use scores, measurement of total serum IgE and IgG, and side effects score. The symptoms and drugs use were assessed according to Creticos score (13).The symptoms score was assessed as the following: individual symptoms of AR in the nose include: sneezing, blockage, and rhinorrhea were recorded on a scale of 0 to 3 with a score of 0 indicating no symptoms and 1, 2, and 3 indicating mild, moderate, and severe symptoms respectively. The drug score was calculated as follow: patients not taking drugs were given a score of 0, each dose of nasal inhaler of beconase was given a score of 1,and each allermine or prednisolone tablets was given a score of 2.The total level of IgE was measured as recommended by Monobind company (USA),while the total level of IgG was measured according to LTA company (Italy) recommendations. Side effects were assessed according to Creticos score as shown in table (2).

Statistical analysis :

Statistical analysis was performed using the SPSS programme. Analysis of variance (ANOVA) was used to evaluate changes over time between groups. T test was also used in this study for comparison between both immunotherapy and control groups. P values of less than or equal to 0.05 were considered to indicate statistical significance (14).

Results and Discussion:

Table (1) showed the mean age± standard error of mean (SEM) of the patients´ groups. The ages of patients ranged from 20-60 years. There was no significant difference in ages between the studied groups (p >0.05).This ages range was selected because the wheal and flare are not clear beyond these ages, moreover the level of IgE is usually stable and constant at this age group (15).

Table(1) Age of patients and control groups

Group	Number	Age (years) mean±SEM	P value
Immunotherapy group (IT)	45	37.35±1.9	
Control group	30	33.6±2.9	p>0.05

The patients were sensitive to HDM more than pollen. Some patients were sensitive to both HDM and pollen. The percentage of patients who were sensitive to HDM alone was 67%, to both HDM and pollen was 20%, and to pollen alone was 13%.

The mean levels of total IgE were significantly decreased after immunotherapy in immunotherapy group in comparison to control group (P≤0.05). In addition, the mean levels were significantly decreased within the same immunotherapy group at the three times of follow-up as shown in figure (2), while the mean levels of total immunoglobulin G (IgG) were significantly increased (p≤0.05), they were also significantly increased within the same immunotherapy group at the three times of follow-up (figure 3). The observed increase in IgG had led to the concept that this immunoglobulin act as a blocking antibody. Circulating IgG may block access of the allergen to mast cells, or it may bind to the mast cells and through recruitment of inhibitory IgE receptors inhibit the mast cell response (3;11).

Tahamilar and his colleagues (2009) pointed that allergen immunotherapy was associated with a marked increase in blocking IgG antibodies and decrease in allergen specific IgE concentrations that occurs due to immune deviation from T_{H2} response with dominant production of IL-4 and IL-5 toward T_{H1} response with production of interferon gamma (IN-γ) and IL-2 and this deviation occurs because of induction of a subset of T-regulatory cells with allergen specific increase in the production of IL-10 and transforming growth factor beta (TGF-β) (8).

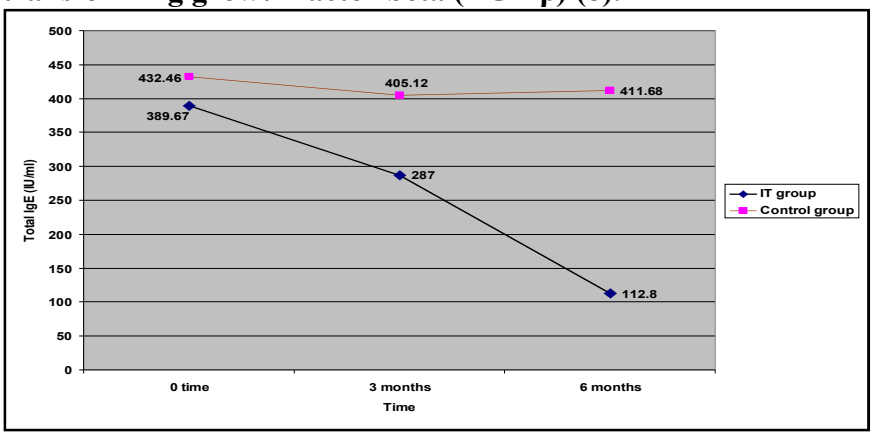

Figure (2) : The mean levels of total immunoglobulin E in immunotherapy and control groups at three times(0 time, after 3 months, and after 6 months) (the mean difference was significant at 0.05 level).

