Immunotherapy Management of the Allergic Patient with Asthma and Lower Airway Inflammation

by Diego Saporta, MD

Abstract

Administration of immunotherapy is rewarding but challenging. The reward is observing how a patient exhibits progressive symptom improvement while at the same time requiring less medication, even to the point of not requiring medications any more. The problem is the specter of a reaction to the immunotherapy injections. Even though the frequency of reactions to testing or immunotherapy administration is low, if a severe reaction were to develop it could have devastating consequences. The patient most at risk for this type of reaction is the asthmatic patient.

The purpose of this article is to bring awareness, both to patients and practitioners, that there are patients with allergy symptoms that are not considered to be allergic because their tests are negative; that there is a large group of patients that have evidence of inflammation of the lower airway but that usually are not identified as asthmatics. Their management should include the same precautions taken to manage the asthmatic patients. Lastly, perceptions of the significance of immunotherapy for the management of the allergic patient, mainly the asthmatic one, will be presented and a discussion about the management of such patient will follow.

Introduction

Allergy, a word derived from two Greek words meaning "different" (Allos) and "mechanism" (Ergos) describes the reactivity of an organism to the surrounding environment. Certainly, since the discovery of IgE in 1965,[1] the word "allergy" has been redefined as a phenomenon exclusively mediated by IgE even though Gell and Coombs had previously described four mechanisms by which the immunological system can react.[2]

Type I reactivity or hypersensitivity reaction is the mechanism that involves IgE. It is logical to think that the immunological system reacts as a whole, rather than with only one of its components. This common-sense thought is backed by multiple clinical observations of patients with clear symptoms of allergic disease but with negative RAST tests for IgE and/or negative prick tests. Is it possible that terms like "non-allergic rhinitis,"[3] described as a chronic nasal inflammation not caused by systemic IgE-dependent mechanisms, or Non-Allergic Rhinitis with Eosinophilia Syndrome (NARES) described as a syndrome consisting of allergic rhinitis (AR) symptoms with negative tests and nasal cytology showing greater than 20% eosinophils,[4] have been coined to describe these cases of clear allergic symptoms with a test that is negative?

Published evidence suggests that there is allergic reactivity not mediated by IgE. In this regard, IgG with its subclasses and IgA are currently being investigated for their role in allergic disease.[5] Allergic reactions induced by IgG, including anaphylaxis mediated by IgG, were studied in mice.[6] Mast cells and basophils can be activated in vitro independently of the presence of IgE, again suggesting that non-IgE pathways for hypersensitivity reactions exist.[7] Also, bronchial hyperreactivity and airway inflammation can develop via activation of mast cells without involving IgE.[8] The patient with inhalant allergies frequently develops reactivity to multiple foods. In this case the role of IgG is more significant.[9]

Mainstream medicine continues to define "allergy" as a phenomenon solely mediated by IgE. Sensitization is defined by the results of a positive test and the most common tests used for diagnosis are a blood test for IgE (usually known as "RAST'' test even though in most cases ELISA technology is used) or skin prick test. Often times these tests will be negative, either because the patient has reactivity that is not mediated by IgE, therefore the IgE-RAST will be non-reactive, or because the prick test lacks the sensitivity of an intradermal test.[10]

This produces an apparently contradictory situation: a patient with clear allergic symptoms and negative tests can be diagnosed as being non-allergic or having "non-allergic rhinitis" or similar. All this, despite evidence that in these "non-allergic" events there is inflammation[3] which is the hallmark of the allergic disease. Cases like NARES have an increase in eosinophils, cells that are always involved in the allergic response.

