Progress in The Management of Allergic Diseases

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Improved techniques in molecular biology have led to a rapid progress in the understanding of the patho genesis of allergic diseases during the past two decades. It is not only the understanding of the types of T helper cells (TH_1 and TH_2 cells) and their cytokines but also their gene products and their transcriptions that help to propel scientists as well as clinicians to search for new modalities of treatment for allergic diseases. It is now firmly established that T helper cell type-2 (TH_2) and their cytokines (mainly IL-4 and IL-5) are directly related to severity of allergic diseases such as in asthma.[1] IL-4 stimulates B-cells to isotype switch to produce IgE whereas IL-5 stimulates the development and prolongs longevity of eosinophils. IgE, thereafter, interacts with allergens and other effector cells (such as mast cells, basophils, eosinophils, macrophages, and others) to release mediators of inflammation (such as histamine, prostaglandins, leukotrienes, etc.). These mediators produce vasodilatation, plasma leakage, and stimulation of nerve endings and chemotaxis of further cellular components of inflammation (eosinophils, neutrophils, macrophages, lymphocytes and others) to enhance degree of allergic inflammation. The net results are symptoms and signs of allergic diseases such as in asthma, allergic rhinitis and atopic dermatitis.

Anti-IgE

Since there are firm evidences to support the link between serum IgE level and severity of allergic diseases,[2-4] attempts have been made to modify disease manifestion by interfering with IgE-IgE receptor interaction. Such attempt was made possible by the synthesis of a hybrid molecule of anti-IgE such as omalizumab. Omalizumab is the combination of mouse and human component of anti-IgE (IgG) produced by a recombinant technology (Fig 1).[5] It recognizes IgE through is interaction with CH_2-CH_3 domains of the Fc portion of IgE molecule. Injection of omalizumab into laboratory animals completely abrogated serum free IgE to a very low level.[5] In human, both adult and childhood asthmatics, omalizumab decreased asthma symptoms, doses of inhaled and systemic corticosteroids as well as improved quality of life among treated subjects.[7,8] It is now licensed for treatment of moderate to severe allergic asthma in the United States. Similarly, omalizumab was found to be effective in reducing symptoms of allergic rhinitis during pollen seasons as well as decrease side effects of specific immunotherapy for allergic rhinitis.[9,10] Another anti-IgE product, the TNX-901, was found to be effective in preventing severe food-induced reactions among peanut-sensitive individuals.[11] Thus, anti-IgE will have an expanded role in the treatment of varieties of allergic diseases in the future.

Combination therapy between long-acting, beta-agonists (LABA) and new generation of inhaled corticosteroids (ICS) in asthma

Long-acting beta-agonist such as salmeterol and formoterol, besides their prolonged duration of effects (up to 12 hours), interact with a chaperone protein-glucocorticoid receptor complex in cytoplasmic environment to release active glucocorticoid receptor (GCR)[12]. Active GCR, then, possesses an improved affinity to interact with glucocorticoid molecule. Such knowledge has led to trials to compare combination of LABA+ICS with high dose ICS in severe asthma. These studies well demonstrated that combination therapy out-performed high dose ICS in improving lung function as well as symptom reductions and preventing asthma exacerbations (Fig 2).[13,14] Recently, a similar trial in pediatric population confirmed such efficacy of combination therapy[15]. Marketing of these new products has dramatically revolutionalized asthma treatment (with a much more simplistic approach of asthma therapy) and brings about a much improved quality of life among severe asthmatics. In children, such combination has led a much easy-to-follow regimen of therapy and subsequently, an improved compliance. These combinations (salmeterol+fluticasone-Seretide™ and formoterol+budesonide-Symbicort™) are available both in metered-dose as well as dry powder inhaler formulations.

Sublingual Immunotherapy (SLIT)

Specific allergen immunotherapy (SIT) was introduced in 1912 by Noon and Freeman for the treatment of allergic rhinitis.[16] It soon followed that such therapy was also effective for allergic asthma although negative studies existed.[17-18] Abramson and colleagues, in the Cochrane analyses, performed meta-analyses and confirmed the efficacy of SIT in asthma.[18] It was determined that SIT was highly efficacious among those sensitized to house dust mites and it was necessary to treat three individuals to prevent an asthmatic attack. SIT, given in its conventional form (subcutaneous injections, weekly to monthly) is inconvenient and could lead to systemic anaphylactic reactions.[19] SIT given through sublingual route (SLIT) was then tried both in adult and childhood patients over the past two decades. Positive results were documented among cases with allergic rhinitis and asthma.

