Allergy and Immunotherapy

by Diego Saporta, MD, FAAOA

Introduction

The word *allergy*, derived from two Greek words, *allos* (different) and *ergos* (mechanism), was coined by von Pirquet (circa 1905) to describe a state of altered reactivity.[1] This concept remained in use until IgE was discovered by Johansson and associates in Sweden and finally characterized by Ishizaka and associates in the US.[2] After IgE's discovery, allergy was considered a phenomenon related to the presence of IgE. Early on it was observed that IgE was elevated in patients with asthma.[3] With the introduction of in vitro technology, the idea that IgE caused the allergic reaction was strengthened and led to the notion that a skin test only diagnosed IgE-related phenomena, even though the hypersensitivity reactions described by Gell and Coombs involved four different types of immunological reactions.[4–6]

The allergic reaction affects the whole body. Nasal allergies, allergic conjunctivitis, asthma, dermatitis (eczema or urticaria), some cases of migraine, and others are different manifestations of the allergic condition.

Allergy Management

The management of allergic conditions is based on the use of environmental modification maneuvers, use of medications, or administration of immunotherapy.

Environmental modifications: They are important, as allergen avoidance will obviously decrease or even eliminate the symptoms, but they will not alter the potential for reactivity of the immunological system.

Medical management: prevents the bioactive chemicals generated during the allergic reaction from activating the receptors of the effector cells. When effective, the symptoms will not be produced but the allergic reaction will continue unimpaired.

Immunotherapy: modifies the dysfunctional immunological system, shifting it from a Th2 weighted system into a Th1 nonreactive system, leading into symptom resolution.[7]

Diet modifications, vitamins, supplements, and optimization of hormonal levels can strengthen the altered immunological system, but immunotherapy is the only treatment that elicits a long-standing improvement of the altered immunological system.[8]

Immunotherapy

Immunotherapy consists in the repeated administration of small but increasing amounts of the allergen(s) responsible for symptom production, leading into a change in reactivity of the immunological system.[7] The responsible allergens are diagnosed with an allergy test. If immunotherapy is successful, the patient will stop reacting to those allergens.

Allergy Tests

Charles Blackley described the first allergy test. He applied a drop of pollen over abraded skin. The resultant wheal and flare led him to conclude that exposure to pollen elicited hay fever. Skin tests eventually developed into three different modalities:

Scratch test: A drop of allergen is applied to the skin. A lancet is used to excoriate the skin through the drop of allergen. Reactive cases are called positive; nonreactive, negative. This type of test was found to be unreliable. In 1987 the AMA advised not to use this test anymore.[10]

Prick test: A drop of allergen is applied to the skin and an instrument is used to prick the skin without piercing it. Initially this was done with a needle; therefore, it required a certain amount of dexterity to avoid injuring the skin. At the present time this test can be done with the Morrow Brown needle (single prick device) or with a device that holds several prongs called the multiprick device, which has the advantage of allowing several allergens to be tested at the same time. Application takes seconds and requires minimal training.

Intradermal test: A small amount of allergen is injected into the dermis which is heavily populated with mast cells.[11] This explains why this test potentially can elicit severe reactions. The diameter of the skin wheal is measured immediately, and 10 to 20 minutes after the injection. A growth in wheal diameter implies that the test is positive.

Allergy tests can also be run in a sample of the patient's blood (without risk to the patient). In vitro technology became commercially available in 1967.[4] Specific immunoglobulins (sIg) that bind to an antigen are measured. Measurement depends on using a "labeled" anti-sIg antibody. The

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prototype of in vitro testing is the radioallergosorbent test (RAST), which uses radioactive anti-sIg antibodies.[4] Modern "RAST-like" tests use nonradioactive technologies.

Is There a Better Test?

There is a long-standing controversy as to which test is better. The skin prick test (SPT) is the most commonly used allergy test. Guidelines advise that negative SPTs are followed by an intradermal test.[12] According to the same guidelines, intradermal tests are more sensitive and permit identification of a larger number of clinically reactive patients, especially those with lower skin test sensitivity (i.e., a higher-potency concentration of the allergen is required to elicit a skin response), and they are also useful in evaluating skin sensitivity to low-potency allergenic extracts (i.e., diluted allergen which implies that there is a state of higher skin reactivity). SPTs are sensitive enough to detect clinically relevant IgE antibodies when potent extracts, such as grass and cat, are used. Other allergens may require intradermal tests for diagnosis.[13]

The problem with intradermal tests is the potential danger of a severe reaction.[14,15] This would be an exceptional occurrence with SPTs. While the reason for this difference is not clearly explained in the literature, it is likely related to the mast cells being present mainly in the dermis, but rarely in the epidermis.[11] The intradermal tests place the allergen immediately next to the mast cells, but the SPT does not penetrate the skin; therefore, the allergen will not easily interact with the mast cells.

