REVIEW ARTICLE

New horizons in allergy diagnostics and treatment

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KEY WORDS

allergy, asthma, new treatments

ABSTRACT

Numerous studies show that both physicians and patients look forward to new therapies for allergic diseases. Since antileukotrienes and omalizumab were introduced to asthma treatment, no new class of drugs has been approved for use in asthma or allergic rhinitis. Drug development in allergy covers several pathways, most of which are quite promising. In this review, some aspects of new drug development are discussed. New drug classes, such as cytokine antagonists, kinase inhibitors, and transcription factor antagonists, may soon be introduced as treatment options for allergic diseases. Moreover, new anti-immunoglobulin E antibodies and phosphodiesterase-4 inhibitors have been recently introduced and a rapid development in molecular diagnosis of sensitization has been observed. Unfortunately, the available studies have not provided new methods for the prevention of allergic diseases.

Introduction Over the last decade, the number of patients with allergy and newly diagnosed asthma reached a plateau. However, the prevalence of allergic rhinitis in children is increasing in Europe,[1,2] and so is the number of patients diagnosed with food allergy.[3,4] The above data may suggest that we are facing the second wave of allergy tsunami. The first one came in the late 1980s and early 1990s, mostly due to an increase in the prevalence of asthma both in children and adults. Epidemiologists, educators, scientists, and allergists should think of intervention tools to prevent early childhood sensitization and development of food allergy.

Allergy prevention and early treatment Considering that the prevalence of allergic rhinitis and food allergy is increasing, new methods focused on allergy prevention rather than treatment are needed. During the last decade, several papers have been published reporting pre- and posnatal administration of *Lactobacillus rhamnosus* (LGG) or *Bifidobacter lactis* (BL) in pregnant women, newborns, and children at risk as a method of preventing atopic dermatitis and future allergic sensitization.[5] Interestingly, there are relatively strong animal and experimental data suggesting that LGG or BL may decrease allergen-specific immunoglobulin (Ig) E response and its production via Toll-like receptors, diminish the synthesis of T-helper 2 (Th2) cytokines, and suppress airway inflammation. Moreover, it also enhances IgA production, which may be beneficial in allergen-exposed patients. Several large pre- and postnatal studies reported a moderate effect of LGG on the prevalence and severity of atopic dermatitis, and none of the studies have shown a preventive effect on sensitization or the prevalence of other allergic diseases.[6-9] A recent study by Jensen et al.[10] has shown no effect of postnatal administration of *Lactobacillus acidophilus* on the prevalence of any physician-diagnosed allergic diseases. An enterovirus vaccine as a factor that may prevent allergic sensitization has been recently patented in the United States, but we are still awaiting data from recent large clinical trials. Early data coming from one such trial showed that the vaccine was effective in certain populations of children.[11]

A large Danish cohort study suggested that peanut and tree nut consumption during pregnancy may decrease the risk of asthma in children to the age of 18 (odds ratio, 0.66; 95% confidence interval, 0.44–0.98).[12] For children already diagnosed with food allergy, oral and sublingual immunotherapy with milk and peanut allergens may be an effective treatment of choice as shown in recent studies.[13] Although the protective effect decreases in some patients after the treatment is stopped, immunotherapy as a preventive

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method might be still the treatment of choice in food allergy. An interesting trial showed that patients on a baked egg diet were 14.6 times more likely to develop regular egg tolerance than controls (P <0.0001).[14]

All the above studies suggest that the future of allergy prevention is still unclear and the intervention with oral or sublingual immunotherapy may be the only approach to prevent the epidemics of food allergy.

Allergy diagnostics In IgE-mediated allergy, diagnostic skin-prick tests, allergen-specific IgE levels, and oral food challenge, evaluated together with allergen exposure data, are the basis of clinical diagnosis. Recent studies have shown that allergen microarray chips are the novel tools for high-resolution IgE profiling in patients with atopic dermatitis and in multisensitized adult patients with respiratory symptoms,[7] and lead to a more precise diagnosis of sensitization.[15-20] According to one publication, allergen chips might be especially useful in defining the principles of food allergy and cross-reactivity. They are commercially available and might be extremely useful in diagnosing sensitization to a number of allergen components. This, compared with clinical data, may move allergy diagnostics from the diagnosis of allergen sensitization to the identification of allergen components that participate in the pathogenesis of a disease in a given patient.

Hong et al.,[21] in a recent paper published in the *Allergy*, have shown that IgE against Ara h 2 may help discriminate between patients with clinical allergy to peanuts and patients with asymptomatic allergic sensitization. However, this test could not differentiate peanut anaphylaxis from nonanaphylactic peanut allergy. In a recent study, isolated sensitization to Ara h 8 suggested that a patient might tolerate roasted peanuts.[22] In a small clinical trial component resolved IgE testing helped elucidate the pattern of double positivity in venom allergy. This technique is very promising and may provide a useful tool for clinical practice. For the first time, allergists may use a laboratory test to discriminate between asymptomatic sensitization and clinical allergy. Microarray chip detection of IgE sensitization to allergen epitopes is the most important development in allergy diagnostics since IgE discovery in 1966.

