# THE IMMUNOLOGICAL ASPECT OF THE NASAL MUCOSA AND ITS RESPONSE TO IMMUNOTHERAPY IN PATIENTS WITH ALLERGIC RHINITIS

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## ABSTRACT

*Background:* Allergic rhinitis (AR) is regulated by the local production and release of several cytokines. Allergen specific immunotherapy (IT) has been widely used for many years as a specific treatment of allergic diseases. *Objective:* This study aimed to investigate the changes in clinical and immunologic markers before and after IT and to evaluate which immunological parameters correlate with clinical improvement after Phoenix dactylifera IT in AR patients. *Methods:* Total symptom score and levels of Total IgE, IFN-γ, TNF and IL-10 were measured in the serum and nasal samples of thirty non-atopic healthy controls and thirty patients with allergic rhinitis before and after 15 months of IT. *Results:* We found significantly higher concentrations of serum TNF and nasal TNF with significantly lower concentration of nasal IL-10 in allergic patients than in non-allergic. Mean symptom score, skin test reactivity and nasal TNF were significantly decreased in the patients after IT. Moreover, serum and nasal IL-10 increased significantly after IT. However, there was neither a significant reduction in Total IgE nor a significant increase in IFN-γ at the end of IT. *Conclusions:* Our data show a clinical improvement associated with a decline in inflammation parameters after IT, supporting the hypothesis that treatment with a major allergen is able to change the course of AR. Moreover, date palm IT significantly induced an increase in serum and nasal IL-10 levels.

## INTRODUCTION

Allergic rhinitis (AR) is a chronic inflammatory disorder of the upper airways that produces characteristic signs and symptoms in sensitized individuals exposed to relevant allergens [1] Despite advances in immunology, allergic rhinitis remains a significant health issue affecting approximately 30% of adults and 40% of children [2]. Furthermore, AR is a symptomatic disorder of the nose induced after exposure to allergens via IgE-mediated hypersensitivity reactions, which are characterized by 4 cardinal symptoms of watery rhinorrhea, nasal obstruction, nasal itching and sneezing [3]. It is associated with a shift in the balance between Th1 and Th2 towards a Th2 predominance [4].The diagnosis is based on clinical manifestations, a positive skin prick test (SPT), elevated serum IgE levels and/or serum specific IgE antibodies to allergens [5]. Recommended treatments depend on severity of the disease [1]. Treatments include allergen avoidance, antihistamines, intranasal steroids, antileukotriene receptor antagonists, mast cell stabilizers, and decongestants. However, immunotherapy has been used with success and is the only treatment that may alter disease activity.

Specific allergen immunotherapy (IT) is an effective prophylactic treatment for atopic IgE-mediated disease, in particular for severe seasonal allergic rhinitis. A variety of immunological changes have been reported following IT [6]. These include an increase of the allergen-specific IgG antibody [7], a reduction in the allergen-specific IgE antibody subsequent to transient increase [8], and a decrease in quantity and activity of basophils and mast cells [9]. Enhanced IFN-γ responses to allergen have been observed after grass pollen IT. Moreover, parallel decreased of skin and nasal late-phase responses to allergen challenge suggest that IT may induce in mucosal T cells a preferential deviation of Th2 in favor of Th1 responses [10].

Grass pollen is a major cause of allergy throughout the world. A number of controlled trials demonstrated the efficacy

of IT in grass pollen allergic subjects, most using extracts of multiple grasses but some using extracts of a single grass. The optimal grass extract for IT has not yet been established [11]. Date palm (*Phoenix dactylifera*) is commonly planted in the Middle East and the neighboring countries (Mediterranean, central Africa, western Asia, Australia, and North America) for fruit. Their grains are potent allergen [12, 13]. The common offending allergens causing allergic rhinitis in Egypt are house dust mites and tree pollen. A retrospective study of 1000 patients undergoing SPT performed at the Allergy and Immunology Unit of the Zagazig University, Egypt between January 2009 and February 2010 revealed that the local population is more sensitized to outdoor rather than indoor allergens especially *Phoenix dactylifera* allergen (unpublished data).