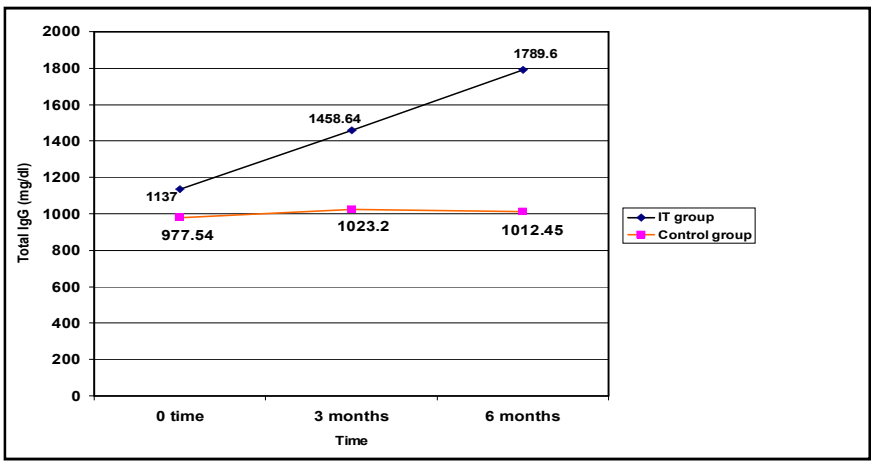

Figure (3) : The mean levels of total immunoglobulin G in immunotherapy (IT) and control groups at three times(0 time, after 3 months, and after 6 months) (the mean difference was significant at 0.05 level).

Figure (4) showed the mean symptoms score in the immunotherapy (IT) and control groups at 0 time, 3 months, and 6 months. Both groups showed a continuous reduction in symptoms scores over the period of the study. The results of scores of medications use according to the time were apparent in figure (5) which showed the mean medications use in the IT and control groups at 0 time,3 months, and 6 months. Both groups showed a continuous reduction in medications use over the period of the study. The study showed reduction in symptoms scores in patients taking immunotherapy more than patients taking pharmacotherapy, also more reduction in medication scores in the immunotherapy group than the control group and this means more reduction in use of drugs in the immunotherapy group but the difference was nonsignificant between the immunotherapy and control groups in both symptoms and medication use score. This might be due to the short period of the study although many studies also lasted for six months and some with significant results while others with nonsignificant results.

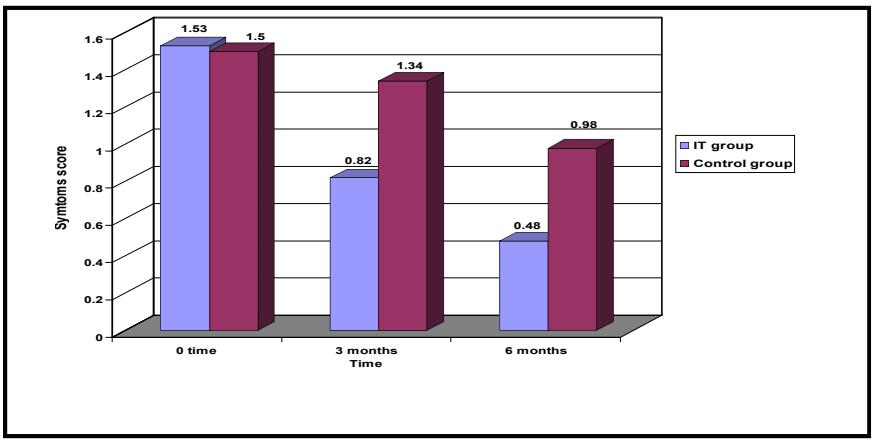

Figure (4): Allergic rhinitis symptoms score in immunotherapy (IT) and control group at 0 time, after 3 months, and after 6 months ($p>0.05$).

