PAST, PRESENT and THE FUTURE of IMMUNOTHERAPY (HYPOSENSITIZATION) in EXTRINSIC ATOPIC BRONCHIAL ASTHMA

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Abstract:

In specific therapy of extrinsic bronchial asthmatic cases, in which the atopic character is well identified with early type skin test positivity against external allergens and increased serum IgE levels, the elimination of responsible allergens seems practically impossible. That is why the concept of allergen immunotherapy (hyposensitization) has been developed at the beginning of 20th century.

In classical application, (conventional systemic immunotherapy) the dosage of aqueus allergen solutions is increased at weekly intervals until the maximum tolerated dosage (MTD) is reached. Then the therapy continues at MTD for 2-3 years.

In order to shorten the long lasting therapy "Rush" or "Cluster" treatment regimes have been developed and depot extract contained preparates are widely used.

Clinically, the effect of immunotherapy is mostly observed by the improvement in symptoms and signs. The decrease in reactivity in skin and bronchial provocation tests and the effect of suppression are observed in some immuno-serologic tests.

On the other hand, with the use of non-antigenic materials and modified allergen extracts helping IgE suppression in the extrinsic atopic bronchial asthma is believed to be an effective, thrusting, low-costing and fast-recovering treatment method in the years ahead.

Introduction

Bronchial asthma is a syndrome which has a relative high incidence in the population (2% of total population) and which can occur by variety of stimuli. Despite the fact that the exact etiology of the syndrome is unknown, the immuno-allergic factors are mostly incriminated. Inherited or aquired imbalance in adrenergic, cholinergic and probably purinergic (non-adrenergic and non-cholinergic) controls of airway diameter, has also been implicated (9).

In asthmatic individuals with hyperreactive bronchi; bronchocontriction may persist at subclinical levels (even when they are asymptomatic)(27). Allergic diseases are mostly due to the high degree of sensitivity developed against normally harmless substances. This hypersensitivity, probably developed by inherited predisposition, is commonly called as "atopy" (23). In atopic individuals hay fever, urticaria and allergic conjunctivitis are observed together with bronchial asthma.

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The mechanism of allergic reactions:

Early type of hypersensitivity reactions were first detected in early 1900's (4,6) on skin of various bronchial asthmatic patients. Atopic individuals are capable of producing large amounts of reaginic antibodies which being homocytotrophic by nature, are fixed to the mast cells or basophils. This skin sensitizing antibody IgE, produced by submucosal plasma cells and lymph nodes in respiratory and gastrointestinal systems (30) was isolated within past 20 years (12).

On re-exposure to the same allergen, the antigen-antibody reaction results in liberation of chemical mediators which in turn trigger allergic reactions.

Chemical mediators such as histamine, leucotriens, ECF-A etc. also cause vasodilatation, increased capillary permeability and bronchial smooth muscle contraction in bronchial asthma (13).

The atopic character in bronchial asthma is well determined by skin test positivity and increased IgE antibody (25). Allergic skin tests are customarily performed to detect environmental allergens, (depending on patient's history) playing etiologic roles (28). The allergic character of a patient in bronchial asthma is determined by the history, the relation of the syptoms to the environment, to seasonal and situational variations and his/her clinical course (26).

Diagnostic skin test procedure:

In our center, commercially available allergens are applied during skin tests. The prick test method, being usually safer due to the small amount of antigen, is preferred (24). The skin is punctured 3-5 cm. apart on the flexor aspects of the forearm by a darning needle or by a lancet. Some clinicians also use the back or abdominal sites for puncture (31). A drop of glycerine-preparated test extract solutions is placed on each scratches and controls are performed simultaneously (the diluent-saline-as negative control and 0.1 mg/ml. histamine chloride as positive control). In the intradermal test, a tuberculin syringe with short-bevel no. 26 (hypodermic) needle is used to inject 0.01-0.02 ml. of a lyophilized test extract of allergen solutions into the skin (32). International classifications are used to interpret all skin test results (20). On the other hand, in some cases negative results arise from the use of original crude extracts. In order to obtain satisfactory results, it is necessary to develop more purified, standardized and well-characterized allergenic extract (3).