The clinical efficacy of immunotherapy has been demonstrated in patients with pollinosis but little is known about the effect of *Phoenix dactylifera* IT in patients with allergic rhinitis. For these reasons, we aimed at studying and characterize the nasal inflammation in date palm allergic rhinitis patients and investigating the clinical and immunologic changes after 15 months of *Phoenix dactylifera* immunotherapy.

## SUBJECTS & METHODS

### *Subjects:*

This study was carried out at the Departments of Otorhinolaryngology and Microbiology (Immunology unite) of the Faculty of Medicine, Zagazig, Egypt between August 2009 and December 2010. The study started in the pollen season and finished at the end of the second consecutive pollen season. 30 nonatopic healthy volunteers (ages: 18-42 years old, 14 females and 16 males) and 30 patients (ages: 18-36 years old, 17 females and 13 males) with allergic rhinitis to date palm pollen, were studied. The study was approved by the ethical committee of the hospital and written informed consent was obtained from each individual. A detailed clinical history and a complete physical examination were carried out for each patient. Each subject in the nonatopic group was chosen on the basis of the following criteria: no history of allergic disease or nasal diseases, no pregnancy or lactation, and negative skin prick test. Each subject in the allergic group was chosen randomly from allergic rhinitis patients attending to the allergy outpatient clinic on the basis of the following criteria: history of persistent rhinitis for at least 2 years, positive skin prick test to *Phoenix dactylifera* pollen only (>5-mm wheal) and no evidence of treatment with IT during the previous 10 years.

### *Symptom score:*

The allergic patients recorded the nasal symptoms of obstruction, rhinorhea, sneezing, and itching one week before IT and at the end of IT course (15 months later). The following scale was used to score each symptom: 0 = no symptom, 1 = mild (symptom was present but was of short duration and not annoying or troublesome, 2 = moderate (symptom was frequently troublesome but did not interfere with either normal daily activity or sleep), or 3 = severe (symptom was troublesome and interfered with normal daily activity or sleep). The total nasal symptom score (TNSS) was the sum of the scores for the individual symptoms. TNSS values (0-12) were categorized as mild (0-4), moderate (5-8), or severe (9-12) [14].

### *SPT:*

SPTs were performed at the volar site of each forearm by the same experienced personnel by application of 1 drop of each allergen extract of a panel containing house dust mite, *Aspergillus* species mix, cottonwood mix, ash mix, Tobacco leaf, ryegrass, and *Phoenix dactylifera* pollen (AL, Allergy Laboratories, inc., USA) to the skin, at least 3 cm apart, according to a previously validated protocol [15]. Histamine was used as positive control and diluents of each allergen as a negative control (AL, Allergy Laboratories, inc.,

USA). The sensitivity of the skin test was estimated by the size of the wheal. The largest diameter of the wheal was evaluated as the size of the wheal after 20 minutes. A wheal diameter 3 mm or greater, accompanied by erythema, was defined as a positive reaction.

***Nasal samples:***

Nasal samples were collected from nasal cavities of all subjects. Briefly, after nasal scrapping, the sample was immersed in phosphate- buffered saline (PBS) and transferred to an eppendorf tube and stored at – 20 $^0$C.

***Mode of IT:***

The treatment followed the manufacturers' instructions. The patients were given subcutaneous injections of standardized *Phoenix dactylifera* pollen extracts (AL, Allergy Laboratories, inc., USA). Injections were administrated twice weekly up to a maintenance dose thereafter injections were administrated twice monthly. The injection period of our study lasted 15 months. The maximum tolerated dose 1:1000 of 5% *Phoenix dactylifera* pollen extracts preparation was attained in 9 months. After each injection, the patient was asked to remain under our supervision for a minimum of 30 min and to report any symptoms they may have experienced. Only oral antihistamines and mid-potency topical steroids were used concomitantly with the IT during the pollen season. However, medication was withdrawn at least 4 weeks before drawing blood and nasal samples.