There are 2 types of intradermal tests:

Intradermal test with one single dilution: Usually a 1:1000 weight/volume dilution of the allergen is injected, and if reactive, the result is considered positive.[12]

Intradermal Dilutional Test (IDT): Serial dilutions of the same allergen are injected, starting with a weak dilution (weaker than 1/1000 wt/vol), and advancing to more concentrated allergen (potentially to 1:100 wt/vol) until either one of the dilutions react (positive result) or none react (negative result).[10] Because the IDT starts by injecting a dilution that has been clinically established over many years to be safe, advancing to stronger concentrations only if there is no reaction to the previous injection, the test is inherently safe and the possibility of a severe reaction during testing is small.[10,16]

If the diagnostic power of the SPT is compared with the IDT, it appears that the SPT will only diagnose cases of high reactivity. These cases would elicit a reaction on an IDT with very diluted allergen (1:12,500 wt/vol to 1:312,000 wt/vol).[12,17]

There are also problems with the RAST-like tests. It is a common observation that their results do not match the clinical diagnosis. For example, a patient clinically reactive to cat may show a negative RAST test. Because of the assumption that allergy is exclusively related to the presence of IgE, a negative RAST result is often interpreted as "patient has no allergies."[18] The activating mechanism via IgE requires that an allergen bridges two IgE molecules in the surface of the mast cell, but IgG-allergen immune complexes can also activate mast cells.[11,20] A negative RAST test simply means that the specific immunoglobulin being measured for that allergen (usually IgE) is not present. In support of this statement, in vitro tests simultaneously measuring different immunoglobulins give results more consistent with the clinical presentation and more in agreement with the IDT.[21]

Over the years, the author has observed that RAST tests fail to match the clinical presentation and that SPT usually diagnoses only a few of the allergens to which the patient reacts but the IDT can identify the majority. The clinical implications of this observation become clear when patients with persistent symptoms while on immunotherapy based on SPT and/or single dilution intradermal tests come for consultation, and improve when additional allergens diagnosed by IDT are added to the treatment vaccine.

Administration of Immunotherapy

Immunotherapy is the administration of increasing quantities of the allergens to which the patient is reactive, producing immune tolerance and improving allergic symptoms. The involved mechanisms are complex, including inducing a shift from the Th2 proallergic system toward a Th1 nonreactive system, with an increase in T-regulatory cells, which through IL-10 secretion inhibit IgE production, increase IgG_4 and promote suppression of T-effector cell function.[22,23]

Immunotherapy can be administered as injections (subcutaneous injection immunotherapy; SCIT) or orally (sublingual immunotherapy; SLIT). The key to a successful treatment is based on the ability to diagnose the majority of the allergens responsible for patients' symptoms and mix them into a vaccine to be administered at short intervals with increasing dosages. When an aggressive dose advancement is pursued (beyond the symptom-relief dose), and a maintenance dose is administered for a total time of 3 to 5 years, long-term effects will be observed upon discontinuation.[24] The author has observed that longer treatments (5–6 years) give more consistent long-term effects after discontinuation.

There are two different therapeutic approaches: either the patient is treated with only a few clinically relevant allergens, or all the reactive allergens are included in the treatment vaccine.[12,25] By utilizing all positive allergens, the treatment results are better as more of the patient's allergic load is treated. The type of test utilized for diagnosis plays a role in this difference, as the SPT or even the intradermal test with a single

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dilution will not be able to diagnose all the allergens to which the patient is reactive.

A patient whose skin reacts only to more highly concentrated (potent) allergens will be misdiagnosed as "negative" unless an IDT is used. While the significance of allergens diagnosed with potent (concentrated) doses is controversial, when these results are taken into consideration there is a significant clinical improvement.[26] The author's personal experience is in agreement with these findings.

An important advantage of the IDT is that it establishes the strongest safe starting dose for immunotherapy; therefore clinical improvement occurs from the beginning of treatment and the risk for a reaction is minimized.[27]

SCIT

The injectable route requires weekly injections. This treatment modality has risks, as any injection can elicit a reaction, potentially severe, including anaphylaxis and death.[14,15] Some practitioners do not advance beyond the symptom-relief dose. While this is safe, the patient will not attain long-term relief.[24]

For safety reasons, it is recommended that SCIT be administered at the doctor's office exclusively. Patients should wait 20 to 30 minutes following intradermal tests or injections and an adrenaline autoinjector should be prescribed, as the risk for a reaction persists up to 24 hours after the injection.[13,25]

