JHPOR | Journal of Health Policy & Outcomes Research

Immunomodulation as the desired therapy in some cases of allergic diseases

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Keywords:
allergy, autoantibody, autoimmunity, immunomodulatory drugs

DOI: DOI: 10.7365/JHPOR.2014.5.3
JHPOR, 2014, 1, 32-45

ABSTRACT

There has been a strong belief for many years that there is no pathogenic connection between allergy and autoimmunity. Academic books usually describe the disparate immune mechanisms playing pivotal role in pathogenesis of allergic and autoimmune diseases. A simplified hypothesis of Th1/Th2 balance disorder represents an accepted model of the diseases. Recent findings have suggested that there is no clear dichotomy between allergy and autoimmunity. Both of them result from dysregulation of the immune system. The systematic review of the literature was performed searching electronic databases for the pathologic and clinical intersection of allergic a autoimmune conditions. Research is currently focused on the key elements that regulate the immune response. Mast cells, which play important role in allergic inflammation, make it likely that they have profound effects on numerous autoimmune conditions. Environmental stress and proinflammatory cytokines may activate the protein kinases in both conditions. The presence of autoantibodies in some allergic conditions such asthma or atopic dermatitis may point out an autoimmune background in some cases. Genetic factors lead the development and process of immunologic diseases. Data suggest a close relation between genepolymorphism of HLA and cytokines and development of autoimmunity and allergy. The infection also may play an important role in the induction of the diseases. Despite the use of more effective anti-inflammatory drugs, the progressionof many allergic and autoimmune diseases may not be halted. Better knowledge about the considerable communication between complex signalling pathways pointout immunomodulation as the key to successful therapy of both allergic and autoimmune conditions.

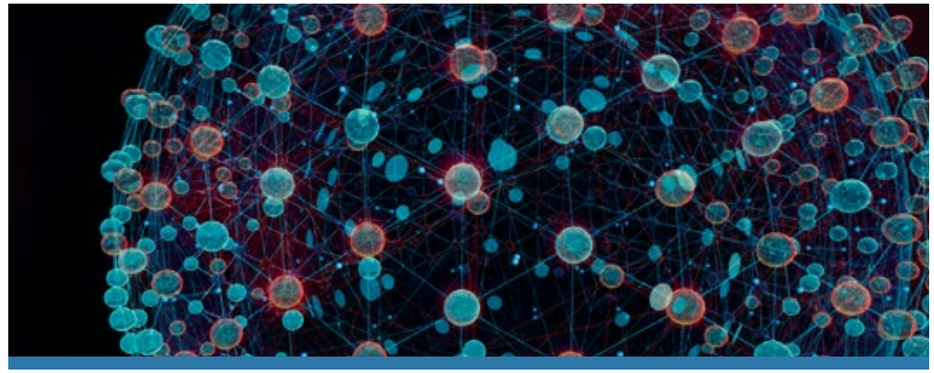
INTRODUCTION

Allergic diseases are very common and represent a major health problem worldwide. There has been observed an epidemic increase in prevalence of allergy in the last decades in some countries. It is estimated that 10 – 30% of the population is affected [1,2]. Because of their chronic, incurable, and sometimes life-threatening course, these diseases may be a significant socioeconomic burden. In many cases the diagnosis and treatment of affected individuals is insufficient and/or inadequate. In spite of great progress in research into the pathogenesis and treatment of allergy in the last few decades, there are still many problems to be resolved. Allergic diseases show a wide heterogeneity involving different organs such eyes, skin, respiratory and digestive tract. Allergic problems present variability in severity and clinical course which are at the present time only poorly defined. More precise definition of the clinical subtypes (phenotypes) of allergic patients appears important and necessary to address the right therapy to the right patient [1]. Some authors of academic books underline clear border between allergy and autoimmunity. The typical pathologic pictures would not suggest a similarity in pathogenesis of allergic and autoimmune disorders. Most cases of rhino-conjunctivitis or asthma are characterised by activity of Th2 (T-helper type 2) lymphocytes and Th2-derived cytokines as interleukins: IL-4, IL-5, IL-13 and stimulation of and eosinophil-predominant inflammation. On the contrary putative autoimmune disorders such as rheumatoid arthritis or type 1 of diabetes mellitus are thought to be mediated by Th1 (T-helper type 1) lymphocytes and Th1-derived cytokines as interleukins: IL-2, IFNγ. The most popular simplified hypothesis of Th1/Th2 imbalance attempts to explain ethiopathology of certain diseases [3,4]. However, in recent years, findings of some studies have suggested that there is no clear dichotomy between allergy and autoimmunity. Both of them result from dysregulation of the immune system. In recent years interest of investigators is focused on the key elements that regulate the immune response in many allergic and autoimmune diseases: mast cells, autoantibodies, T-cells, cytokines and genetic determinants [5,6,7,8,9,10]. It is obvious that mast cells play important role in allergic inflammation. But they may have also profound effects on numerous autoimmune conditions. Another factors such as environmental stress and proinflammatory cytokines may activate the protein kinases in both allergic and autoimmune diseases. There are studies in which autoantibodies have been found in some allergic conditions such asthma or atopic dermatitis and they may point out an autoimmune background in some cases. Some recent discoveries have provided additional insight into roles of Th17 cells and T regulatory cells [9,11,12]. It is obvious that genetic factors play an important role in the development and process of immunologic diseases. The studies from recent years suggest a close relation between gene polymorphism of HLA and cytokines and development of autoimmunity and allergy. The gene polymorphisms may act as risk or as protective factors [13,14,15]. The role of the infection also may be important in the induction of allergy and autoimmunity [16,17,18]. In some cases similar clinical manifestations of both immunopathologies are observed and may result sometimes in diagnostic problems. Ever-expanding knowledge about the considerable communication between complex signalling pathways point out immunomodulation as the key to successful therapy of both allergic and autoimmune conditions [12]. It also helps to identify promising areas for future research.