The concept of immunotherapy:

The complete avoidance (elimination) of allergens being mostly difficult in the therapy of extrinsic atopic bronchial asthma. The procedure of hyposensitization was introduced for the treatment of pollenosis (hay fever) in 1911 (19). In this form of therapy (conventional systemic hyposensitization) the gradually increasing subcutaneous aqueus allergen extract solutions are used to increase the tolerance of the patient against offending allergens.

Depending on the patient's reaction, injections continue at 1-7 days intervals up to the maximal tolerated dosage (MTD) or until a preset maximal dosage (usually 1.000.-10.000 times greater than initial dosage). The allergen extracts are injected either solely or by multiple regular intervals; perennial, pre-seasonal or co-seasonal in pollen allergies (18).

The chances of satisfactory results are 90%, if used regularly over a period of two to three years. Beneficial results reaching 90% can be obtained (11, 21, 29). It is often necessary to give 20 or more injections before the maintenance dose is reached; therefore, some investigators have employed "rush" or "cluster" hyposensitization to titrate up to a higher dose more rapidly (17). Increased dosages are given every 1-2 hours, under close observation (hospitalization). Once the first interim maintenance dose is reached, the standard dose is then followed.

Local hyposensitization with direct stimulation of the shock organ has been used since 1951, initially against bronchial asthma (10, 16, 33). Numerous studies have described clinical effects but well-controlled, double-blind investigations are necessary to uncover any potential effects of the treatment.

Following the development of allergen immunotherapy and its adaptation as a form of standard practice, a number of clinical and scientific questions were raised about its nature. With the use of appropriate patient populations, doses of antigens and methods of evaluation, there exist clear demonstration of efficacy.

It is of considerable importance, in both clinical practice and trials, that the allergen immunotherapy results in a reduction but not elimination of symptoms. With the evaluation of allergen immunotherapy, studies on the mechanism of action are conducted by clinical investigators. It was later recognized that the term desensitization was not appropriate, because even after continued therapy and apparent clinical improvement the patients remained reactive to allergens. The latter was also demonstrated by the continued presence of some symptoms and immediate type skin reactivity which led investigators to use the term hyposensitization therapy instead of desensitization therapy and more recently the broader and less mechanistic term allergen immunotherapy (22).

The clinical improvement following hyposensitization therapy has also been shown to be dose related and should be tailored to the need of the patient.

In order to fulfill the needs of an appropriate therapy it is extremely important to obtain a progress report of the symptoms befor writing the treatment extract. The objective evaluation of efficacy in the therapy has been the response to bronchial provocation tests in clinical observation (1, 3).

Immunologic efficacy parameters:

Most of the scientific knowledge on the mechanism of action of allergen immunotherapy is yet very recent and insufficient. Therefore, it seems appropriate to try to fully understand immunologic mechanisms responsible for the results of immunotherapy and to hope that the principles learned will allow the evaluation of efficacy by techniques simpler than full-scale clinical studies. Immunologic studies appear to strive to the goal but final answers have yet to be obtained. As noted earlier, immunization by current methods tends to induce a partial degree of suppression of IgE antibody responses. The mechanism by which this occurs in human beings has not yet been worked out.

But parallel experiments in mice strongly suggest

that suppression of IgE antibodies comes about through the stimulation of supressor T-cells (specific for IgE antibodies toward the antigen which the animal has received by parenteral injections). Although hyposensitization is being employed now for 70 years, it has not been possible to clarify the immunological mechanisms or to establish any certain effect parameters (21).

Complete decreased levels of either serum total IgE, serum specific IgE (SS IgE) or both, was not observed during the allergen immunotherapy of extrinsic atopic bronchial asthma (18). Following the application of allergen immunotherapy, serum totally IgG, SSIgG and SS IgG/SS IgE ratio usually increases to relatively higher levels (8).

Some trials indicated reduced basophilic histamine release (cell sensitivity index) during hyposensitization (15). Studies on lymphocyte activity have shown an increase in T-suppressor cells and a post-treatment reduction on lymphoblast transformation (LT), mitogenic factor(MF) and in migration inhibitory factor (MIF) (5, 7). On the other hand, during immunotherapy it has been shown that some serum specific suppressor substances were also particularly detected against IgE (14). The inhibited histamine-induced suppressor factor (HSF) which is released from T-suppressor cells (previously found as inhibited) gradually increased following the allergen immunotherapy in the atopic individuals (2).