"Allergy" should be defined as the reactivity of the individual to the surrounding environment. This is a complex process that not only affects the whole body[11] but also involves one or

more of the immunological mechanisms described by Gell and Coombs. For management of the allergic patient, I rely mostly on the Intradermal Dilutional Test or IDT (previously known as Skin End Point Titration or SET) to determine which are the involved allergens. I evaluate not only the immediate skin response (ISR), but also the delayed skin response (DSR) that develops 24 or more hours after the injection of the allergen being tested.[12]

A skin response that occurs many hours after the injection of the allergen is, in all probability, not related to an IgE-dependent mechanism, rather to other immunological mechanisms. The papules of the DSRs are indurated, not well defined, often with significant erythema and they can persist for days and even weeks.[12] Delayed reactivity has clinical significance. For example, asthma can occur as a delayed response, and clinical improvement and decrease in the need for controlling medication can be attained if immunotherapy is administered.[13]

The ISR starts developing usually about 5-10 minutes after the prick or intradermal skin tests. The main allergy community defines these ISRs as being exclusively mediated by IgE. To be able to make that assertion would require histological studies of the papule developed after the skin test, for cellular and immuno-electrophoresis analysis. Otherwise, it cannot be asserted that the skin reactivity was mediated by one or another of the potential mechanisms by which the immunological system can respond to a stimulus.

Management of the Allergic Patient – The Role of Immunotherapy

Allergen Specific Immunotherapy (SIT) is the only treatment capable of modifying the inflammatory response[14] characteristic of the allergic conditions. Not only can it have a preventative effect on AR and asthma, but also can prevent further development of new sensitizations, progression of AR into asthma, and can even alter the natural history of asthma itself.[14-17] SIT was found to promote asthma resolution, and this effect was more pronounced with higher doses of allergen-immunotherapy.[18]

In the best of cases. immunotherapy administration can lead to a cure of the allergic condition affecting the whole body. In the worst of cases, it will produce an incomplete response. In general, it should be expected that some improvement will always occur when immunotherapy is administered.

Complications of Immunotherapy

Immunotherapy uses extracts of the same allergens responsible for patient's symptoms; therefore the extracts contain only natural proteins. This explains why immunotherapy has no side effects from the injected allergens themselves. This does not mean the patient cannot have an immunological reaction to the injected allergens. It is a fact that administration of allergens to which one is sensitized can trigger symptoms. Allergic disease is characterized by reactivity. Symptom development will follow exposure to the reactive allergens present in the environment. This "natural reactivity" triggers the usual allergy symptoms, which can be mild or severe. Occasionally, a serious reaction can develop. Example: the case of a cat-allergic patient that develops a bad asthma attack just by entering a home where there is a cat.

So, it is not surprising that when administering extracts from these allergens, symptoms can be triggered. In this case, these symptoms are called "reactions." When the administration is by injection, the reaction has the potential for severity. Most reactions develop at the injection site. They are known as local arm reactions, consisting of inflammation, swelling, and pain. They may alter the course of immunotherapy treatment, but usually they resolve without intervention. An injected allergen can also trigger systemic symptoms, which can be mild or severe. Severe systemic reactions are rare, but they can lead to anaphylaxis of which mortality, an infrequent outcome, is unfortunately a possibility. There are reports of mortality due to the administration of injectable immunotherapy (properly known as Subcutaneous Injection Immunotherapy or SCIT) or even during intradermal testing. It has been observed that severe reactions that required emergency intervention or that produced mortality occurred more frequently in asthmatic patients.[19-22] This is why it is of extreme importance for the allergy practitioner to become proficient in identifying and managing patients with potential inflammation of the lower airway. These severe reactions are rare; therefore, publishing a series as in the references above, requires reviewing reports in the literature over the span of several years.

"Allergy" should be defined as the reactivity of the individual to the surrounding environment.

Asthma

To recognize an asthmatic patient is not always straightforward. The National Asthma Education and Prevention Program, in the Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma[23] defines asthma (p.12) as a chronic disorder of the airways, characterized by an underlying inflammation. This produces bronchial hyperresponsiveness and, therefore, airflow obstruction, which are responsible for the characteristic symptoms including cough, chest tightness, shortness of breath (SOB), and wheezing. Cough, when present, is usually more significant at night. These symptoms usually respond to the administration of inhaled bronchodilators (Short Acting Broncho Agonists or SABA).[24] They are recurrent and can develop in any combination.

The term "cough variant asthma" (p.46) is used to describe cases of chronic cough that occur mainly in children. In these cases, cough is the principal or only manifestation. Response of this variant to usual asthma medications helps establish the diagnosis.