RELATIONSHIPS BETWEEN AUTOIMMUNITY AND MAST CELL-RELATED DISEASES

Epidemiological data

Epidemiological data on the coexistence of both types of these mentioned disorders are scarce. Studies of the possible association between allergy and autoimmunity at the population level have come to varying conclusions. For



example in the last few decades, a positive correlation between the prevalence of asthma and the incidence of type-1 diabetes has been found at the population level, but not in the individual. Both of these immune-mediated disorders are positively associated with the gross national product [7]. In another study Tirosh et al. analyzed data from nearly 3-years of follow up of about 450 000 population of Israeli soldiers aged from 18 to 21 years. Studies have shown an inverse correlation between the occurrence of asthma and autoimmune disorders. Autoimmune diseases are often related to women. The inflammatory bowel diseases, vasculitis, arthritis, and autoimmune thrombocytopenia occurred more frequently in women who have not suffered from asthma while type-1 of diabetes in men without a history of asthma [19]. According to some experts opinions, extrapolating the results of this study to the general population can lead to erroneous conclusions [5]. In the Medline database one can find a few publications that prove a lower incidence of autoimmune diseases in patients with allergy or atopy, or indicate a negligible difference in the appearance of autoimmune disorders in patients with previously diagnosed allergic disease in contrast to controls without allergy [10]. Conversely, there are also reports arguing that there may be risk of developing autoimmune disease in allergic patients. In children with allergic diseases, more frequently than in the control group, the elevated antibody titers against peroxidase [20,21] and anticardiolipin antibodies [22] were found. Similar results were obtained in the group of 200 Iranian women. Half of them was suffering from asthma. A significant percent of asthmatic women had increased levels of anti-thyroid autoantibodies, but in the majority without clinical evidence of thyroid disease [23]. Agache et al. observed a frequent incidence of antinuclear antibodies in patients with severe asthma [24]. Similar reports were presented by Canadian researchers. The study included 3 groups of patients: patients with atopic asthma, patients with non-atopic asthma and patients with asthma and concomitant systemic lupus (SLE). Antinuclear antibodies in significance number of patients with non-atopic asthma were found in contrary to atopic asthma group but in lower titers compared to the group suffering from asthma and coexistent SLE. Moreover, the positive skin test to autologous serum in patients with non-atopic asthma and asthmatic patients with SLE was observed. It may suggest participation in the pathogenesis of autoimmune inflammation in non-atopic asthma [25]. Analysis of adult data from one of large American national studies demonstrated that common allergic disorders diagnosed by doctors were positively associated with incidence of physician-diagnosed autoimmune diseases. An interesting issue is a quite common occurrence of respiratory symptoms and bronchial hyperreactivity (BHR) in patients suffering from autoimmune diseases. Researchers emphasize that BHR in these patients is likely to be a consequence of structural changes and infiltration of inflammatory cells [7]. On the basis of previous studies we can say that the coexistence of both types of disease is still considered uncommon, although possible phenomenon.