SLIT

The sublingual (oral) route has unique advantages: It is efficacious, safe, and easy to administer. There are no efficacy differences between SCIT and SLIT, but SLIT is inherently much safer. SLIT is ideal for the management of the young and/or asthmatic patient.[28–33] Given its great safety, the patient does not need to come to the office, making it an ideal "home-based therapy." There are a few reports of severe reactions after SLIT administration.[34–37] These patients were predominantly asthmatics treated with a rush advancement protocol. The author successfully uses a SLIT protocol with daily drop-administration that never elicited a severe reaction.[38,39] Problems with this technique do not occur often, probably because the dose is advanced very slowly and it is reduced if symptom provocation occurs.[39]

There are multiple protocols for SLIT administration. It is now advised that drops be administered daily.[40] SLIT is widely used and accepted in Europe.[41,42] In the US, SLIT is not FDA approved. Insurance companies do not reimburse for it. Yet SLIT should be considered an important tool for the management of the young child with allergies, more so if asthmatic.[28,31–33,44] SLIT is safe during pregnancy, even for treatment initiation.[45]

A variation of SLIT is the use of allergy tablets (AT) introduced by pharmaceutical companies that have recently been approved by the FDA.[46–48] These tablets deliver a few allergens only at one constant concentration, which is a flaw in treatment effectiveness.[49] The prescribing information includes a boxed warning to inform that severe allergic reactions may occur, and the label insert advises carrying an adrenaline injector.[50]

Low-Dose Allergen Immunotherapy (LDA)

This treatment modality, while being effective, does not conform to "usual" immunotherapy. With LDA, allergens are diluted to the order of 10^{-6} to 10^{-17}. A major controversy about this treatment is a lack of understanding about its mechanisms. An attempt to get approved by the FDA failed.[51] LDA efficacy information is mostly anecdotal. It uses proprietary information in its formulation, and there is only one source for the treatment sets.[52] LDA reportedly uses all allergens present in the environment as well as foods. Immediately before administration these allergens are mixed with the enzyme beta-glucuronidase.

Knowledge of LDA stems mainly from observations of Dr. Leonard McEwen, a British allergist who realized that beta-glucuronidase had antiallergenic properties. The treatment was popularized in the US by Dr. Welman Shrader.[51] The most remarkable fact about LDA is that it works. LDA is administered initially once every 2 months. It takes usually 12 to 18 months to attain a 2-month improvement, at which time the interval between administrations is increased. Eventually the patient can be managed with treatments once a year or longer.[51]

LDA advantages:

Administration is based on a clinical diagnosis of the allergic condition. An allergy test is not necessary because:

a. All allergens are covered; therefore there is no need to diagnose which are the responsible allergens.
b. The administered dose is so diluted that it will never give a reaction as can happen with SCIT; therefore the concept of "safe dose to start immunotherapy" does not apply.

The cost of this treatment decreases over time, since the number of administrations diminishes as the patient improves.

LDA administration treats hypersensitivity to not only inhalant allergens but also foods. The prevalence of food reactivities is on the rise worldwide. The patient with allergies commonly reacts to one or more foods. There are no FDA-approved therapies for food allergy.[53] The standard of care consists of allergen avoidance and, if needed, prompt treatment of allergic reactions after accidental ingestion. Oral and sublingual food immunotherapy are being evaluated, and reports are optimistic.[53,54] LDA offers another option for the management of food allergies and reactivities.

Anecdotal information suggests that LDA is effective.[51] In a study comparing results of patients treated with LDA or with standard immunotherapy, no statistical differences between the

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groups were found, but the LDA group included patients who failed standard immunotherapy.[55] If these patients had continued with usual immunotherapy rather than switching to LDA, it could be assumed that the results in the LDA group would have been better than with the standard immunotherapy group.

Lastly, LDA offers the possibility of managing other conditions, including chemical sensitivity or autoimmune conditions.[51]

Summary

Highlights on diagnosis and management of allergies were presented. Immunotherapy is an excellent treatment modality able to induce a change in the dysfunctional immunological system, leading to a cure or at least long-lasting control of the allergic conditions. Different methods of administration have been succinctly described. The value of a safer approach such as SLIT has been underlined. SLIT can be considered for patients with asthma and sometimes in cases where SCIT is considered dangerous or its administration elicited problems. The potential role of LDA for the management of the allergic patient has also been stressed.

Practitioners interested in the management of allergic conditions should consider attending courses offered by mainstream academies (AAOA, AAAI) as well as smaller medical societies such as the Pan American Allergy Society and the American Academy of Environmental Medicine where management of inhalant and food-related allergic conditions, LDA, and other treatment modalities can be learned.

Notes

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