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RESIDENT PHYSICIAN: Jing Shen, MD
FACULTY PHYSICIAN: Matthew W. Ryan, MD
SERIES EDITORS: Francis B. Quinn, Jr., MD and Matthew W. Ryan, MD

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The incidence of allergic diseases has increased over the last few decades, especially in developed countries. For example, the prevalence of rhinoconjunctivitis in 13- to 14-year-old children in 1997 varied from 1.4% to 39.7%, with the lowest prevalence in the Eastern Europe and south Asia and the highest in Canada, Finland, Spain, the United Kingdom, and the United States. The U. S. Center for Disease Control and Prevention also reported a 73.9% increase in self-reported asthma during the period from 1980 to 1996. There have been multiple modalities used to treat allergic disease, including allergen avoidance, pharmacotherapy and immunotherapy. We will briefly review the immunology involved in allergic disease and then will review the proposed mechanism and efficacy of immunotherapy.

Review of Immunology in allergic disease:

The allergic reaction is an exaggerated or inappropriate immune reaction and causes damage to the host. It is also called a hypersensitivity reaction. An allergen is an antigen that commonly causes hypersensitivity or allergic reactions. Gell and Coombs described 4 types of hypersensitivity reactions.

Type I: Immediate Hypersensitivity reactions are mediated by IgE antibodies, which bind to receptors on mast cells and basophils. When cross linked by antigens, the IgE antibodies trigger the mast cells and basophils to release pharmacologically active agents that are responsible for the characteristic symptoms of anaphylaxis. Reactions are rapid, occurring within minutes after exposure to antigen. There is also a late phase reaction, with recruitment of other inflammatory cells.

Type II: Cytotoxic reactions occur when IgM or IgG antibodies bind to antigen on the surface of cells and activate the complement cascade, which culminates in destruction of the cells.

Type III: Immune complex reactions occur when complexes of antigen and IgM or IgG antibody accumulate in the circulation or in tissue and activate the complement cascade. Granulocytes are attracted to the site of activation, and damage results from the release of lytic

enzymes from their granules. Reactions occurs within hours of exposure to antigen.

Type IV: Cell-Mediated Immunity reaction, also called delayed –type hypersensitivity reaction, is mediated by T lymphocytes. On activation, T cells release cytokines that cause accumulation and activation of macrophages, which cause local damage. It has a delayed onset and occurs 1-2 days after antigen exposure.

Clinical allergic diseases are type I IgE mediated hypersensitivity reactions. There are two well-defined phases of the Type I hypersensitivity reaction. 1) Initial response characterized by vasodilatation, vascular leakage, and smooth muscle spasm or glandular secretions. These changes usually occur within 5 to 30 minutes after exposure and tend to subside in 60 minutes. 2) Late phase reaction sets in 2 to 8 hours later without additional exposure to antigen and lasts for several days. It is characterized by more intense infiltration of tissues with eosinophils, neutrophils, basophils, monocytes, and CD4+ T cells as well as tissue destruction in the form of mucosal epithelial cell damage.

Antigen presenting cells (APC) take up antigen, process it inside the cell, and then present the processed antigen on their surface to T lymphocytes. This is the only way that T cells can recognize and bind with antigen. APC includes macrophage, activated T-lymphocytes, B-lymphocytes, and dendritic cells. All antigens that are presented at the APC surface are bound to molecules called major histocompatibility complex (MHC). There are two classes of MHC. MHC class I bind with CD 8+ T cell only. And MHC class II binds with CD4+ cell only.

The CD4+ T cell is central to the type I reaction. It functions as master regulator, and influences T cells, B cells, macrophages, and natural killer cells. Based on the specific cytokines produced by these T cells, CD4+ T cells can be divided into 2 subsets: Th1 or Th2.

Th1 cells alone produce IL-2, IL-12, interferon (IFN)-gamma. Th2 cells alone produce IL-4, IL-5, and IL-10. Th1 cells are involved in elimination of intracellular pathogen, facilitate delayed hypersensitivity, and stimulate macrophage activation. Th2 cells are involved in allergic inflammation and disease mediated by IgE antibodies. The effector functions of Th1 and Th2 cells are considered to be antagonistic.