Treatment **Anti-IgE and CD63var therapy** Omalizumab, an anti-IgE treatment, has been used in the treatment of poorly controlled severe asthma for almost a decade. Recently, several successful trials with omalizumab in chronic urticaria and food allergy have been published.[23-27] Novel anti-IgE antibodies have been recently developed with better properties to reduce circulating IgE.[11] Histamine release from basophiles is not only related to IgE cross-linking but also to cell activation via IgD bound to the cell membrane. Circulating allergen-specific IgDs were found in the serum of patients with an allergy to birch and timothy pollen. Recently, an anti-IgD antibody has been developed and the preliminary data suggest that it may decrease histamine release from basophils.[28] The concept is interesting but we have to wait for evidence from clinical trials. CD63 is a well known marker of activated masts cells. It is often used in research focusing on mast cell activation. The monoclonal antibody against the CD63 variant may be used to control and reduce the level of circulating mast cells.[29] No clinical trials have been performed so far to prove this concept.

Immunotherapy Specific-allergen immunotherapy has been used in allergic rhinitis, venom allergy, and asthma treatment for more than a century. The available data suggest that this approach may not only decrease symptoms and drug consumption but also prevent new sensitizations. Recent trials have suggested that immunotherapy is effective in allergic conjunctivitis and food allergy. Moreover, allergen modification (e.g., pepsin-digested peanut allergen) or the use of recombinant allergens is associated with higher safety and better efficacy.

Der p 1, Der f 1, Der p 2, and Der f 2 recombinant allergen fragments were used in immunotherapy in patients with allergic rhinitis sensitized to house dust mites.[30,31] Similar trials were done with Ara h 2 peptides in the treatment of nut allergy and in Fel d 1 peptides in patients with allergic rhinitis sensitized to cat allergens.[32,33] Peptides are designed to retain T-cell receptor binding affinity but they are unable to bind to IgE and B-cell receptors. Experimental data have shown that this approach may decrease Th1 cytokine synthesis and increase interferon-γ production. Clinical trials will hopefully prove its safety and efficacy. This approach may lead to the development of more personalized allergy treatment.

Infusion pumps are widely used in subcutaneous delivery of insulin and painkillers. Recently, the use of a subcutaneous infusion pump to deliver subcutaneous allergen-specific immunotherapy in rush immunotherapy in the hospital has been proposed. This may be a particularly useful invention, which may soon be introduced into clinical pratice.[11]

Novel treatment options for bronchial asthma and allergic rhinitis Several recently completed clinical trials with new inhaled glucocorticosteroids (GCs) and long-acting β-agonists (LABAs) support once-daily use of new agents in asthma treatment. There are also several ongoing clinical trials on a 3-drug antiasthma therapy (GCs and LABAs plus long-acting muscarinic antagonists).

New molecules in asthma treatment comprise anti-Fas antibodies and anti-Fas receptor-related kinase inhibitor. These molecules reduce the development and activation of mast cells. Successful trials with this compounds have been conducted in the field of rheumatology. In asthma, the ongoing trials are in the recruitment or treatment

phase. Recently, several compounds mimicking GC actions have been developed and patented. Most of them affect the activator protein 1 (AP-1) or NF-κB transcription factors binding to the promoters of proinflammatory genes decreasing their transcription. Thus, these peptides may have anti-inflammatory properties. No clinical studies are available to prove the efficacy and clinical tolerance of AP-1 and NF- κB antagonists.[11] Similarly, Gβγ inhibitory peptide may serve as an agent increasing the cAMP level in the smooth muscle when administered in inhalation, causing smooth muscle relaxation. This may be a new class of antiasthmatic drugs. So far, a similar action is obtained in chronic obstructive pulmonary disease (COPD) by the use of phosphodiesterase-4 (PDE4) inhibitors.[34-36] The area of modifying the action of β_2-adrenergic receptors seems to be very promising. Also, several new PDE4 inhibitors are currently being developed and await clinical trials in obstructive airway diseases.