***Determination of total IgE, IFN-γ, TNF and IL-10:***

Blood samples taken from the patients and healthy controls were kept at room temperature for 30 minutes till they coagulate. Then they were centrifuged at 2000 rpm for 10 minutes and serums were obtained. These serums were preserved at – 70 $^0$C and dissolved just before the analysis. Total IgE, IFN-γ, TNF and IL-10 were measured in serum and nasal samples. Total IgE levels were measured by ELISA method according to the kit manufacturer's instructions (Ridascreen, A0141, R-Biopharm AG, Germany). IFN-$\gamma$ and TNF were measured by ELISA method according to the kit manufacturer's instructions (Biosource Europe SA, KAC1231, Nivelles, Belgium and RayBiotech, ELH-TNFalpha-001, USA, respectively). The minimal detection levels of cytokines were 0.03 IU/ml for IFN-$\gamma$ and 30 pg/ml for TNF. IL-10 was measured by ELISA method according to the kit manufacturer's instructions (AviBion Orgenium, IL10001, Vantaa Finland). The minimal detection level of IL-10 was 2 pg/ml.

***Statistical analysis***

For statistical analysis we used a paired *t* test. A P value less than 0.05 was considered statistically significant.

## RESULTS

Thirty allergic rhinitis patients to date palm pollen and 30 nonatopic healthy volunteers entered the study as a control. All patients were symptomatic with a mean TNSS of 5.5 ± 1.3 (0-12) at day 0. The most common symptom was rhinorrhea (70%). Following 15 months of the immunotherapy, there was a highly significant reduction in TNSS 1.7 ± 2 ($p <$ 0.001) (Fig. 1). Clinical improvement in symptoms was accompanied by a reduction in the size of immediate cutaneous response.

***Levels of Total IgE, IFN-γ, TNF and IL-10 in serum***

Results are shown in Table 1. At base line, the serum levels of total IgE in AR patients before IT were statistically highly significant than in the control group ($P < 0.001$). No significant differences were observed between total IgE in AR patients before and after IT. Serum levels of TNF were found significantly higher in untreated group than controls ($P < 0.05$). However, there was no significant reduction in TNF level at the end of the 15 months of IT. In the patient group, serum IL-10 level was 470 ± 259 pg/ml before IT and 695 ± 252

pg/ml after IT. According to these results; IL-10 level after IT was significantly higher than before IT ($P < 0.05$). No significant differences were observed in levels of serum IFN-γ in the three groups (Fig. 2).

***Levels of Total IgE, IFN-γ, TNF and IL-10 in nasal samples***

Nasal levels of total IgE, IFN-γ, TNF and IL-10 were measured in non-allergic controls and allergic rhinitis patients before and after 15 months of IT. The results are shown in Table 1. The nasal samples from allergic rhinitis patients before IT contained significantly higher concentrations of total IgE (37.5 ± 21 IU/ml; $p < 0.001$), TNF (64.5 ± 20 pg/ml; $p < 0.05$), IL-10 (6.5 ± 1.2 pg/ml; $p < 0.05$) compared to the nasal samples from control subjects (4.2 ± 4 IU/ml, 39.7 ± 18 pg/ml and 8.8 ± 2.7 pg/ml respectively, for total IgE, TNF and IL-10). Data in Table 1 show that IL-10 levels in allergic rhinitis patients before IT resulted to be significantly lower compared to after IT (6.5 ± 1.2 vs 7.6 ± 1.4 pg/ml; $p < 0.05$) while TNF levels in allergic rhinitis patients before IT resulted to be significantly higher compared to after IT (64.5 ± 20 vs 48.3 ± 10 pg/ml; $p < 0.05$). In addition, there were no significant differences in IFN-γ concentration between the allergic rhinitis patients before and after IT. However, a slight trend towards increased IFN-γ secretion was found in the allergic rhinitis patients after IT (0.98 ± 1.2 vs 1.4 ± 1.1 pg/ml; $p > 0.05$) (Fig. 3).

