Egyptian Journal of Chest Diseases and Tuberculosis xxx (2016) xxx–xxx

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Contents lists available at ScienceDirect

Egyptian Journal of Chest Diseases and Tuberculosis

journal homepage: www.sciencedirect.com

Clinical and immunological effect of subcutaneous immunotherapy in allergic asthma

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ARTICLE INFO

Article history:
Received 27 September 2016
Accepted 3 October 2016
Available online xxxx

ABSTRACT

Background: Allergen immunotherapy is a potentially curative treatment approach in allergic diseases, subcutaneous immunotherapy is therapeutic option in treatment of allergic asthma.
Aim of the study: In the present study, subcutaneous immunotherapy (SCIT) using multiple allergen was administered to allergic asthmatic patients without allergic rhinitis or mixed allergy aiming to evaluate its efficacy, safety and evaluate the changes in the immune response.
Patients and methods: The study included 56 patients with allergic asthma alone, all patients received SCIT according to the results of skin prick test over a period of 1 year, initial clinical evaluation including the presence of exacerbation and need of inhalers treatment, pulmonary function tests were performed also total immunoglobulin E(IgE), immunoglobulin A(IgA) and leukotriene C4(LTC4) were measured and repeated after 1 year of initiation of the course of SCIT.
Results: There were highly significant clinical improvement as regard exacerbation presence, need for inhalers and improvement of the forced expiratory volume in the first second FEV1 also there were highly significant decrease in total IgE, LTC4 and highly significant increase of IgA, after one year of SCIT.
Conclusion: SCIT is a safe treatment strategy that significantly reduce exacerbation and medication requirement in allergic asthma without mixed allergy also improve immunological response.

Introduction

Asthma is one of the most common chronic inflammatory conditions affecting roughly 300 million patients around the world. It is expected that asthma will affect also an additional 100 million patient by 2025 [1].

Allergic asthma is the most common form of asthma. It is characterized by that the identifiable trigger to which the patient has been sensitized will provoke the symptoms [2].

Although allergen avoidance is an main component of therapy, it is often insufficient and impractical. As a consequence, in allergic disease, the mainstay management has been pharmacotherapy, especially antihistamines, inhaled corticosteroids, and bronchodilators.

Targeted to regulate inflammation of the upper and lower airways. Although these treatments are effective and safe in most cases, they offer no lasting benefit once treatment is stopped because they have limited disease-modifying effects. it has become apparent that allergic diseases are the result of immune dysregulation that reflects an impairment in the natural tolerance that develops to allergens [3].

Allergy immunotherapy (AIT) is an effective treatment option for allergic asthma, rhinitis and venom-induced anaphylaxis, AIT can change the course of allergic disease and induce allergen-specific immune tolerance in addition to reducing symptoms. In current clinical practice; the route of delivery of immunotherapy either subcutaneously or sublingually, both of them appear to have a duration of efficacy of up to 12 years, and both can prevent the appearance of asthma in allergic rhinitis and prevent development of new allergen sensitivities [4].

Subcutaneous allergen immunotherapy(SCIT) is clearly beneficial in the treatment of selected patients with asthma or allergic rhinitis. However, this therapy is underused, because it requires administration in a medical facility [5].

The ultimate goal of therapy in the immunologic diseases is to induce immune tolerance and a change in the immune response

Peer review under responsibility of The Egyptian Society of Chest Diseases and Tuberculosis.
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http://dx.doi.org/10.1016/j.ejcdt.2016.10.004
0422-7638/

to specific antigens so the discontinuation of the therapy results in sustained long-lasting therapeutic benefits [6].

AIT delivery through the nasal, epicutaneous, bronchial, intra–lymph node or intraepithelial routes has been investigated [7].

Asthma has been supposed as mainly a Th2 cell mediated disorder. However, in recent years, many other cell types such as Th1, Th17and Treg are also discovered to be involved in pathological process of asthma [8].

AIT builts up immunological tolerance as shown by persistence of improvement both in clinical and immunologic parameters after the cessation of treatment. Additional benefits of AIT include prevention of sensitizations of new allergen and progression from allergic rhinitis to asthma [9].

So, (AIT) is a unique therapy which capable to change the natural evolution of allergic diseases [10].

With this treatment mode, allergens are given to the patients in repeated and increasing doses aiming to provide immune tolerance [11].

Multiple mechanisms in this treatment option related to T- and B-cell regulation and play a role in allergen tolerance [12].

In most studies, effectiveness of AIT has been assessed primarily in patients with allergic rhinitis, and the results concerning allergic asthma mostly were given as a secondary outcome. Thus,there are a few researches which were organized to evaluate the efficacy of AIT specifically in allergic asthma without allergic rhinitis or other mixed allergy, In the current study we aim to evaluate efficacy, safety of subcutaneous Immunotherapy (SCIT) and the changes in the immune response by evaluation of some allergen specific antibodies.

