Allergy and Biopharmaceutical Therapy, Part 1: Background and Current Treatment Regimens

Introduction

A fairly good knowledge base concerning various steps in allergic reactions now exists, but despite this knowledge the prevalence of allergic diseases is still increasing: in some areas of the industrialised world up to 50% of the population is affected. More research is needed to further understand allergic sensitisation and how it can be prevented and treated, and novel biopharmaceutical drugs are needed to increase the treatments available to prescribing physicians and their patients. This paper is the first in a two-part series. It describes the pathological role of immunoglobulin E (IgE) in allergic reactions, and how identification of this role has allowed physicians to treat reactions by addressing the underlying immunological mechanisms. The second paper in the series will discuss unique challenges for clinical trials in this therapeutic area.

Prevalence of Allergies

An allergy is the body's immune system response to specific elements in the environment.[1,2] Allergy is characterised by an overreaction of the immune system to a foreign protein, an allergen that somehow finds its way into the body, e.g., being eaten, breathed into the lungs, injected, or touched. This overreaction can result in a wide range of symptoms, e.g., coughing, sneezing, itchy eyes, runny nose, and scratchy throat. In severe cases it can also result in rashes, hives, lower blood pressure, difficulty breathing, asthma attacks, and even death.[3]

The following information and statistics, presented on the Allergy and Asthma Foundation of America's website[3] makes the importance of prevention and treatment very clear, since there are no known cures for allergies:

- An estimated 60 million Americans (20%) suffer from some types of allergies: this is approximately twice as many as suffer from diabetes, and many times more than suffer from other high-profile diseases such as Alzheimer's disease.
- Allergy is the fifth leading chronic disease in the US among all ages, and the third most common chronic disease among children under 18 years old.
- Approximately 40 million Americans have indoor/outdoor allergies as their primary allergy. Approximately 10 million people are allergic to cat dander, the most common pet allergy. The most common indoor/outdoor allergy triggers are: tree, grass and weed pollen; mould spores; dust mite and cockroach allergen; and, cat, dog and rodent dander.
- Approximately 6% of allergy sufferers have food/drug allergies as their primary allergy. Food allergy is more common among children than adults (as are many allergies). 90% of all food allergy reactions are caused by eight foods: milk, soy, eggs, wheat, peanuts, tree nuts, fish and shellfish. For drug allergies, penicillin is the most common allergy trigger.
- Each year, allergies account for more than 17 million outpatient office visits, which show seasonal influences. Skin allergies account for more than 7 million outpatient visits each year.
- Food allergies account for 30,000 visits to the emergency room each year.
- Each year, nearly 400 Americans die due to drug allergies from penicillin, around 200 die due to food allergies, and nearly 100 die due to insect allergies.
- Allergies have a genetic component. If both parents have allergies it is much more likely that their children will have allergies than if only one parent has allergies.

Table 1 provides various examples of causes of allergenic physiopathology.

Table 1: Examples of Causes of Allergenic Physiopathology

Category	Examples
Inhalants	Mites: Der. Pteronissiums, farinae, … Pollens: Grass (ryegrass, timothy-grass), weeds (ragweed, plantago, nettle, artemisia vulgaris, chenopodium album, sorrel), trees (birch, alder, hazel, hornbeam, aesculus, willow, poplar, platanus, tilia, olea, Ashe juniper), animal danders (cat, dog, rabbit, horse), fungal (moulds, yeasts), insect waste (bee, wasp).
Food	Milk, peanuts , tree nuts, fish, crustacea, eggs, soyabeans, sesame, celery and some fruits (apples, peaches…)
Occupational sources	Isocianates, flour, grain, resins, metals.
Pollutants	Both outdoor (carbon monoxide, nitrogen monoxide or nitric oxide, metals) and indoor (indoor gas pollutants)

Immunoglobulin E

Allergens are antigens which induce and react with specific immunoglobulin (Ig) antibodies. Antibodies are proteins that are used by the immune system to identify, attack, and neutralise xenobiotics, i.e., foreign substances in the body. These include bacteria and viruses, and neutralisation of these substances is a desirable outcome. They also attack allergens, but if this immune system response is too strong, allergies and hypersensitivities can occur. IgE antibodies are found in the human lungs, skin, and mucous membranes.