Table 1. Laboratory data (serum and nasal mucosa levels of total IgE, TNF, IL-10 and IFN-γ).

| | | Control group | AR patients before IT | AR patients after IT |
|---|---|---|---|---|
| ***Serum*** | | | | |
| Total IgE | IU/ml | 27.9 ± 28 | 233.6 ± 89 * | 230 ± 87 * |
| TNF | pg/ml | 91.3 ± 27 | 121.8 ± 46 * | 88 ± 50 |
| IL-10 | pg/ml | 515 ± 281 | 470 ± 259 ** | 695 ± 252 |
| IFN-γ | IU/ml | 7.6 ± 5.5 | 4.9 ± 1.6 | 5 ± 3 |
| ***Nasal specimen*** | | | | |
| Total IgE | IU/ml | 4.2 ± 4 | 37.5 ± 21* | 27.5 ± 19 * |
| TNF | pg/ml | 39.7 ± 18 | 64.5 ± 20 *, ** | 48.3 ± 10 |
| IL-10 | pg/ml | 8.8 ± 2.7 | 6.5 ± 1.2 *, ** | 7.6 ± 1.4 * |
| IFN-γ | IU/ml | 1.7 ± 1.4 | 0.98 ± 1.2 | 1.4 ± 1.1 |

*Data expressed as mean ± SD.*

* *Significant differences with control group.*

** *Significant differences with AR patients after IT.*

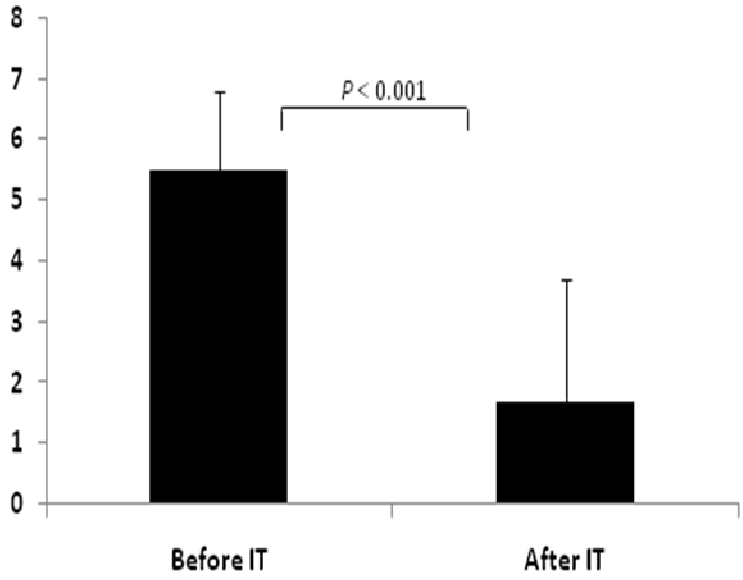


Figure 1. Reduction in symptom scores after 15 months of immunotherapy. Data expressed as mean ± SD.

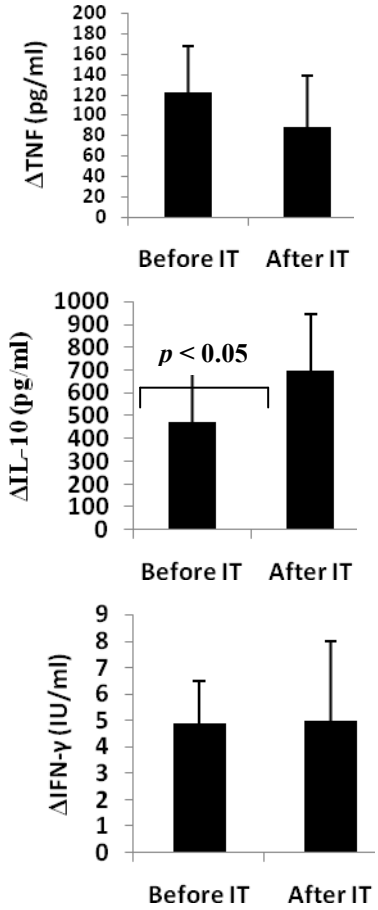


Figure 2. Levels of TNF, IL-10 and IFN-γ in serum of allergic rhinitis patients before and after IT. Data expressed as mean ± SD.