Th2 cells are pivotal in the pathogenesis of type I reaction. Cytokines derived from Th2 cells mediate allergic inflammation through activating eosinophils, promoting mast cell development, regulating immunoglobulin isotype switching to IgE, and modulating adhesion molecule expression. The pathogenesis of typical allergic reactions is believed to be caused by a preferential activation of Th2 cells in predisposed atopic individuals. Th1 cytokines such as IFN-gamma inhibit IgE synthesis and the development of Th2 clones. Imbalance between Th1 and Th2 cells appear to be responsible for development of allergic conditions.

Mast cells and basophils are also important in the pathogenesis of type I hypersensitivity. Mast cells are bone marrow-derived cells. They are found near blood vessels and nerves and in subepithelial sites. Mast cell cytoplasm contains granules that possess a variety of biologically active mediators. In the type I reaction, mast cells are activated by cross-linking of high affinity IgE receptors. But there are other stimuli that can activate mast cell to degranulate such as complement components C5a and C3a, IL-8, codeine, morphine, heat, and cold. The basophil is

similar to the mast cell except that it circulates in the blood and is not present in the tissues.

The pathogenesis of a type I hypersensitivity reaction starts with IgE antibody production, also called the sensitization phase. Antigen is presented by antigen presenting cells to CD4⁺ Th2 cells. The activated Th2 cells then produces a cluster of cytokines, including IL-3, IL4, IL-5, IL-13 and GM-CSF. IL-4 is absolutely essential for turning on the IgE –producing B cells and for sustaining the development of Th2 cells. IL-3 and IL-5 promote the survival of eosinophils. IgE antibodies produced by B cells quickly attach to mast cells and basophils. When mast cells and basophils are exposed to antigen again, antigen binds to the IgE antibodies on the surface of these cells. Multivalent antigen causes cross-linking of IgE antibodies, which activates cell degranulation with discharge of preformed mediators and de novo synthesis of mediators. These mediators are responsible for the observed increased vascular permeability, increased mucus secretion, and smooth muscle contraction in the allergic reaction. These mediators also have chemotactic properties. Eosinophils, neutrophils, and monocytes are recruited and release additional waves of mediators. The recruited cells amplify and sustain the inflammatory response without additional exposure to the triggering antigen. This is the late phase reaction.

Immunotherapy

Immunotherapy is a medical procedure that uses controlled exposure to known allergens to reduce the severity of allergic disorders. The diseases treated by immunotherapy are allergic rhinitis, allergic asthma, allergic conjunctivitis, and insect sting hypersensitivity. Treatment of food allergy, urticaria, and atopic dermatitis with immunotherapy is not considered appropriate.

Immunotherapy started in the early 1900's. Curtis immunized people with aqueous extract of whole weeds in 1900. In 1903, Dunbar immunized subjects who had grass-sensitive hay fever with animal derived (horse and goose) grass pollen antisera to subject's nasal mucosa. Besredka and Steinhardt published their results in 1907 to show that the anaphylactic reaction encountered during immunotherapy is due to immunizing too rapidly or with too large dose of allergen. Noon and Cantab introduced weight units for pollen doses and quantitation of individual sensitivity by in vivo testing.

1914 Freeman and Koessler reported that immunotherapy produced long lasting results. And in 1915 Cooke formally introduced immunotherapy into the USA by reporting the treatment by pollen immunization of 114 patients with hay fever and asthma.

Even though immunotherapy has been in practice for more than 90 years, the exact mechanism of its action is still not clear. There are several mechanisms proposed for its beneficial clinical effects. And so far there is no reliable correlation that can be established between any changes in immunological parameters and the clinical outcome.