Pathophysiological background

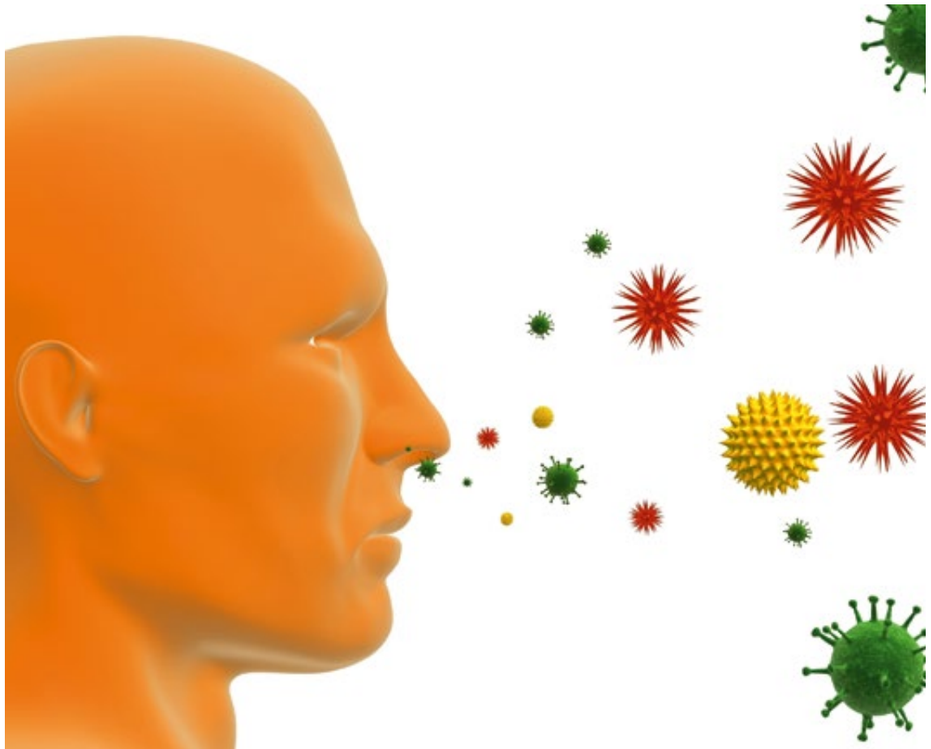
Both processes allergy and autoimmunity may show some similarities in their clinical course. Mast cell related conditions and autoimmune syndromes are inflammatory processes caused by dysregulated immune response. Both disorders are complex and result from the interaction between several factors: enviromental, genetic and individual. But the immune mechanisms involve similar types of cells, cytokines, antibodies, and mediators [7,8,9,12]. Recent studies have also shown close proximity of the certain genes regulating the occurrence and course of the two types of diseases [15].

Mast cell is associated mainly with the early phase of the allergic reaction. Antigens interact with the specific IgE molecules already bound to high affinity Fc receptors on the surface of mast cells to induce degranulation. The mast cell releases a mixture of compounds, including histamine, heparin, chymase, tryptase from its cytoplasmic granules. Releasing of mediators determines the course of the early phase of an allergic reaction. But contact with the allergen also provides for the production of a number of mediators and cytokines (prostaglandins, leukotrienes, TNF-a), which will be gradually released and determine the development of the so-called late phase of allergic inflammation, which is very complicated and dependent on the number of cells receptors, cytokines and mediators. The role of mast cells in the pathogenesis of allergic diseases has been well established [2,3,4]. However, recent studies have shown the possible involvement of mast cells in the disease as: multiple sclerosis, rheumatoid arthritis, bullous pemphigoid, Sjögren's syndrome, autoimmune thyroiditis and systemic sclerosis [5,8,12,26,27]. In previous studies it was found that not only exogenous factors can activate mast cells. For example contact with other cells such as T lymphocytes may result in degranulation of mast cells [26,27]. Other IgE-independent signals can lead to mast cell activation, including the interaction some molecules with the surface receptors Fcg I and III, anaphylatoxins, low molecular weight peptides such as substance P or a calcitonin gene-dependent peptide [12,26,27]. Mast cells and B-limfocytes have been found in the increased number in the synovial fluid of patients with rheumatoid arthritis. The increase in mast cell number is strongly correlated with activity of the disease. The studies of a murine model of inflammation demonstrated that transgenic mast cell-deficient mice were resistant to erosive arthritis induced by the arthritogenic antibodies [12]. It is widely known that mast cells are a source of TNF - a, which is the main mediator of inflammation. TNF - a is also the major cytokine present in the rheumatoid joints. TNF - a stimulates the production and release of inflammatory factors such as the matrix-damaging proteases, prostanoids, IL - 6 and GM- CSF. Similarly, an increased number of mast cells and elevated levels of tryptase and other mast-cell derived mediators were detected in cerebrospinal fluid obtained from individuals with multiple sclerosis. Mast cells were also observed in plaques and sites of demyelination. Although their presence in tissues affected by an autoimmune process seems to be obvious, there is still debate of their direct participation in the pathogenesis of this type of inflammation [12,30].