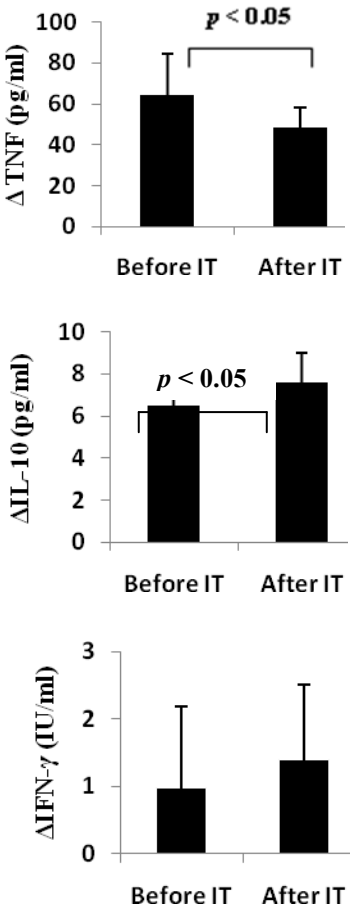


Figure 3. Levels of TNF, IL-10 and IFN-γ in nasal mucosa of allergic rhinitis patients before and after IT. Data expressed as mean ± SD.

## DISCUSSION

Atopy is characterized by a Th2 polarization, including IL-4, IL-5 and IL-13 that play important roles in causing allergic inflammation [16]. Not only the Th2, but also, the Th1 response is considered to differ between atopic and non atopic individuals. IFN-γ secreted by Th1 cells is generally considered to play a reciprocal role against the activities of Th2- type cytokines, because IFN-γ inhibits IgE synthesis by B lymphocytes and the development of Th2 clones [17]. Serum IgE level is often increased in allergic diseases. However, a normal serum IgE level does not mean that atopy does not exist. On the other hand, very high serum IgE level can be considered as one of the cardinal markers of allergy in patients without parasitic infection [18]. Studies of AR due to *Phoenix dactylifera* are few. The effect of *Phoenix dactylifera* IT on peripheral blood T cell responses remains controversial in Egypt.

The main aim of the study was to test the reproducibility of several inflammatory biomarkers and cytokines in serum and nasal samples of allergic rhinitis patients to *Phoenix dactylifera* that is commonly planted in the Middle East and the neighboring countries and to investigate whether the immunotherapy could affect spontaneous synthesis of these markers. We compared the levels of Total IgE, IFN-γ, TNF and IL-10 in the serum and nasal samples of allergic rhinitis patients versus a control group. Moreover, we reported the effects of a course of *Phoenix dactylifera* IT on expression of these markers within

the serum and nasal samples of allergic rhinitis patients.

Our data seem to be in agreement with the dichotomy of the Th2 cells predominance over Th1 cells in allergic diseases [19]. We found higher levels of total IgE in the serum and nasal samples of allergic rhinitis patients versus the control group. The level of IFN-γ in the serum and nasal samples is higher in the control subjects than in patients. However this result is not statistically significant.

It is remarkable that IL-10 concentrations in the serum and nasal samples of allergic rhinitis patients were significantly lower than the control subjects. This result is not consistent with other reports indicating an increase of IL-10 in atopic allergy and asthma [20, 21]. However, the roles of IL-10 in allergic inflammation and airway hyperresponsiveness are apparently contradictory. Nevertheless, its evident immunosuppressive properties in animal models and in vitro suggest that IL-10 could function as a therapeutic strategy for treating allergic inflammation and asthma [22]. In our study, TNF levels of the serum and nasal samples in allergic rhinitis patients were significantly higher than in the control group. A possible explanation of high TNF could be due to it is a principal mediator of the acute inflammatory response, including allergic rhinitis [24,25] and could be related to the lower levels of IL-10. A reduction of IL-10 with the increase of TNF could be attributed to the worsening of the allergy. Therefore, from all of these aspects we demonstrated differences in cytokine profile between allergic rhinitis and non allergic subjects to *Phoenix dactylifera* in the serum and nasal samples and we underlined the close association regarding the relationship between the immunological markers and allergic rhinitis to *Phoenix dactylifera* especially at nasal level.