Several changes in antibody production have been noted:

1) Gradual increase of allergen-specific IgG antibodies -- especially IgG4 subclasses. IgG4 antibody has been described as blocking antibody that may block IgE mediated mechanisms by inhibiting the release of inflammatory mediators from mast cells and basophils

either by direct competition with IgE for allergen binding or possibly by the binding of IgE-allergen-IgG complexes to the low affinity IgG receptor with resulting co-aggregation with the high affinity IgE receptor and the consequent inhibition of IgE receptor triggering. However the correlation between increased synthesis of IgG4 and efficacy of immunotherapy is not clear.

2) Decreased allergen-specific IgE antibodies production.

3) Increase IgA and IgM antigen-specific B lymphocytes. They have potential beneficial effects on mucosal immune barrier function and may limit antigen penetration into the body.

Multiple studies have been conducted to evaluate the effect of immunotherapy on the T-cell response or cytokine production. It is believed that immunotherapy altered the cytokine profile. Most of the studies select IL-4 and IFN-gamma as the most representative Th2-type and Th1-type cytokines involved in airway allergic disease. One of the popular theories is that immunotherapy causes a switch from a Th2 cytokine dominated response with IL-4 and IL-5 to a Th1-type response with a local accumulation of cells producing IFN-gamma. However the results from studies are conflicting. While some studies showed decreased IL-4 or IL-5 production, others showed decreased or unaltered IFN-gamma production. Also the correlation between these changes and clinical improvement is not well established.

Ohashi studied spontaneous and Der f 1-induced synthesis of IL-5 and IFN-gamma from peripheral blood mononuclear cells of 15 non-atopic subjects and 76 patients (18 untreated and 58 treated with immunotherapy) with perennial allergic rhinitis. The level of Der f 1-induced synthesis of IL-5 was significantly higher in the untreated group than in the non-atopic group, whereas Der f 1-induced synthesis of IFN-gamma was significantly lower in the untreated group than in the non-atopic group. Immunotherapy decreased the enhanced IL-5 synthesis, and further decreased the suppressed IFN-gamma synthesis as the therapy proceeded. IL-5 synthesis did not differ between non-atopic individuals and patients whose duration of immunotherapy was 10 or more years. Therefore, Ohashi proposed that immunotherapy possibly suppressed both IL-5 and IFN-gamma production (Th1 and Th2 anergy), but the suppression of IL-5 is exclusively linked to the clinical efficacy of immunotherapy.

The long term clinical efficacy of immunotherapy has been investigated to show the advantage of immunotherapy over pharmacotherapy. Study results are conflicting. Norman and Lichtenstein showed discontinuation of pollen immunotherapy in patients treated for 5 years lead to a partial relapse after 1 year, and after 2 years to a return to previous symptoms. But another study showed clinical efficacy lasted 6 years after stopping the immunotherapy for seasonal allergic rhinitis. Durham et al. conducted a randomized, placebo-controlled, double-blind study, in which patients with severe grass-pollen rhinitis uncontrolled by standard anti-allergic drugs including topical steroids showed a reduction in symptoms and a reduction in need of rescue drugs of more than 60% compared with placebo treatment after less than 1 year of grass-pollen immunotherapy. After 3 more years of active treatment, patients were then re-randomized to continue with active immunotherapy or to receive placebo. At termination of the study 3 years later, no significant difference in symptom and medication scores between patients continuing or discontinuing immunotherapy was found. Compared with a matched control group of hay fever patients not receiving immunotherapy, the reduction in disease severity was more than 75%. Based on immunologic parameters, the dramatically reduced late-phase skin response observed

in the original study was maintained in both groups and significantly reduced compared with the control group. Late-phase skin biopsy showed a sustained decrease in CD3+ T-lymphocytes and cells containing IL-4 mRNA indicating a long-term immunologic effect after termination of immunotherapy. The continued decrease in the number of cells expressing IL-4 suggests that persistent suppression of Th2 responses may be responsible for the sustained clinical improvement after terminating immunotherapy.