BOTH PROCESSES ALLERGY AND AUTOIMMUNITY MAY SHOW SOME SIMILARITIES IN THEIR CLINICAL COURSE. MAST CELL RELATED CONDITIONS AND AUTOIMMUNE SYNDROMES ARE INFLAMMATORY PROCESSES CAUSED BY DYSREGULATED IMMUNE RESPONSE.

T lymphocytes may be another link between the two processes. Autoreactive Th1 lymphocytes play a crucial role in autoimmune disease such as rheumatoid arthritis, systemic lupus erythematosus, autoimmune type 1 diabetes melitus, multiple sclerosis and autoimmune thyroid disease [4]. However many studies have shown that Th1 and Th2 are not the only cells that pave the directions of inflammation. More recently several different types of Th lymphocytes have been described: Th17, Th22 and Th9. The researchers focused their attention on the Th17 lymphocytes that are involved in chronic inflammation. They differentiate under the influence of strong pro-inflammatory cytokines such as IL-6, IL-21, IL-13 or TGF-β. Th17 cells are the source of IL-17 group of cytokines, which may have different functions in the inflammatory response. While the IL- 17F is correlated positively with the severity of asthma , IL-17A in an answer to allergen rechallenge decreases airway inflammation, which suggests a regulatory role of this cytokine in the lungs [13,28,29]. The role of Th17 and IL -17 is also emphasized in diseases such as multiple sclerosis, rheumatoid arthritis, type 1 diabetes, psoriasis, SLE [31]. Increased activity of these cells was observed also in patients with allergic rhinitis and the presence of nose polyps, atopic dermatitis (AD). In patients with AD, number of Th17 cells positively correlated with the severity of the disease, perhaps by reducing the effect on the expression of mRNA for filaggrin, as shown by other studies [9,3]. An interesting issue is of plasticity of some T lymphocytes. Under the influence of different environmental factors, the nature and function of cells may be converted. Observations have shown that during the environmental allergen challenge, transformation of cells releasing IL- 17 in Th1 cells may occur [13]. An important recent finding (in studies of animal inflammation models) is that initiate Toll-like receptors (particularly- TLR4/inflammasome) activation can increase Th1- and Th17- types of immune response, which are frequently associated with autoimmune diseases. Recent reviews underlines the role of pathogen in activating of Toll-like receptors and inflammasome. Many adjuvants such as alum or Pertussis toxin may induce autoimmunity disorder in this way in animal models of inflammation [16].

Regulatory T cells - Treg - (CD4+ CD25 + FoxP3+) appear to be responsible for the homeostasis of immune system in the healthy subjects. It is a heterogeneous group of cells. Augmentation of Treg cell function might control Th2 mediated inflammation. Downregulation of these cells



function may give serious effects. The classical theory of autoimmune disorders is the loss of the ability to distinguish between their own and foreign antigens [3]. However it seems likely that the activation of the process of autoimmunity is due to specific stimulus- a so called “danger signal”, which makes an antigen presenting cell recognize an antigen as a stranger, requiring elimination. These signals can be either exogenous or endogenous , it can be caused by inflammatory process [33,34].

Previous research underline the crucial role of B cells in both types of inflammation. They may act as antigen presenting cells in the early phase of the reaction, and after differentiating into plasma cells become a source of various antibodies (IgG, IgM, IgA, IgD, IgE), depending on the type of the immune reaction. Thus B lymphocytes seem to play an important role in the pathophysiology of both allergic and autoimmune disease. B cells have numerous roles in these two types of inflammation, most notably differentiating into plasma cells and producing autoantibodies. Autoantibodies activate immune cells and the secretion of proinflammatory cytokines such as IL-6, IL-10, and TNFα, which may lead to tissue damage. There are also subpopulations of lymphocytes called Breg cells (B regulatory cells) that produce IL- 10, which has been involved in the control and limitation of inflammation. There is also evidence that these cells may have the influence on of Treg differentiation and Th17 and Th1 suppression. Recent studies have shown that there are several subpopulations of these lymphocytes, which indicates the complexity of their role in the process of inflammation. Breg cells were selected on the presence of the cell surface markers CD19 and CD20. There is the interesting question of the potential effects of B cell depleting therapy (rituximab - monoclonal antibodiy directed against the specific B cell surface markers CD20 or CD22) that may exert on Breg [9,29].