If the inflammatory condition becomes persistent over time, it may lead to permanent structural changes known as airway remodeling. It is important to understand that even without smoking or exposure to industrial chemicals or other irritants, an asthmatic patient can develop permanent damage of the lower airways. This airway remodeling is similar to the structural changes in emphysema. This process, the consequence of persistent airway inflammation, will not be prevented by currently available medical treatments.[25]

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Inflammation, the main defining aspect of asthma, is also the cause of the allergy symptoms. In other words, the allergic disease is an inflammatory disease that can affect any organ in the body: the nose and paranasal sinuses, the eyes, the ears – middle ear effusions[26] and other conditions – the upper and the lower airway, the skin, etc. When the lower airway is affected, the smooth muscle of the bronchi can "overreact," leading into bronchospasm and hyper production of mucous by the secretory cells. The bronchial hyperresponsiveness characteristic of the inflamed lower airway facilitates reactivity to a variety of allergic and non-allergic stimuli like exercise, cold air, tobacco smoke, and other irritants.[23] Airway hyperresponsiveness can be diagnosed by challenges with methacholine. In this type of evaluation, the patient inhales increasing doses of the irritant substance, attempting to demonstrate amongst others, a decrease in the functional values of the spirometry. This type of study is done only by pulmonologists under controlled circumstances.[23]

Table I. Symptoms and circumstances evaluated in any patient considered for IDT. (SOB: Shortness of breath).

Note: When patient is under treatment, the symptom scoring sheet will also include the PF value and information on medication use.

Cough
Chest tightness
SOB
Wheezing
Exercise induced symptoms
Exercise cough
Exercise chest tightness
Exercise SOB
Exercise wheezing
Waking at night with symptoms
Which symptom
History of bronchitis
Life time use of inhalers
Recent use of inhalers
Name if possible
When was it used last
Symptoms improved with it

At the present time it is thought that asthma and AR are better described as a continuum of inflammation involving one common airway,[14,27] with rhinitis often preceding asthma onset.[14] In other words, rather than considering AR and asthma as two different conditions, the evidence points to the fact that both are actually expressions of the same inflammatory disease, with different patients having more or less symptoms related to the upper or to the lower airways.

The prevalence of asthma and AR is increasing in the general population and a high proportion of new patients have coexisting upper and lower airway disease.[24,27]

My Personal Experience with Asthma Diagnosis

In the 2020 updates to the Asthma Management Guidelines, it is stated that the diagnosis of asthma is elusive, and depends on gathering information from history, clinical findings, tests, and repeated evaluations over time.[28]

This is why in our history taking, we ask the patient for the presence of asthma. If the answer is "no," we then ask, one by one, for the presence of symptoms or circumstances that could suggest the presence of inflammation of the lower airway (See Table I).

Because of the concept of "one airway-one disease," we incorporated the determination of the Peak Flow (PF) value in patients undergoing immunotherapy. We observed that with successful administration of immunotherapy the PF value improved. This observation prompted a chart review of 60 randomly selected patients[29] which confirmed that the PF exhibited a statistically significant increase when immunotherapy administration was successful. This improvement occurred in all patients even if not asthmatic. This finding strongly supports the concept of "one airway theory."[27]

One unexpected finding in that study was that 71.6% of the patients in this non-selected sample had one or more symptoms associated to inflammation of the lower airway. It became clear from that study that simply asking, "Do you have asthma?" was not enough to assess potential involvement of the lower airway. Self-reported asthma was present in 13/60 (21%) cases. When presence of symptoms suggestive of lower airway inflammation were considered, the percentage of affected patients increased to 71.6%.[29]

For children, the most common finding is cough during exercise, sometimes with SOB. Less frequently only SOB. When the mother denies this problem, if age allows, we also ask the child the same questions and we often find that the answer is affirmative, but the mother was not aware that her child had this problem. For the adult patient population, the most common symptom reported is SOB on exertion. For sedentary people, we ask for SOB when walking briskly or when going upstairs.