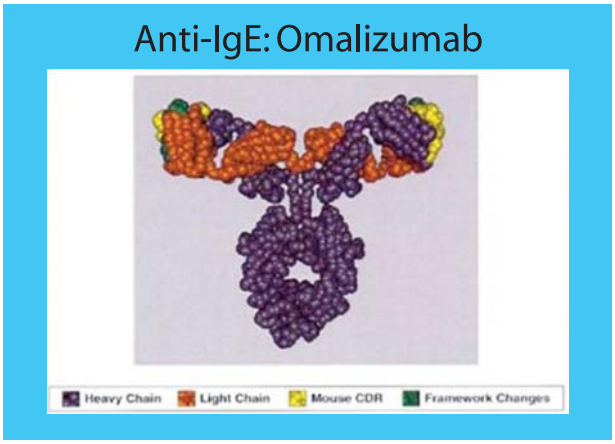

Fig 1. Structure of Omalizumab - the anti-IgE molecule.

Recently, a meta-analysis was conducted and confirmed the efficacy of SLIT in both conditions.[20] SLIT is associated with lower incidence of side-effects both locally and systemically. It is, however, administered more frequently, at higher dose compared to conventional subcutaneous SIT. SLIT therefore is anticipated to be associated with higher cost of allergy vaccines than conventional SIT. However, this will be offset by a decrease cost of treatment for side-effects and decrease cost of visits to physician offices since it could be administered at home. It would be an ideal therapy in young children with allergic diseases, particular those who are highly allergic and also have evidences of atopic march (a progress of one form of atopic disease to another, particularly from atopic dermatitis to allergic rhinitis and/or asthma).

Topical immunodulators

Inhaled corticosteroid is a preferred mode of drug therapy to avoid systemic absorption and side-effects of parenteral administration of these drugs. Other immunomodutors brought into the treatment of allergic diseases were methotrexate, azathioprine, cyclosporine and intravenous immunoglobulin. Actions of these agents mainly interfere with activation of T cells and therefore leading to reduction of productions of cytokines involved in the pathogenesis of allergic inflammation. Perhaps, the most successful and revelant application of such approach is an introduction of topical calcineurin-inhibitors (CI) in the treatment of atopic dermatitis. Since, cyclosporine was not found to be active when applied topically to the skin, other CI's such as pimecrolimus and tacrolimus were tried with dramatic successes.[21] These agents interfere with T-cell activation and thus reduce of IL-4, IL-5 production. Dramatic improvement of skin lesions of atopic dermatitis could be observed within one week of initiation of the drug.[22] Reduction of pruritus is achieved rapidly with these agents applied to itchy skin. Substitution of topical cortico-steroids with these agents is desirable to prevent complications of topical steroids such as thinning of skin, striae formation and systemic absorption through extremely inflamed skin. Although, serious side-effects of these agents, such as carcinoma and hematologic cancer, could be found in laboratory animal, Advisory Board from both the American College of Allergy, Asthma and Immunology as well as the American Academy of Allergy, Asthma and Immunlolgy have recently issued a statement supporting safety of these agents in atopic dermatitis.[23]

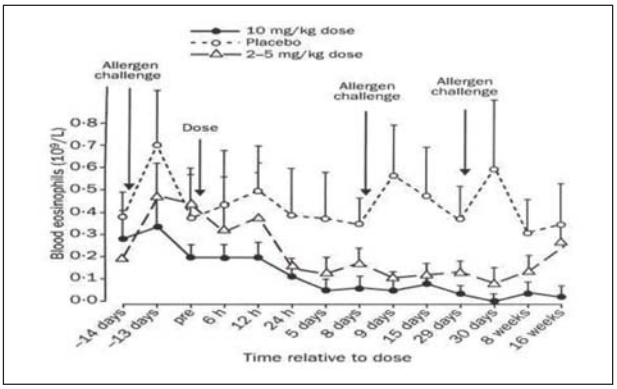

Fig 3. Effect of Increasing doses of anti-IL5 on peripheral blood eosinophils in human subjects with asthma. Although significant suppression of peripheral eosinophil release was seen even after allergen challenge by anti-IL5, no suppression of PC20 was evident. From Reference # 26

Anti-cytokines (anti-IL4 and anti-IL5)

During the past three decades, concept of allergic inflammation has dominated the thinking of most scientists in the pathogenesis of allergic diseases, particularly in asthma. Eosinophils, once thought to be scavenger cells, have been demonstrated to be main effector cells involving in the mechanism in causing injury to airway epithelium in asthma with a subsequent increase in bronchial hyperactivity.[24] Since IL-5 has been shown to be the key cytokine for eosinophil maturation, activation and their prolonged survival, anti-IL5 was synthesized by a recom-

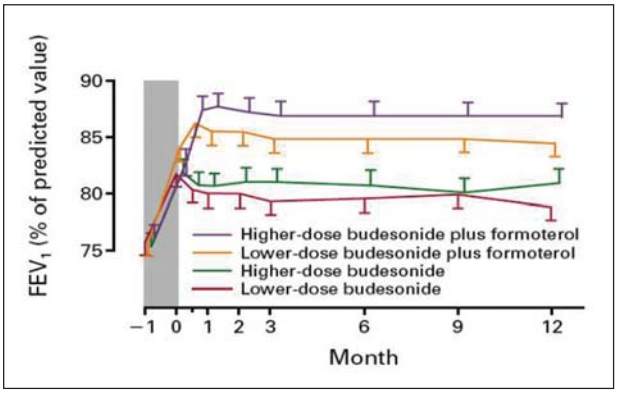

Fig 2. Changes of FEV1 in asthmatics randomized to receive either lower-dose (100 μg) or higher-dose (400 μg) of budesonide with or without formoterol. From Reference #14