Immunotherapy may also prevent progression of rhinitis to asthma in children. In the Preventive Allergy Treatment Study 205 children from 6 pediatric allergy centers in northern Europe aged 6-14 years with grass or birch pollen allergy were studied. They were randomly assigned to specific immunotherapy for 3 years or to a control group. The children who were diagnosed with allergic rhinitis underwent methacholine challenge in the baseline evaluation. The children who were treated with immunotherapy had significantly fewer asthma symptoms after 3 years of immunotherapy as evaluated by clinical diagnosis. Methacholine bronchial provocation test results improved in the treatment group. The conclusion was that the patients who underwent specific immunotherapy had significantly less asthma than the untreated control group.

Immunotherapy may also prevent onset of new sensitization in allergic patients. Forty-four children mono-sensitized to mites were followed on an annual basis for 3 years. The development of new sensitization was recorded. Ten of 22 children who were treated with immunotherapy had no new sensitizations, while all 22 children in control group developed new sensitivities. Another study by Pajno enrolled 134 children (age 5–8 years), who had intermittent asthma with or without rhinitis with isolated mite allergy. Half the children received immunotherapy for 3 years. The remaining children received medication only. All patients are followed for a total of 6 years. All patients were checked for allergic sensitization by skin prick test and serum IgE every year until the end of the follow-up period. Fifty-two out of 69 (75.4%) children in the immunotherapy group showed no new sensitization compared to 18 out of 54 (33.3%) children in the control group. One limitation of this study, however, is that it was not randomized.

Currently subcutaneous immunotherapy is the only approved route of administration in US. Subcutaneous immunotherapy normally involves a weekly subcutaneous injection of an extract of the allergen in solution, in increasing doses until a standard maintenance dose is reached. This dose is then injected subcutaneously on a regular basis (at intervals of approximately 20 days) for not less than 3 years for perennial allergens. Shorter term immunotherapy does not affect the cytokine profile and does not have long-term efficacy after discontinuation. Without its long term efficacy, immunotherapy may not be cost effective compare to pharmacotherapy.

Patients who receive immunotherapy need to have proven allergy by skin test or in vitro testing that correlates with their clinical history. Treating patients only on the basis of positive allergy tests without relevant clinical symptoms is not justified. Immunotherapy should be considered in patients who have failed attempted allergen avoidance and also when treatment with pharmacotherapy is not fully successful or when medication is not well tolerated. Last but not the least, patient needs to be patient and motivated and compliant with treatment.

Sublingual immunotherapy:

Subcutaneous immunotherapy can be uncomfortable for patients and minor complications such as injection site swelling occur frequently. Therefore an alternative route of delivery immunotherapy has been explored. In Europe, sublingual immunotherapy has been widely used and investigated. The most common way to administer antigen is to keep the extract under the tongue for a couple of minutes and then swallow it. The dose of allergen used for sublingual immunotherapy is greater than subcutaneous immunotherapy (about 3-300 times higher).

The efficacy of this treatment has been well documented. Wilson, et al. conducted a systemic review of literature in the Cochrane library to investigate whether the symptoms of allergic rhinoconjunctivitis can be relieved by sublingual immunotherapy and whether the intake of symptomatic medication can be reduced. Twenty-two clinical studies involving the application of sublingual therapy published in the English language were reviewed. All of these investigations were double-blinded, placebo-controlled, parallel-group studies to which no methodological objections could be made. The majority of these studies, in which a total of 979 patients participated, were performed in adults. On average, a highly significant reduction in symptoms could be noted, in most cases as early as after one treatment cycle, as well as a definite decrease in medicine intake for symptoms. The results for seasonal allergens were more convincing than those for perennial allergens. The same results apply for the treatment of children. However whether sublingual therapy has equivalent efficacy to subcutaneous immunotherapy is not clear. Studies have shown that sublingual immunotherapy has long-term efficacy in agreement with the observation previously found with subcutaneous injection. And a simple administration schedule has been proposed for the sublingual route.

Summary:

Allergy is a complex disorder resulting from an IgE mediated triggering of mast cells and subsequent accumulation of inflammatory cells at sites of antigen deposition. These events are regulated in large part by the induction of Th2 cells that promote synthesis of IgE and accumulation of inflammatory cells, particular eosinophils. Immunotherapy has the potential for long term efficacy.

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