We have observed in the last few years that patients reporting symptoms of lower airway involvement are much more prevalent. Often the symptoms have developed from a few months to a few years prior to consultation. This could be related to the observed changes of skin sensitivity to intradermal testing after our geographical area was hit by two hurricanes in 2011 and 2012.[30,31] In these reviews, it became clear that after those hurricanes, the general population consulting at our office was more symptomatic, started to develop symptoms at an earlier age, had more involvement of the lower airway, and the number of children consulting for allergy management increased. Allergy testing in post-hurricane patients confirmed an increased sensitivity to tested allergens. These observations support the reports of increased incidence of allergic conditions worldwide[32-34] and of a dramatic increase in asthma prevalence in Westernized countries.[23,24,35]

Because severe reactions during administration of immunotherapy occur more frequently in patients with asthma and because asthma diagnosis is difficult and elusive, we think that isolated symptoms or circumstances pertaining to the lower airway (Table I) are potentially due to the presence of underlying inflammation characteristic of the allergic conditions. If administration of anti-inflammatory therapy, usually inhaled corticosteroids (ICS), leads to symptomatic improvement, we consider this patient to have an inflamed lower airway.

In our experience it is much more likely to find a patient with isolated

lower respiratory symptoms than a patient diagnosed with asthma. These patients do not conform to the usual asthma definition. They often have a normal spirometry, but the functional parameters (Functional Vital Capacity or FVC and Forced Expiratory Volume in the first second or FEV1) are both in the lower end of the range or just below the range, with normal FVC/FEV1 ratio. In these cases, in order to determine if the airway is inflamed, an ICS is used daily. On follow up we determine if the patient reports subjective improvement (for example: breathing better or being able to go upstairs without restriction). It is not unusual to observe a concomitant improvement in the predicted value of the functional parameters. If the patient does not improve, if there is a partial response or if the patient improves but the spirometric values do not, we increase the ICS dose and recheck both patient symptoms and spirometry in a few more weeks. The objective is to attain the best symptom control with the best spirometric value in preparation for intradermal testing in order to provide immunotherapy.

While diagnosing these patients with asthma could be considered controversial, assuming that these patients have an inflamed airway when there is a positive response to an ICS appears appropriate.

Reducing the Risk When Administering Injectable Subcutaneous Immunotherapy (SCIT)

As we discussed, allergen injections, either during testing or during immunotherapy, can trigger symptom provocation. Severe reactions, even though infrequent, can occur at any time during treatment, from the moment after the first injection of an intradermal allergy test to any time during dose escalation or maintenance (when immunotherapy dose does not change from week to week).

Sublingual immunotherapy (SLIT) can also trigger symptoms; but despite their relative frequency, symptoms are usually mild.[36]

That asthmatic patients have increased risk for severe reactions with increased risk of mortality should come as no surprise as the inflamed lower airway and hyperreactivity characteristic of these patients can trigger bronchospasm and mucous hypersecretion that can end with respiratory compromise and even death.[19-22]

Assuming that patients with one or more lower airway symptoms that exhibited improvement with ICS have lower airway inflammation and therefore potential lower airway hyperreactivity led us to implement the following precautionary measures when preparing these patients for intradermal testing (IDT) and subsequent immunotherapy administration:

- After clinical evaluation (Table I), an initial spirometry is obtained. Patient is treated with a daily ICS. Clinical and spirometric re-evaluation is done in 3-4 weeks. Once the best response and spirometric value have been ➤

established, the IDT is scheduled. The test will be done in several smaller sessions, challenging only a few allergens at a time. These tests always start with the weakest dilutions. The patient is kept on an ICS during the whole period of intradermal testing and also during the first few months of immunotherapy when dose is escalated, and symptoms come under control. All patients are trained on indications and use of an auto-injector of adrenaline. The patient needs to exhibit proficiency with a dummy device. At each encounter, for testing or treatment, patient needs to show the device to the allergy nurse, otherwise test or shot gets postponed.

- Patients with suspicion of airway reactivity (and those with asthma as well) have their allergy charts flagged. These patients are required to have a dedicated PF meter. Before treatment begins, an average of the PF value is determined. Before each shot, the PF value is measured. If it is not at 80% or more of the averaged value, the allergy shots will not be administered. If the PF is low, the allergy nurse will refer this patient back to the doctor.
- Attempt to discontinue the ICS is done when symptoms appear to be under control. The ICS dose will be lowered; and as long as symptoms do not relapse and spirometric values do not deteriorate, the ICS-weaning process continues. If appropriate, a rescue inhaler, to be carried at all times, is prescribed.