Grass pollen IT was highly effective in reducing symptoms and medication requirements and there were no significant local or systemic side–effects, which confirm the usefulness of this form of therapy in patients who fail to respond to conventional pharmacotherapy [26]. Studies of AR due to *Phoenix dactylifera* are few. To our knowledge, this is one of the first studies for determination of immunological changes of subcutaneous *Phoenix dactylifera* IT in allergic rhinitis patients in Egypt. Following 15 months of *Phoenix dactylifera* IT, there was a highly significant reduction in TNSS and was accompanied by a reduction in the size of immediate cutaneous response after intradermal allergen challenge. We found in our study that serum levels of IL-10 were statistically significantly higher in allergic rhinitis patients after 15 months of IT than before IT. On the other hand, we could not determine a statistically significant difference between before and after IT in respect of serum levels of IgE, TNF and IFN-γ. At nasal level, there were a significant increase of IL-10 levels and a significant reduction of TNF levels, a proinflamatory cytokine that stimulates numerous cells growth and differentiation, especially T and B lymphocytes. This finding could be explained by higher level of inflammatory reaction in allergic patients than in the nonallergic. There was a trend towards IFN-γ, Th1-type cytokine, increase after IT. However, it is not statistically significant. A possible explanation of this result could be related to short time of IT with a small sample size (30 patients). Taken together, our results suggest that subcutaneous *Phoenix dactylifera* IT influences the nasal cytokine responses in favour of a shift in the Th2 more than the peripheral blood. In conclusion, this study provides evidence that serum and nasal levels of IL-10 can be a sensitive parameter that could correlate with clinical improvement and plays a role in follow up of the disease condition of

AR. Further studies on large groups of patients with longer treatment durations should be performed to better confirm these findings and their clinical relevance.

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## دراسة السمات المناعية للغشاء المخاطى للانف واستجابته للعلاج المناعى فى مرضى حساسية الانف

يعتبر العلاج المناعى احد طرق علاج حساسية الانف. تهدف الدراسة الى بحث التغييرات في العلامات السريرية والمناعيه قبل وبعد العلاج المناعى. اجريت الدراسة على ثلاثين مريضا يعانون من حساسية الانف وثلاثين شخصا سليم ليس لديهم تاريخ مرضى كعينة ضابضة . وتم قياس بعض العلامات المناعية فى الدم وعينات الانف لاشخاص العينات الضابضة وفى المرضى قبل وبعد خمسة عشر شهرا من العلاج المناعى مع تسجيل النتائج.

اثبتت النتائج ان هنلك زيادة ذات دلالة احصائية لعامل نخر الاورام (تى-ان-اف) فى الدم وعينات الانف ،كما ان هنلك نقص ذات دلالة احصائية لعامل الانترلوكين 10 فى مرضى حساسية الانف عن افراد العينة الضابضة. وانخفضت بشكل ملحوظ متوسط درجة اعراض المرض وعامل تى ان اف من الانف فى مرضى حساسية الانف بعد العلاج المناعى وعلاوة على نلك زاد تركيز الانترلوكين 10 فى الدم فى مرضى حساسية الانف. كما سجلت النتائج انه لم يكن هناك انخفاض ملحوظ فى تركيز الاجسام المضادة (IgE) او زيادة ملحوظة فى تركيز الانترفيرون واى فى نهاية العلاج المناعى.س

تدل النتائج السابقة على العلاج المناعى لمرضى حساسية الانف يؤدىلتحسن الاعراض السريرية ونقص ملحوظ فى مستويات عوامل الالتهابات المسببة اوالمصاحبة لحساسية الانف مما يدعم فرضية قدرة ونجاح العلاج المناعى فى علاج المرض.