The presence of increased levels of autoanibodies, sometimes specific for a single tissue, is perceived as a hallmark of autoimmunity. However, several reports suggest a possible role for autoantibodies in allergic diseases [35]. Some patients with asthma, allergic rhinitis or atopic dermatitis have impaired sensitivity to β-adrenergic agents. Autoantibodies directed toward the β-adrenergic receptor were found in the serum of some patients with asthma. These antibodies can block the biologic function of the β2-adrenergic receptor in vitro [5,12]. Previous studies have shown that the levels of IgG autoantibodies to cytokeratin 18, a bronchial epithelial cell antigen, were significantly higher in patients with asthma compared with healthy controls [36]. Also IgG autoantibodies and T-cell reactivity against a common 55-kD antigen shared by platelets and endothelial cells have been found in group of asthmatics. These autoantibodies were mainly restricted to individuals with more severe, glucocorticoids-dependent, non-allergic asthma [7]. Nahm et al reported antibody reactivity against enzyme a-enolase, which is component of bronchial cells. The presence of serum anti-enolase autoantibodies significantly distinguished patients with severe course of the disease and aspirin-induced asthma [37]. Szczeklik et al. found the incidence of antinuclear antibodies in 55 % of patients on aspirin-induced asthma, 39 % of patients with allergic asthma, 41 % of patients with non-allergic asthma in contrast to 11% of the control group [38]. There is theory that antinuclear antibodies do not have a direct role in asthma pathogenesis, but indicate a susceptibility only towards autoimmune processes due to dysregulation of immune system, for example via reducing efficiency of Treg cells, which usually inhibits immune response against autoantibodies [7]. The presence of autoantibodies to β-adrenergic receptors and bronchial epithelium in patients with asthma may demonstrate autoimmune phenomena in allergic conditions, although a causal link between allergy and autoimmunity has not yet been established. It means that a mechanistic link between these antibodies and an allergic condition is yet to be proven [9].

The role of IgE antibodies in the allergic process is obvious. Some investigation showed that the presence of IgE antibodies, however, is not exclusive to atopic disease. Specific IgE antibodies have been observed in autoimmunity: anti-cyclic citrillunated peptides in rheumatoid arthritis, anti-GAD65 antibodies in type 1 diabetes, anti-TSH receptor antibodies in Grave’s disease, and anti-myelin peptides in multiple sclerosis, although the direct pathogenic role is largely unknown [9].

The genetic background of allergic and autoimmune disorders is represented by a complex network of interacting genes. Genome-wide screen studies of asthma have identified a several main regions of genome where genetic variants or disease-causing mutation are placed. Moreover genome-wide screen in families with rheumatoid arthritis has similarly shown linkage near the asthma locus on chromosome 2 and the TCR-α locus on chromosome 14. Some findings suggest that important genes or gene families may be common to several inflammatory and immune disorders. The genes are responsible for the production of specific cytokines and mediators what determines the directions of immune response. Previous studies point out toward the transcription factors such as STAT1, STAT4, GATA3, which expression is associated with production of specific cytokines. While STAT1, and STAT4, ultimately lead to release of interferon gamma (IFN-γ), transforming growth factor (TGF)-β, tumor necrosis factor (TNF)-α, and other cytokines of Th1 response, the transcription factor GATA3 is expressed and promotes further expression of Il-4, Il-5, and Il-10, and B cell-mediated humoral immunity. GATA3 activation also serves to repress IFN-γ secretion [9,13]. Recent report published in Nature in 2013 indicates possible polymorphisms in a single gene of transcription factor BACH2. Genetic polymorphisms within a single locus encoding the transcription factor BACH2 may be associated with numerous autoimmune and allergic diseases. Assessment of the genome-wide function of BACH2, revealed that it represses genes associated with differentiation of effector cell. These findings identify BACH2 as a key regulator of CD4 T-cell differentiation that prevents inflammatory disease by controlling the balance between tolerance and immunity. BACH2 is expressed in B cells. Thus, at both cellu-

lar and molecular level, BACH2 functions to limit immune activation, enabling it to play a critical role in the maintenance of immune homeostasis. These findings help explain the role of BACH2 as a key node in human autoimmunity [14].

Although other findings of gene-wide screen study showed that the single mutation may determine only one specific type of immune response [15]. However, the proximity of location of the genes of determining the course of the inflammatory response may be considered as another link between these two processes. Is it a protective mechanism against the development of both types of reaction, or rather may it predispose to their coexistence? - The answer may be revealed in further research.