When dealing with asthmatic patients, we follow the same steps as above. Asthmatics are advised to carry the rescue inhaler at all times. It is important to verify that all patients with inflamed lower airway understand the difference between the maintenance and rescue inhalers and how to use them. Testing will not be done unless we have a certainty that the patient is stable.

When immunotherapy dose has been advanced and patient appears stable, the ICS dose will be reduced slowly, attempting to wean the patient from this medication. This requires patient re-evaluation every few months. Provided that the patient remains clinically stable and spirometric parameters do not deteriorate, weaning process continues. Eventually, when the ICS is discontinued, the patient is counselled again about the significance of a rescue inhaler and the need to carry it at all times, for at least a period of two-to-three years without having used it once.

It is our experience that after a few months of immunotherapy, many of the patients with asthma or symptoms of lower airway inflammation do not need inhalers any more and continue to be asymptomatic with improved or stable spirometry.

Role of Immunotherapy in the Management of the Asthmatic Patient

Asthma almost always has an allergic basis.[37] From all triggers (allergens, irritants and infections), allergens are the most important.[23] Immunotherapy is effective to treat asthma[14,17,38] and to prevent progression of AR into asthma.[15,16,38] It is accepted that immunotherapy is the only treatment able to modify the allergic disease and therefore able to alter the natural course of asthma,[14] but immunotherapy is frequently not offered to these patients. This is so despite the evidence that asthma incidence is increasing, knowing that anti-inflammatory medical therapy will not arrest the progression of the disease, knowing that some patients will develop airway remodeling, and knowing that there is a risk for exacerbation with potential mortality.

Because immunotherapy is riskier in the asthmatic patient, consideration of the severity level is important as asthma severity and poor medication control increase the likelihood of a severe attack.[39] But it has also been reported that 58% of the patients that died from asthma only had a mild or moderate disease,[40] which implies that the risk of mortality is not necessarily related to the severity of the disease. This is important, as patients and heath care professionals alike may think that having mild asthma, with minimal use of medications, perhaps affecting the individual only in a particular season or only when doing physical activity is a sign of safety, when this is not so. For example, sudden fatal asthma exacerbations have occurred in competitive and recreational athletes during exertion.[39] Also it is important to understand that ubiquitous allergens like molds, commonly present in indoor environments mainly if damp, can trigger asthma. Many cases of severe asthma with near fatal or fatal outcomes occurred in patients that were allergic to mold. In a report on 11 cases of respiratory arrest due to asthma, 10/11 cases had a positive skin test to Alternaria.[41]

From all this information, it should be expected that immunotherapy would play a predominant role in asthma management, but this is not so. The guidelines for asthma management from the National Asthma Education and Prevention Program[23] and the 2020 updates[28] state that the main objective of asthma management is to find the lowest dose of medication that will lead to symptom-control. Control is based on anti-inflammatory therapy, mostly ICS, but oral steroids are frequently used during exacerbations or when a loss of symptom control develops, knowing that medication use will not prevent disease progression. There is emphasis on environmental controls, considered one of the four cornerstones of asthma management.[23]

Modification of the sufferer's environment, by education on how to decrease exposure at home and/or at work, are obviously important interventions that will help decrease the level of reactivity and the need for controlling medication; but ultimately these interventions will not cure the patient nor arrest the progression of the disease. This can only be attained with immunotherapy.

SCIT is considered, in the asthma guidelines, as an adjunct treatment to standard pharmacotherapy if the patient cannot attain good control with medications, when it is suspected that the person reacts when exposed to a certain allergen and if sensitization to the allergen can be proven by a positive blood or skin test.[23,28] Sensitization is defined as the production of specific IgE, demonstrated in a positive blood or skin prick test. It is stated that SCIT is considered to provide only small benefits; therefore, the patient should consider the risks versus the potential benefits of this modality.[28]

In reference to sublingual immunotherapy (SLIT), there is a conditional recommendation against its use for asthma management[28] because the literature reviewed suggested that SLIT provided only a "trivial benefit" to prevent exacerbations, asthma control, and quality of life; and SLIT frequently produced reactions, either local reactions – in up to 80% of the cases – or systemic. It is acknowledged that no mortality cases were reported in the literature.