Immunoglobulin E (IgE) is one subclass of antibodies. Given that allergic responses typically affect the

skin, gut, and respiratory tract, the major sites of parasitic invasion, it is thought that IgE evolved in humans as a defense against parasitic infestation.[3] The IgE test measures the blood level of IgE, one of five subclasses of antibodies. It is often performed as part of an initial screen for allergies.

Symptoms of allergies may include hives, itchy eyes or nose, sneezing, nasal congestion, tight throat, and trouble breathing. Some patients suffer from mild symptoms, but others may suffer life-threatening allergic reactions. In general, the quality of life of allergic patients is impaired, although some symptoms may be seasonal (those due to pollen or moulds) or year-long (e.g., mites allergies, animal or food allergies). It is quite unlikely that allergic patients only present one symptom through their life: rather, the "atopic march" is common, as shown in Figure 1.

Skin Tests for Identifying Allergen Sensitivity

There are several kinds of tests for identifying allergen sensitivity. The rationale is to induce the reaction with the studied allergen. The patient's medical history will guide which test must be performed. They can be performed in skin, eyes, bronchial regions, and also via food challenges. As an example, Table 2 summarises the different types of skin test.

Consider one kind, the skin prick tests. These tests provide an inexpensive, rapid, and accurate method of identifying allergen sensitivity, and they are the most commonly performed tests. The mechanism of action behind their employment is that mast-cell activation causes a characteristic 'weal and flare.' There is the possibility of both false positive results ('identifying' an allergic response that in truth is not present) and false negative results (failing to identify one when in truth one is present). Therefore, positive and negative controls are always incorporated into the testing procedure.

There is a long-standing tradition of extrapolating data from the skin to the airways in clinical practice, largely based on correlations between skin and upper respiratory effects of antihistamines. But skin tests can be affected by a multitude of factors. These include the quality of the extract, the age of the patient (responses in the elderly are generally less than for other age groups), seasonal variation (skin sensitivity increases after the pollen season and then declines until the next season), and pharmaceutical medicines. Additionally, while a positive skin prick test response identifies sensitisations to a particular allergen, it does not determine the clinical relevance of this sensitisation. On the other hand, a negative skin prick test response has an excellent negative predictive value for excluding IgE reaction. As one last consideration here, the clinical relevance of inhalant allergen sensitisations may differ significantly depending on the allergen.

Correlations between Different Tests

Serum-specific IgE, skin prick tests, and allergen challenge do not have the same biological and clinical relevance and are not interchangeable. The weakest correlations have been obtained with mould, food extracts, and non-standardised extracts. There are significant correlations between a strongly positive response to a skin test and the detection of serum-specific IgE, and also between a negative response to a prick test and the lack of detection of serum-specific IgE.

However, small weals induced by prick tests and positive results of intradermal tests with concentrated extracts are less frequently associated with the detection of serum-specific IgE. Moreover, low levels of serum-specific IgE are less