Allergic inflammation as a target to immunomodulation

Despite remarkable advances in diagnosis and use of potent anti-inflammatory drugs, asthma and many other allergic diseases are still incurable. It seems that progression of airway inflammation may not be halted. Understanding of pathological features of allergic inflammation showed that the process is highly complex with multiple features that include infiltration of the airways mucosa or skin by activated lymphocytes, eosinophils, and neutrophils, degranulated mast cells, and activated epithelium cells. Asthmatic epithelium exhibits sloughing and denudation, and cilia dysfunction together with collagen deposition in the epithelial sub-basement membrane area [2]. Allergic pathology is associated with the release of pro-inflammatory substances including inflammatory peptides, chemokines, lipid mediators, cytokines, and growth factors. In addition to infiltrating leukocytes, structural cells in the affected tissue, including smooth muscle cells in airways, endothelial cells, fibroblasts, and airway epithelial cells, are all important sources of symptoms of the diseases causing or enhancing mediators. Leukocyte migration and cellular activation are controlled by cell adhesion molecules, such as selectins, integrins, and members of the immunoglobulin superfamily.

The expression and function of these adhesion molecules and the subsequent chemotactic attraction and activation of infiltrating pro-inflammatory cells are controlled by a numerous of cytokines, chemokines, and mediators. Moreover structural cells may play important roles in the inflammatory processes. These inflammatory processes are coordinated by a complex cytokine network [2,3,4,12]. However, depending on the inflammatory context, cytokines often exert opposing actions and they often exhibit redundancy in their functions. Modulating the cytokine network in allergic diseases, sometimes with severe course, such as asthma or atopic dermatitis with biological therapy presents a new but challenging paradigm for treatment of these disorders. The basis for immunomodulation therapy of allergic diseases was initiated by the development of Th2 predominant response. It is associated with unique cytokine profile: IL-4, IL-5, IL-9, IL-13, IL-25 and IL-33. Therapy based on this hypothesis concentrates on changing the balance of the immune system towards Th1 response. This can be done in two ways: blocking Th2 derived cytokines with antagonists (monoclonal antibodies, soluble receptors) or by stimulating Th1 response, boosting by addition of recombinant cytokines for example [39,40]. Some studies showed that IFN-g had potent local and systemic effects on the airway epithelium. This cytokine plays role in activation of antigen-presenting cells, IL-12 production and differentiation of naive T lymphocytes into Th1 [41,42]. IL -12 was considered as the additional target of immunomodulation, because mouse studies revealed that administration of this cytokine suppresses antigen-induced tissue eosinophilia and inhibits IgE production. Unfortunately due to significant toxicity IFN-g and IL-12 did not come to general use [41,43].

There are promising results of studies on unmethylated cytosine-guanine dinucleotides, known as CpG motifs. These motifs, as the adjuvant to immunotherapy, promote Th1 response, preventing tissue eosinophylia and reducing IgE production, and bronchial hyperresponsivenes. Il-18 also appears to play complex role in up-regulating Th1 response [41]. Although there is no certainty whether stimulating of Th1 response is beneficial in any case of allergic disease.

Recently most research is focused on down-regulation of Th2 immune response. The inhibition of eosinophil accumulation in asthma therefore represents a potential therapeutic strategy. Evidence from research showing IL-5 tissue localization in allergic diseases together with studies in IL-5-knockout, transgenic mice, suggest IL-5 is crucial to the development and release of eosinophils from the bone marrow and their enhanced adhesion to endothelial cells and their activation and secretion in the tissues. The presence of tissue eosinophils is evident feature of several allergic diseases including asthma, rhinitis, eosinophilic esophagitis and idiopathic hypereosinophilic syndrome [43,49].

DESPITE REMARKABLE ADVANCES IN DIAGNOSIS AND USE OF POTENT ANTI-INFLAMMATORY DRUGS, ASTHMA AND MANY OTHER ALLERGIC DISEASES ARE STILL INCURABLE.