According to the asthma guidelines[28] SLIT can be administered as drops or as allergy tablets, emphasizing that the FDA has approved the use of allergy tablets for the treatment of allergic rhinitis and rhinoconjunctivitis but that SLIT as oral (sublingual) drops is not FDA approved.[28]

Allergy tablets are rapidly dissolving tablets that carry only one type of allergen, either grass, short ragweed, or a mixture of two types of dust mites.[42] To prescribe these tablets it is necessary to obtain a positive skin test or in vitro testing for IgE antibodies against the allergen being treated. The package information includes a black box warning stating that patients using allergy tablets should carry an auto injector of adrenaline in case a life-threatening allergic reaction such as anaphylaxis might develop.[42]

At the present time there is no effort in the main allergy community to distinguish between SLIT as the usual mixture of allergens according to the results of an allergy test, and SLIT referring to prescribing allergy tablets. SLIT is used liberally to describe either one of these completely different modalities.

The assumption that immunotherapy may not be very effective could be based on the following:

1. *Allergy test used for diagnosis.* The results of the allergy test are dependent on the type of test used for diagnosis.[10] The RAST-IgE will miss all reactivities that are not mediated by IgE but that still have clinical significance. Only a skin test can diagnose overall reactivity to the allergen mediated either by IgE or by one or more of the other immunological mechanisms. From the skin tests, the intradermal tests are much more sensitive than prick tests as with intradermal tests the allergen is injected in the dermis where the mast cells reside, rather than being applied over the epidermis as happens with the prick tests. Only an Intradermal Dilutional Test (IDT) can safely administer progressively stronger (more concentrated) dosages of the allergen being tested, increasing the possibility of finding a positive skin response. Not using an IDT will miss the majority of the positive skin tests.[31] For practitioners using the IDT, it is clear that most allergens react when a large amount of allergen is injected and injecting strong doses of allergens can be dangerous without knowing the reactivity of weaker allergen doses.[10] This explains the discordance between clinical history and test results, when a patient has clear reactivity to an allergen, but the skin test is negative. In this case, and according to the above guidelines, the patient will not receive immunotherapy. Example: the patient that develops asthma when exposed to cat, or nasal and ocular symptoms when exposed to dust but either the RAST or prick tests are negative.

2. *Concept of the allergy load.* By the concept of Total Body Load,[43] it is suggested that symptoms develop as a consequence of all the pollutants that are inside the body at one time. The more aggressors, the more symptoms. Any aspect of the load that can be removed will lead into some degree of improvement.

The same concept can be applied to allergies. All the allergens to which a patient is reactive determine the patient's "allergy load." Following this concept, removal of as many of the reactive allergens as the practitioner can treat, the better the clinical outcome. Certainly, some allergens will have more clinical relevance than others, but the overall results will be better if many or most of the involved allergens are treated.

Immunotherapy

The only test that enables the practitioner to diagnose most if not all of the reactive allergens is the IDT. If immunotherapy is implemented based on the results of tests of poor performance, only a small portion of the total allergy load will be "removed"; and the results of that immunotherapy will not be very significant.

The objective should be to desensitize the patient to as many of the reactive allergens as possible. Choosing the allergens to be incorporated in the vaccine based on clinical reactivity is not always easy. For example, it is a common finding to see a patient that may develop nasal obstruction and sinus pressure or pain upon going to bed or during wintertime who denies reactivity when exposed to dust. This patient should be suspected of being reactive to one or more of the allergens in the dust and dander panel. If the test proves such reactivity, desensitization to those positive allergens often leads to symptomatic improvement. This type of patient often has one or more chronic, persistent symptoms but lacks the typical symptom-fluctuation of seasonal allergies and may lack typical allergy symptoms like sneezing, itching of eyes, nose, and throat.

These patients frequently are not identified as allergic because the usual tests notoriously fail to demonstrate reactivity to common indoor allergens like molds or even dust mites, and clinical history is not the "typical allergic history." In these cases, immunotherapy

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will usually not be considered. The affected person will be condemned to having poor quality of life with chronic nasal obstruction at night and poor sleep. The significance of the IDT is again emphasized. If the concept of the total allergy load is not considered, many patients that could benefit fully from immunotherapy will not, as many of the allergens will not be diagnosed; or if diagnosed, they may not be deemed important as it is difficult to establish a clinical correlation and therefore those allergens will not be included in the allergy vaccine.