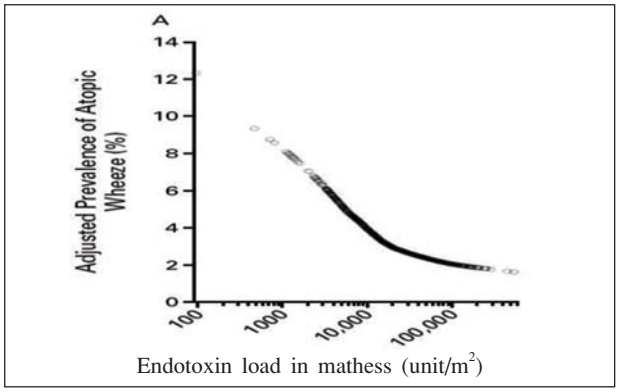

Fig 4. Association of adjusted prevalence of atopic wheeze with endotoxin load in mattress among children who lived in a farming environment. From Reference #31

binant technology and an early trial in a murine model of asthma has shown that this agent was effective in reducing blood eosinophil and a subsequent reduction of a late phase, allergen challenge reaction.[25] Surprisingly, a key trial of anti-IL5 in human failed to support such animal findings (Fig 3), i.e., no reduction of late-phase, allergic asthma reaction despite a profound drop in blood eosinophil count in human challenge.[26] It is possible that in human anti-IL5 acts in conjunction with other cytokines in producing asthmatic reactions. Currently, all trials involving anti-IL5 have been halted.

On the other hand, anti-IL5 was found to be highly effective in treating idiopathic hypereosinophilc syndrome, an entity of unknown etiology with a poor prognosis.[27] Like IL-5, IL-4 plays a major role in allergic inflammation through its stimulation of B cells to produce IgE. Early trials of anti-IL4 in asthmatics given through inhalation route showed a promising result.[28] However, a large unpublished trial failed to confirm such early result and led to a termination of all use of anti-IL4 in asthma. These failures of anti-cytokine trials in asthma indicated that in allergic diseases such as asthma, allergic rhinitis and atopic dermatitis, multiple involvements of pathways of inflammatory mediators, cytokines, chemokines, adhesion molecules occur. It is unlikely that a single use of anti-cytokine or anti-mediator will be extremely successful in the treatment of allergic diseases. The exception of which is, of course, the use of anti-IgE which interferes with allergy inflammation mainly in the upstream position of the inflammatory cascade.

The Hygiene Hypothesis

David Strachan forwarded a theory that with an improved hygiene environment, allergic inflammation is enhanced perhaps through the interference of normal perinatal switch of TH_2 dominance to TH_1 dominance in early life.[29] TH_2 environment is necessary for a successful pregnancy through its cytokine actions (IL-4, IL-5 but not IFN-γ) occurs through stimulation of enteric bacteria and other infections in infantile period mainly through bacteria which produce endotoxin. Endotoxin (lipopolysaccharide) stimulates the production of IL-12 (the main TH_1 cytokine) through its interaction with Toll-like receptor-4 (TLR-4) at cell membrane of T cell progenitors.[30] IL-12 then activates and promotes the switching of TH_0 into TH_1 rather than TH_2. Progress into an allergic condition is then halted by such bacterial stimulation during early childhood period, through such bacterial exposures. Children who are raised with a better hygienic environment are then devoid of such balance and are exposed to a higher risk for development of allergic diseases, hence the name "Hygiene Hypothesis". Such hypothesis has recently been substantiated and confirmed in several elegant studies such as that by Braun-Fahrlander, et al among European children raised in a farming environment vs. those living in urban environment.[31] Prevalence of asthma was found to be much higher among urban children than among children in rural area. There was an inverse correlation between endotoxin level found in dwellings of these children and observed prevalence of asthma (Fig 4). Moreover, there was a direct relationship between endotoxin level and TH_1 cytokine production (IL-12, IFN-γ) among these children confirming the rationale behind the Hygiene Hypothesis. Early simulation of these force of nature was attempted by use of probiotics among mothers and infants who were at high risk for developing allergic diseases.[32] There was a decrease in the incidence of atopic dermatitis among treated families. It such studies are confirmed, there will be a possible way to curb a rise in prevalence of atopic diseases observed globally throughout the past three decades.

In conclusion, exciting scientific discoveries have occurred recently in the field of allergic diseases both on an epidemiologic ground and on a molecular basis. It is envisioned that rapid application of these knowledge in the treatment and prevention of allergic diseases will occur in a very near future. It is therefore necessary that general practitioners keep abreast with such knowledge to familiarize oneself to newer modalities of therapy which will be rapidly introduced within the next few years.

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