Both Il-4 and IL-13 are very important cytokines for the tissue accumulation of eosinophils and they are main factors of IgE synthesis by B lymphocytes. Both exert its effects through the special receptor complex (IL-4Rα/IL-13Rα1) which then activates the transcription factor STAT-6. It has an important role in activating genes associated with the differentiation of naive T-cells into Th2 cells, airway inflammation, and bronchial hyperreactivity. Studies with soluble IL-4R given in a nebulized form demonstrated an improvement in the course of moderate asthma. However, despite these promising findings subsequent trials have not been as successful and consequently this treatment is no longer being developed [41,44,45]. Airway hyperresponsivenes, mucous hyperproduction, up-regulation of eotaxin and IgE production and eosinophilis recruitment are regulated by Il-13. Many recent studies are focused on blocking action of IL-13 with promising results [41,45]. IL-33 belongs to the IL-1 superfamily. IL-33 and its receptor ST2 promote various activities related to the up-regulation of TH2 response. This cytokine is released predominantly by damaged cells. It suggests that IL-33 function as an endogenous danger signal particularly in epithelial and endothelial cells is directly exposed to environmental challenge. The experimental models of asthma revealed that the blockade of IL-33 and its receptors reduces the severity of the disease [46].

TNF-α is one of the most important cytokines in innate immune response that has been implicated in several chronic inflammatory diseases including also autoimmune disorders. Anti-TNF-α therapy proving useful in these conditions. TNF-α is produced by macrophages and other pro-inflammatory cells including dendritic cells, monocytes, B and T lymphocytes, neutrophils, and what important for pathogenesis of allergic diseases by mast cells and eosinophils, which together with the structural cells including fibroblasts, epithelial cells, and smooth muscle cells represent significant sources of this mediator. TNF-α exerts pro-inflammatory effects on various cells and may play a key role in amplifying airway inflammation through activation of transcription factors: NF-κB and AP-1. Because TNF-α is thought to be the main mediator contributed to bronchial hyperreactivity, airway remodeling, and resistance to steroids in asthma and atopic dermatitis therefore represents a potential target for therapy [2,7,45].

Receptor for IL-17 (very important proinflammatory cytokine) has become the newest target for immunomodulatory drugs [47,48]. For recent years attention of researchers is focused on the chemokine receptors, especially CCR3. Chemokines are a family of small, secreted proteins that control migration of many cells. Eotaxin is an inducible chemokine secreted in asthma that promotes selective recruitment of eosinophils from the blood into inflammatory tissues via CCR3, a seven-transmembrane-spanning Gprotein-coupled receptor.

Another approach to immunomodulation is targering transcription factors. Attempting to modulate STAT-6 or GATA-3 and the signaling pathways may be essential to modification of the course of inflammation. But it presents serious challenge to researchers because these molecules are intracellular [41].

IgE plays a very important role in the pathogenesis of diseases associated with immediate hypersensitivity reactions, including allergic asthma, atopic dermatitis, urticaria, food allergies and others. IgE-dependent symptoms are a result of it binding to high-affinity receptors (FcεRI) on mast cells and basophils and to low-affinity receptors (FcεRII) on macrophages, dendritic cells, and B lymphocytes. Allergen mole-

cules join to the Fab components of IgE binding on the cell surface thereby activating intracellular signal transduction. In mast cells, this leads to the degranulation and release of preformed mediators and the rapid synthesis and release of other mediators responsible for allergic inflammation. Therefore, blocking the action of IgE using antibodies that do not result in cell activation is an attractive therapy approach [2,3,4,49].

Immunomodulatory drugs in treatment of allergic disorders

There is a group of patients with severe course of asthma or/and atopic dermatitis who does not respond to standard therapy despite the use of maximal dose. Moreover it is well known that steroid therapy does not prevent the airway remodeling in asthmatic patients and does not influence the natural course of the diseases as well as topical steroids in atopic dermatitis [2,32,50]. In allergic asthma due to exogenous allergens efficacy of immunotherapy has been confirmed in numerous clinical studies [2]. Whereas in non-allergic, intrinsic asthma the airway inflammation is triggered by complex mechanisms, probably also involving IgE and perhaps, autoimmunity [7,8]. In the past, various, potentially immunosuppressive drugs such as methotrexate, ciclosporin, gold salts and troleandomycin, have been used in patients with severe steroid-dependent or steroid-resistant asthma. Most of these drugs gave significant steroid-sparing effects. However numerous adverse events during the therapies were observed. Many studies have failed to demonstrate an unacceptable risk-benefit ratio [7]. GINA report does not recommend these drugs as the standard therapies as well as macrolides nad anti-TNF-a agents. As a novel therapy omalizumab is recommended as add-on therapy in very severe atopic asthma [2]. Cyclosporine has been still used in chronic urticaria refractory to other therapies [51]. Several studies have examined the therapeutic efficacy of macrolides in patients with asthma. Because of their pleiotropic effects: anti-inflammatory and immunomodulatory in addition to antibacterial there were trials of maintenance treatment with low-dose macrolides. The Azithromycin in Severe Asthma Trial has demonstrated efficacy and safety of this therapy. A significant reduction in number of exacerbations was observed in patients with severe, non-eosinophilic asthma. Although chronic therapy with macrolides is associated with the risk of population antimicrobial resistance, than it should be reserved to special selected cases [52].