Recent developments in immunotherapy:

It has been the goal of many investigators to improve the preparations used in allergen immunotherapy which will aid to reduce the number of injections and increase the therapeutic safety. In order to reduce the number of injections slow-release preparations such as oil-emulsions, alum-precipitation and tyrosine adsorption ect. have been investigated. Emulsions in oil, resulting in unacceptable local reaction, fail to provide adequate efficacy and dropped from consideration because of potential carcinogenicity

Alum-precipitation requiring a course of 7 to 10 injections appears to be reasonably efficacious and the incidence of symptoms following the shots is reduced. To prevent the larger local reactions the extract is prepared with pyridine but, questions arise as to the efficacy of treatment when this organic solvent is used (17).

In L-tyrosine adsorbed depot extracts the release of antigens is slow, but the efficacy was diminished compared to other depot extract (18). Recent advances in immunotherapy clearly show us that when modified allergens are used the allergenicity is reduced while still retaining effect of immunogenicity. The allergenicity is defined as the ability to elicit an IgE mediated response where the immunogenicity being the ability the induce an IgG antibody response.

If the allergenicity can be reduced by polymerization of monomeric antigens (due to the concealed antigenic determinants in the polymer) than the amount of allergen administered could be increased. In this form, the immunogenicity should be retained because the antigenic determinants are still available for processing by macrophages and initates an IgG antibody response. An equal weight of polymeric antigens would have a lower molecular concentration and decreased opportunity to bridge IgE antibody molecules on mast cells. The selection of allergens included in the treatment extract is based on clinical history and the allergy skin tests (22).

A different way to reduce allergic reactions is to modify the allergen by various chemical treatments. The allergenicity is then greatly reduced, while maintaining the necessary antigenicity required for the desired immunologic responses. One of the methods used to modify allergens is a formaldehyde or glutaraldehyde treatment. Formaldehyde-treated materials have been referred as allergoids, a term derived from allergen as toxoid from toxin. Indeed, allergoid materials do show less allergenic potential by more than hundred folds. The patient can be immunized with fewer doses instead of increased doses given by injection.

Allergoids, appearing to be an improvement over present techniques of immunization, are still under trial and not yet available to the practicing physician. There also exist two modified allergens to mention for parenteral immunization. The first modified material combines extraction with the organic solvent, pyridine, followed by alum-precipitation. The second material is obtained by the treatment of allergens with glutaraldehyde; followed by adsorption to suspensions of L-thyrosine (18).

The future of immunotherapy:

Immunologic comparisons with standard allergenic extract are not available currently and the method requires further evaluation. Moreover, new area accumulating a great interest in terms of immunologic management of allergies is to be mentioned despite its unknown practical value.

Urea-denaturated materials are non-antigenic and stimulate little or no IgG antibody response but produce suppression of IgE synthesis. To date, to degree of suppression of IgE synthesis has been too small to be clinically useful, but deserves further investigations.

Other methods of inducing T cell suppression have also been tried. Polyethylene glycol-substituted allergens have been offered as a way of either producing stimulation of suppressor T-cell or inducing some other suppression mechanisms of IgE synthesis. It is also possible to induce a B cell tolerance in animals by adding short chained constituents to antigens (principally a copolymer of D-Glutamic acid and D-lysine).

It has been suggested that suppression of antibody

responses can be induced by the administration of allergen-antibody conjugate and experiments in animals have been producing interesting results in this direction (18).

Conclusion:

Controlled observations have confirmed many, but not all, of the empirical observations on the clinical effects of immunization with allergenic extracts. These immunologic methods provide valuable but yet imcomplete clues for the mechanisms of immunization. Such observations do however, provide clues for better ways of immunizing patients. Shorter courses of immunization with less side effects do also appear to be possible in the near future.

We hope to see reliable improvements in immunotherapy that will further shorten the course of immunization, eliminate allergic side effects and improve efficacy in the years ahead.

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