3. *Consideration of the Delayed Reaction.* Even the results of an IDT may be completely negative. In these cases, it is not uncommon to observe that at the site of the injection, a wheal develops many hours after the test. This is known as delayed reactivity. Delayed reactions are not considered of clinical significance by the main allergy community.[44] Despite evidence that they have clinical relevance,[13] few practitioners consider them for treatment.[12] Including the information provided by the delayed reaction improves the degree of improvement or response to immunotherapy treatment.

4. *Referring to SLIT specifically*. It should be imperative that the use of allergy tablets be clearly distinguished from the administration of a mixture of allergens usually (but not necessarily) mixed at the practitioner's office and provided as oral drops to be administered under the sublingual mucosa.

The fact that SLIT is not strongly recommended in the asthma guidelines[23] is probably related to poor results obtained by treating patients with one or just a few allergens. (Monotherapy for allergy tablets, oligotherapy for SLIT – oral drops – as diagnosed by prick or RAST tests).

Dr. Saporta completed his training in 1990 at Columbia Presbyterian Hospital in New York City. He is board certified in otolaryngology and has been a fellow of the American Academy of Otolaryngic Allergy (AAOA) since 2001. His private practice in Elizabeth, New Jersey, is heavily oriented to the management of allergic conditions. Interested in the use of oral vaccines since early in his practice, Dr. Saporta presented a protocol for sublingual immunotherapy at the 64th annual meeting of the AAOA that since then has been successfully used for the management of allergic rhinitis with or without asthma.

My Personal Experience with Immunotherapy

In my experience, immunotherapy is highly successful for the management of allergic conditions, including allergic rhinitis, allergic conjunctivitis, chronic sinusitis (even though some cases will require surgery despite intervention), some ear problems, asthma and even some cases of eczema or other types of skin rashes. SCIT and SLIT were found to be equally effective[45,46] as in both cases the full range of allergens diagnosed by an IDT was used.

SLIT has been reported to be effective for the management of children with asthma.[47-49] In my experience this is a correct statement supported by a report on the use of SLIT in a small group of children with asthma[50] and confirmed over the years by good clinical results when SLIT was administered to asthmatic patients, both children or adults.

When SLIT is mixed based on the results of an IDT, the results are the same as with SCIT[46] with the difference that SLIT is a much safer technique. There are no cases of mortality reported, related to the administration of sublingual immunotherapy.[28,51]

Our technique for SLIT administration[45] is based on daily administration with slow increment of the treatment dose. While some mild reactions can occur, we have never encountered a reaction that required administration of any parenteral medication (glucocorticoids, antihistamine or adrenaline).[36]

Therefore, poor results after immunotherapy are not related to the administration route of the allergy vaccine. It does not matter if the mixture of allergens responsible for a patient's symptoms is given as injections (SCIT) or oral drops (SLIT) rather to the factors above discussed. When only a few allergens are used, either because they are considered the most relevant or just because they are the only ones diagnosed with the allergy test, the clinical improvement will be commensurate with the number of allergens included in the vaccine from the total number of allergens that actually affect the allergy patient.

SLIT should be considered as the treatment of choice when treating the asthmatic patient or a child (with or without asthma) because of its excellent safety profile compared to the risk of a severe reaction when administering SCIT. Of note is that a few cases of severe reactions after SLIT administration have been reported. Review of those reports[36] showed that the patients that developed complications (asthma attacks sometimes requiring emergency room care) were mostly patients that did not tolerate shots – because of reactions – and therefore were switched to SLIT, often using a rush protocol. With this technique of SLIT administration, the dose is rapidly incremented until attaining a pre-established maintenance dose.

Using a protocol characterized by daily administration and slow advancement of the treatment dose, we never encountered a single severe reaction to SLIT (which does not mean this technique will not trigger reactions that require some intervention).[36] The concept of reaching the maintenance dose, for practitioners trained at the AAOA, AAEM or PAAS societies, is a clinical one. The maintenance dose is not a preset dose that needs to be attained, rather it is established by observing the response of the patient over time. Once attained, it is not a set dose, as it can be reassessed and changed if necessary.