Patients and methods

This study comprised of 56 patients with mean age 29.89 ± 8.28 (22 males and 34 females), these patients were proved to have allergic asthma, diagnosis of asthma was based on the presence of recurrent cough, chest tightness, shortness of breath or wheezing also having a spirometry respond to the administration of short acting beta-agonist (SABA), according to GINA 2011 guidelines [13].

Allergic asthma documented by positive skin test, a person of the atopic constitution may develop typical allergic symptoms of asthma, rhino-conjunctivitis, or eczema [14].

Patients were selected at allergy and immunology unit in the chest department, Mansoura university hospital, patients were evaluated initially by medical history, clinical examination, pulmonary function test(forced expiratory volume in first second was the parameter used in this study), skin prick test with common allergen,

Assessment of the status of clinical asthma control and treatment efficacy

1) as regard the need of rescue treatment using the asthma control test(ACT) as follow:

(1) need of inhalers3 or more times per day,
(2) need of inhalers 1 or 2 times per day,
(3) need of inhalers 2 or 3 times per week,
(4) need of inhalers Once a week or less.

2) as regard the assessment of presence or absence of exacerbation.

Skin prick test

Skin prick testing (SPT) was performed using a standard method [15] with a panel of common local allergens. SPT include testing with positive control solution (10 mg mL^{-1} of histamine hydrochloride) and negative control solution (buffer -solution). The response to SPT in the form of Skin reaction (wheal) was evaluated after 15 min. The mean skin reaction (mean wheal diameter) was calculated according to the formula (D + d)/2, where D represented the largest longitudinal diameter and d its midpoint orthogonal diameter in mm. Statistical evaluation of the SPT results is the difference between mean skin reaction to each allergen and negative control solution. The results of SPT were considered positive when the wheal diameter was larger than the negative control diameter for 3 mm or more in at least one tested allergen.

Immunotherapy

Therapeutic vaccines containing allergen extracts for Allergen Immunotherapy(AIT), were prepared using stock formulations. Aqueous extracts was used to achieve a concentrate of 1:100 wt/vol unit of the mixed extract.

A potency of 1:100 indicates that 1 g of dry allergen was added to 100 cc of a buffer (phenol saline) for extraction. The allergen was eluted for a time, and then the solid material was filtered out, leaving an aqueous solution [16].

The allergen selected for immunotherapy were the allergen showed strong positivity by skin prick test.

Separate vials were used for mites, moulds and grass pollen extracts to reduce proteolytic degradation. All extracts were stored at 4 °C. Therapeutic vaccine varied with each individual patient based on specific allergens identified during testing. Most patients received a variety of aeroallergens including a combination of grass-pollens, grass, moulds and mites, immunotherapy was administered for each patient with 10-fold increase in concentration (0.2, 0.4, 0.6, 0.8 and 1 ml of each vial) of allergen extract were injected subcutaneously.

Subcutaneous immunotherapy uses a protocol of weekly injections with gradually increasing dosages of allergen extract until a maintenance dose is achieved. Subsequently, the maintenance dose administration is reduced to bi-weekly and then to monthly intervals.

Patients who were unable to tolerate higher concentration due to local or systemic reactions were maintained on the highest concentration they were able to tolerate, no food allergen were used for AIT.

Laboratory methods

Venous blood samples blood was collected from each patient before and after one year treatment. Blood samples were left undisturbed for about half an hour for complete clot formation. The samples were then centrifuged to separate the serum from the clot. After centrifugation the serum was stored at −20 °C in eppendorf tubes untill the analysis was done.

Serum measurements

Determination of serum immunoglobulin E(Ig E). Serum levels of Ig E was assayed by an enzyme-linked immunosorbent assay (ELISA) kit (Calbiotech Inc., Spring Valley, CA, USA) based on the sandwich technique according to the instruction provided. The assay based on the competitive enzyme immunoassay system**.** The sensitivity of the assay for Ig E was 0.7 IU/ml. Absorbance of standards and samples were measured at 450 nm using automated microprocessor controlled microplate ELISA reader (Tecan-sunrise Absorbance Reader, Tecan, Austaria, GmbH- Magellan software).

Determination of serum immunoglobulin A (Ig A). Serum levels of IgA were measured by immunoturbidimetry (Biochemical Enterprise, Milano, Italy). Non haemolysed and non lipemic serum were used.

Please cite this article in press as: E.O. Arram et al., Clinical and immunological effect of subcutaneous immunotherapy in allergic asthma, Egypt. J. Chest Dis. Tuberc. (2016), http://dx.doi.org/10.1016/j.ejcdt.2016.10.004