A number of compounds affecting the proinflammatory cytokine levels or actions have recently been developed. Antitumor necrosis factor (TNF) treatment is used in rheumatoid arthritis, psoriatic arthritis, and Crohn's disease. Several successful trials have been conducted in severe asthma with anti-TNF receptor blocker (etanercept) or anti-TNF antibodies (infliximab or golimumab). These data guided researchers to use a similar approach in the treatment of allergic rhinitis and allergic conjunctivitis. Locally used anti-TNF compounds (nasal spray or eye drops) together with locally used second-generation antihistamine drug, might be a novel treatment for allergic rhinitis and conjunctivitis. The animal studies conducted so far provide promising results. Th17 cells and interleukin (IL) 17 play a role not only in autoimmune diseases but also (mainly IL-17F) in mast cell activation, mucosal inflammation, and possibly in airway remodeling. Recently, several anti-IL17F antibodies have been developed and tested in in-vitro models.[37-40] This approach might be useful in COPD treatment or in asthma neutrophilic phenotypes. The role of IL-13 in allergy and asthma have been well-established for more than 15 years. Recently, several anti-IL-13 antibodies have been developed and dual IL-4/IL-13 inhibitory protein has been tested in in-vitro and animal models. Interestingly, the last protein compound was designed to be delivered as an inhalation powder.[41-43]

The role of Toll-like receptors in allergy prevention and treatment had been established even before the receptors were cloned and identified. The Strachan's hygiene hypothesis is a cornerstone in the pathogenesis of allergic sensitization and development of impaired Th1/Th2 cell and cytokine balance. Unfortunately, several approaches to utilize Toll-like receptor agonists (mostly as CpG nucleotides), applied mainly in allergen-specific immunotherapy, failed to be effective. We are still awaiting a safe and efficient Toll-like receptor agonist that might be used especially in the prevention of primary allergy prevention.

TABLE Novel therapies in asthma and allergic rhinitis

AP-1 inhibitory peptide
NF-κB inhibitor
JAK/STAT kinase inhibitors
IL-4/IL-13 dual inhibitor
IL-17F antagonists
novel anti-IgE antibodies
local administration of anti-TNF treatments
anti-Fas/anti-Fas ligand proteins
protein G modulators
c-kit antagonists
novel PDE4 inhibitors

Abbreviations: AP-1 – activator protein 1, IgE – immunoglobulin E, IL – interleukin, JAK/STAT – Janus kinase / signal transducer and activator of transcription, PDE4 – phosphodiesterase-4, TNF – tumor necrosis factor

Vitamin D in allergic diseases During the past 3 years, investigators have been trying to establish the effect of 1,25-dihydroxyvitamin D_3 on the risk of asthma and the severity of asthma and COPD. A few clinical intervention trials with vitamin D_3 are ongoing in severe asthma and COPD.[44-46] Hopefully, in a few months' time, it will be clear whether a low vitamin D_3 concentration affects the severity of inflammation in airway diseases or whether this is just an epiphenomenon. Moreover, several primary prevention trials involving vitamin D_3 supplementation are currently recruiting patients.

Prospective therapies in asthma and allergic rhinitis are summarized in the TABLE.

Conclusions Although the overall prevalence of allergy in the Western countries is not increasing, its clinical picture is changing. The outbreak of food allergy has now affected also the continental Europe. Therefore, new tools are needed to make allergy diagnosis more precise. Fortunately, allergy chips made the molecular diagnosis of allergic sensitization available. However, currently, there are no new approaches to diagnose type IV allergy or to prevent allergic sensitization. Therefore, new developments and research are crucial in this area to prevent new sensitization. This is the only way to stop an increasing number of new patients suffering not only from asthma but also from allergic rhinitis and food allergy. Several new treatments are currently being developed. The most promising approach is the use of local treatment in asthma, rhinitis, or conjunctivitis utilizing newly developed anticytokine or antitranscription factors or signal transducer inhibitors. Thus, the future belongs to local treatments of allergic diseases with biological agents. A number of these agents are now in clinical studies. Within the next few years, several of them might become available as a prescription drug.

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ARTYKUŁ POGLĄDOWY

Nowe horyzonty w diagnostyce i leczeniu chorób alergicznych

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SŁOWA KLUCZOWE

alergia, astma, nowe leki

STRESZCZENIE

Dane z wielu badań wskazują na to, że lekarze i pacjenci oczekują nowych sposobów leczenia chorób alergicznych. Po wprowadzeniu do terapii leków antyleukotrienowych oraz omalizumabu właściwie nie zarejestrowano żadnych nowych leków do leczenia astmy czy alergicznego nieżytu nosa. Postęp w dziedzinie poszukiwania nowych leków w chorobach alergicznych odbywa się kilkoma drogami, większość z nich wydaje się być obiecujących. W niniejszym artykule przedyskutowano niektóre aspekty rozwoju nowych leków. Do nowych klas leków, które być może znajdą niedługo zastosowanie w leczeniu chorób alergicznych należą antagoniści cytokin, inhibitory kinaz oraz antagoniści czynników transkrypcyjnych. Ponadto w ostatnim czasie pojawiły się nowe przeciwciała anty-IgE oraz grupa nowych inhibitorów fosfodiesterazy-4, co więcej mamy dziś do czynienia z szybkim rozwojem diagnostyki molekularnej uczulenia. Niestety, dotychczasowe badania nie dostarczyły żadnych nowych metod pozwalających na profilaktykę chorób alergicznych.

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