Figure 1: The Atopic March

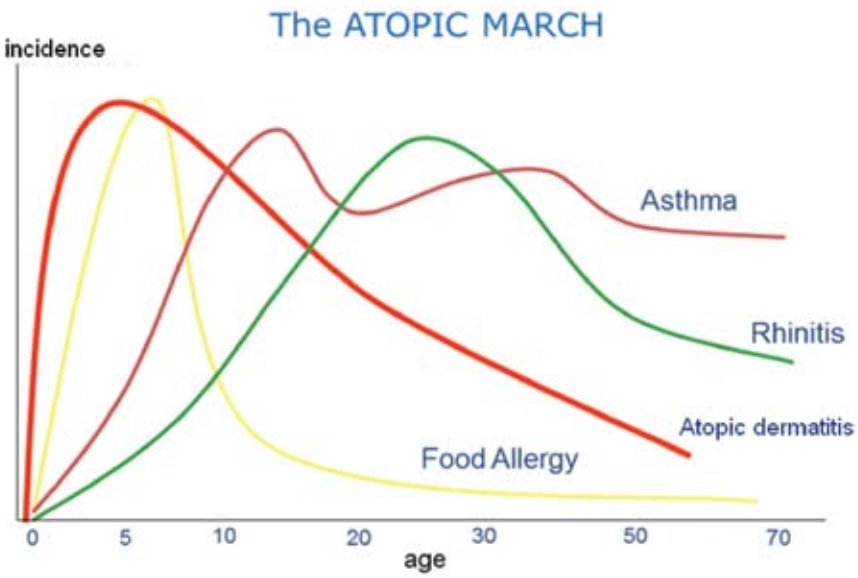

Table 2: Examples of Allergy Skin Tests

Category of test	Description
Prick	Involves introducing a small amount of allergen into the skin by making a small puncture through a drop of the allergen extract. Test results are available within 15 minutes of testing, and the wound heals within 30 minutes.
Prick-prick	These tests with fresh fruits were introduced to reduce the poor standardisation of food extracts commercially available. They are not standardised and should be restricted to foods for which no recombinant allergen is available.
Intradermal	Involves injecting a small amount of allergen under the skin with a syringe. This form of testing is more sensitive than the prick skin test method, and may be used if the prick skin tests are negative.
Patch	Involves epicutaneous patch tests with allergens known to elicit IgE-mediated reactions. Commercial reagents are available for a few allergens. They have been standardised regarding the use of vehicle and dose–response relationships.
Scratch	Involves abrading the skin and then dropping the allergen on the abraded site. (Note: This test should no longer be used because of poor reproducibility and possible systemic reactions.)

often associated with symptoms than higher levels, but they do not exclude allergic symptoms. Correlations between responses to skin tests or serum-specific IgE and nasal challenges are less consistent because of the non-specific hyperreactivity.

Currently Available Therapies

Antihistamines have been used for years as a mainstay for the treatment of allergies, including allergic rhinitis.[4] There are many different oral antihistamines, which are classified as first generation or second generation depending upon their pharmacologic properties and side-effect profiles. Antihistamines are available as oral, topical and nasal spray.

Allergic rhinitis and asthma share a common airway, common mediators, cytokines, and chemokines from mast cells and basophils that are of central importance to the inflammatory response and the series of events that lead to it.[5] As Bachert et al. noted, histamine is the "salient mediator released after immunologic challenge, initiating multiple pathologic processes of the allergic reaction that result in bronchial smooth muscle contraction, vasodilation, mucus hypersecretion, and edema."[5] These authors reviewed 14 clinical trials of second-generation non-sedating antihistamines, and concluded that H1-antihistamines attenuate the symptoms associated with early- and late-phase allergic reactions. Taken together with inhaled anti-inflammatory compounds and bronchodilators, clinical evidence indicates that H1-antihistamines may have a beneficial effect on asthma symptoms and improve quality of life (QoL).

Zazzali et al.[6] reviewed the cost, utilisation, and treatment regimens associated with chronic idiopathic urticaria. Urticaria is characterised by hives or weals. The term idiopathic indicates that the precise underlying mechanisms of a patient's chronic condition are not known. They found that antihistamines were the most common treatment, although oral corticosteroids were also commonly prescribed.

Therapeutic monoclonal antibodies (mAbs) are increasingly receiving marketing approval. Reichert[7] presented data for 34 mAbs that were approved in either Europe or the United States as of March 2012. One of them was omalizumab, a humanized monoclonal antibody that binds circulating IgE antibody. Omalizumab reduces IgE-mediated airway inflammation, and as such is a treatment option for patients with moderate to severe allergic asthma whose asthma is poorly controlled with inhaled corticosteroids and inhaled long-acting ß2 agonist bronchodilators.[8]

New approvals by the FDA (May 2012) include the combination of antihistamine + corticosteroid as a fixed combination nasal spray. This approval opens a new combination therapy that was not available yet as a single compound, although was commonly used as individual elements together.

Allergen-specific immunotherapy is the only approach which may alter the natural course of allergic diseases. Subcutaneous immunotherapy appears to be effective several years after its cessation. During the last decades, allergen-specific immunotherapy was traditionally administered by the subcutaneous route. Now, more convenient oral routes have been developed (oral drops, sublingual administrations).

Further Drug Development for Allergy

Given the very high prevalence of allergic reactions, as noted previously, there is still a large unmet medical need in this therapeutic area. Further drug development is needed. However, there are unique challenges in the clinical trials required to bring such drugs to market. Part 2 of this mini-series will address these.

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