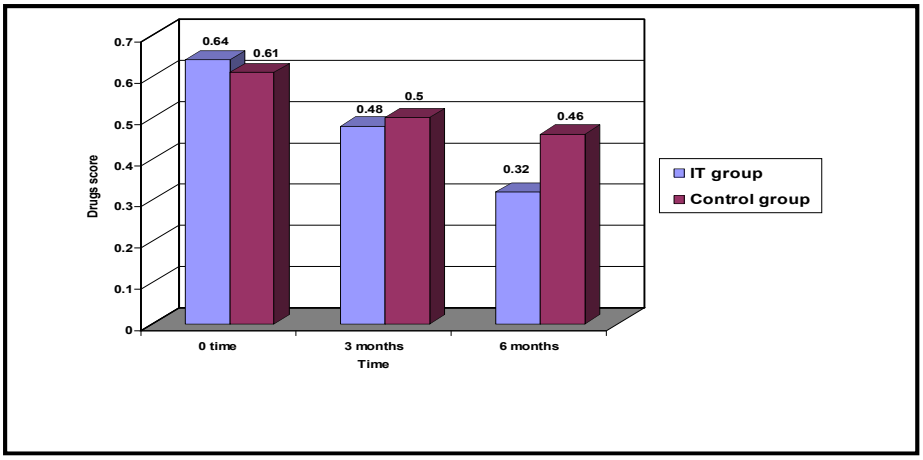

Figure (5): Allergic rhinitis drugs score in immunotherapy (IT) and control group at 0 time, after 3 months, and after 6 months (p>0.05).

Side-effects were recorded according to Creticos score (13), of the 45 asthmatic patients who underwent AI, only 2(5%) patients had generalized urticaria, 3 (9%) patients had local reactions larger than 3 cm and these reactions were treated with antihistamines, all the remaining 40 (86%) patients had local reactions less than 3cm and resolved spontaneously as shown in table (2). The table also showed that no severe side-effects were reported. The mean score of side-effects was 0.3±0.2. Immunotherapy was tolerated by most patients and the incidence of side-effects was low. No severe systemic side-effects were reported, only two patients had generalized urticaria and were treated well with anti-histamines. The reactions occurred within 20-30 minutes following injections. This was similar to many studies like Zeldin *etal.*,(2008) who found that only 8% of patients developed immediate mild to moderate systemic reactions, and all reactions were successfully treated in the clinic (16).

Table (2) Side-effects reaction score of allergen immunotherapy in immunotherapy group.

Reaction	score	No. of patients	Final score	Mean score
Local				
Enduration and/or erythema < 3 cm	0	40	0	0.3
Enduration and /or erythema >3 cm	1	3	3	
Systemic				
Generalized urticaria	2	2	4	
Generalizd pruritus and sneezing, nasal congestion	3	0	0	
Wheezing, tachypnea, and decrease of peak expiratory flow rate	4	0	0	
Anaphylaxis, hypotention, severe wheezing, and laryngeal edema	5	0	0	
Cardiopulmonary arrest	6	0	0	
Total	21	45	7	

Conclusions

We conclude that allergen immunotherapy is a safe procedure and should be strongly considered for patients with poor disease control or adverse reactions to medications, in addition there is association between HDM and pollen and can occur in the same patient frequently.

Recommendations

From the results expressed above we recommend that allergen immunotherapy should be used on a routine basis in patients sensitive to house dust mite and pollen, and it should be administered only in hospitals or in specialized centers to counteract adverse reactions.

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