Again, immunotherapy is a challenging therapy with potential for reactions, but it is important to underline that not all the administration techniques are the same. For example, and in contrast to the references cited above, a survey done by the AAOA[52] reported that there were no cases of mortality in the survey group and that the overall rate of reactions was 0.3%. Using the technique sponsored by the AAOA, AAEM or PAAS and applying the concepts here discussed provides for a safer way to administer immunotherapy.

Discussion

Immunotherapy should be considered the primary intervention for the management of the allergic patient as it is the only treatment modality that can lead to a resolution of the underlying inflammation present in allergic disease and asthma.

The management of a patient with asthma or with any isolated symptom suggestive of inflamed lower airway is complicated.

As the prevalence of lower airway involvement is rapidly increasing, the concepts here discussed become more relevant. The patient with asthma faces the following difficult situation: Either choosing immunotherapy because it is a treatment that realistically can lead into a cure or choosing to continue using inhalers and potentially other medications (even if only occasionally), knowing that pharmacotherapy will not alter the course of the disease, knowing there is always the specter of a sudden onset severe asthma attack (usually triggered by unexpected exposure to allergens or chemical irritants) regardless of asthma severity, knowing that there is a risk of developing airway remodeling with subsequent life-long impairment and finally knowing that, not frequently but realistically, there is a risk of developing a severe asthma attack with potential serious complications and even risk of mortality.

The conundrum is that the milder the disease, the smaller the risk for treatment complications and the more severe the disease, the higher that risk; but on the other hand, the more severe the disease the more important it should be to decrease and treat the underlying inflammation.

With experience, the allergy practitioner learns to recognize the patient that has an unstable lower airway. These patients should never be tested with any type of intradermal test until symptoms stabilize. To bring a patient under control implies acquiring proficiency in the use of inhaled corticosteroids as monotherapy or in association with long-acting bronchodilators and the use of rescue inhalers. It is also important to pay attention to patient's home and work environments and to patient's diet. Some cases are difficult to stabilize. In those cases, adequate vitamin and supplement support, optimization of thyroid function, and balancing other hormones when indicated are necessary interventions that have been and continue to be discussed in the *Townsend Letter*.

When the lower airway is inflamed, any stimulus can trigger reactivity leading to muscle spasm (bronchoconstriction) and mucus hyperproduction, which are responsible for the development of the usual lower airway symptoms in any combination. If immunotherapy administration is successful, it is often observed that the reactivity to many of those non-specific irritants will decrease and sometimes resolve. These are common observations for cold and exercise, not so common for cases of chemical reactivity.

A key question is why is the airway inflamed? If it is because of exposure to an irritant, removing the patient from the exposure should lead to a cure. Obviously, removing exposure to an irritant will lead to an improvement of patient's symptoms, but it is clinically observed that these interventions are not enough to lead to a cure. So, it is logical to assume that in these cases, the irritant behaves as an aggravating but not a causal factor.

Asthmatic patients, when receiving immunotherapy, should be treated with a slow dose advancement protocol. They should not be tested if they are not well controlled. When treating an asthmatic patient with SCIT, dose progression is often delayed or even reduced if the PF value decreases from expected, or if the patient has fever or any lower respiratory symptom, or if the patient skipped shots. Interrupting the treatment when an asthmatic patient is not controlled is not unusual. Safety is more important than expediency. The objective is to help decrease the inflammatory condition, which will bring symptom control rather than following a rigid protocol of dose advancement regardless of patient's clinical presentation.

The management of an asthmatic patient with SLIT is less troublesome than when using SCIT. Using our protocol,[45] SLIT dose advancement is, in general, uneventful.

Conclusion

To increase safety during immunotherapy administration, it is imperative to recognize the patient that has an inflamed lower airway as these patients are more at risk for reactions that potentially can be severe. This requires a high index of suspicion and the need for an in-depth history taking. This type of patient requires the same type of precautions as with the clearly asthmatic patients before considering testing in preparation for immunotherapy treatment.

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References and article are available online at www.townsendletter.com.