Humanized murine anti-TNF-α antibody - infliximab and soluble TNF-α receptor linked to human IgG1-etanercept have been developed and preliminary clinical studies in asthma showed significant improvements in lung function, reduction of airway hyperreactivity, and number of exacerbations, particularly in patients with severe asthma refractory to treatment with glucocorticosteroids [53]. There were few attempts of treatment with both of these drugs the patients with atopic dermatitis, but without the expected success [32]. However, a following clinical trial with the anti-TNF-α biologic golimumab in patients with severe, uncontrolled asthma reported negative clinical findings. Moreover, this study was terminated early due to unacceptable adverse events including frequent serious infections and eight cases of malignancies in the active-treatment group compared with the placebo group [45].

Omalizumab is a humanized monoclonal antibody directed to the FcεRI binding domain of human IgE resulting in a rapid decline in circulating levels of unbound IgE. Omalizumab does not bind to IgE bound to specific receptors on cells but down-regulates expression of high-affinity receptors by these cells. Omalizumab inhibited early-phase and late-phase allergen-induced asthmatic reactions and reduced serum free IgE concentrations and has progressed through clinical development [49]. In several studies omalizumab has been shown to be beneficial as an add-on therapy in severe persistent asthmatics with inadequately controlled symptoms while a pooled analysis of six controlled clinical trials that evaluated the effect of add-on omalizumab in patients with severe persistent allergic asthma reported significant improvements in quality of life indices. Omalizumab reduced the frequency of exacerbations and improved symptom control while allowing a reduction in the use of glucocorticoids and β2-agonists. It also improved patients' quality of life and produced a significant improvement in lung function. Moreover, in patients with severe asthma, omalizumab significantly reduced disease exacerbations and hospital admissions compared with control subjects. It appears to be well tolerated but more long-term studies are needed to fully demonstrate the benefit and safety of anti-IgE therapy in asthma. A number of studies have also examined the use of omalizumab as a treatment for other allergic diseases including food-allergy, mastocytosis, allergic rhino-conjunctivitis, chronic idiopathic urticaria, atopic dermatitis, hymenoptera venom allergy, and Churg-Strauss syndrome. But these conditions have not become still indications for this biologic agent [7,9]. Omalizumab has not been yet tested in patients with non-allergic asthma, but there are some findings provide the rationale for use in these group of patients. Elevation of total serum IgE was found in some of these individuals, supporting the role of this immunoglobulin, independent of allergy for developing of asthma symptom. In some patients with non-allergic asthma local production of IgE in bronchial biopsies has been demonstrated [7]. Previous observations revealed that the response to omalizumab is variable and difficult to predict. It seems that some biomarkers may help to predict the response to anti-IgE therapy and can identify potential responders. Among these biomarkers

were fractional excretion of nitric oxide (FENO), peripheral blood eosinophil count, and the novel one - serum periostin (a matricellular protein which is secreted by bronchial epithelial cells when stimulated by Th2 cytokines). Omalizumab as well as lebrikizumab, pitrakinra, dupilumab and tralokinumab were associated with greater effects in specific high-biomarker groups. Similarly the proof of the need for personalized medicine in asthma and other allergic diseases was provided by study with lebrikizumab (humanized IgG4 monoclonal IL-13 neutralizing antibody administered intravenously). In the study, pre-treatment measurements of th2 inflammation (serum IgE and ostepontin - biomarker from epithelial cells for IL-13 action). Although the response of the overall population was minimal, the high-biomarker group showed a rapid and sustained increase in pre-bronchodilator FEV1 after 12 weeks therapy. A major advance in personalized medicine will be the identification of particular endotypes of diseases and help to guide the use of specific biologics in the appropriate patients. It may allow to modify the activity of the innate immune response in individuals who manifest specific pathway activation [54]. With the exception of omalizumab and dupilumab the majority of biologics have proven inadequate in the clinical setting in asthma even though they were highly effective in animal models of asthma. Conflicting evidence exists regarding efficacy of omalizumab as well as rituximab in atopic dermatitis [32,55].

The immunotherapy is the oldest and the most widely used method of immunomodulation in allergic diseases. It was first developed at St Mary's Hospital in London at the end of the 19th century. The basic principles were described by Freeman and Noon, and many of them remain valid today. This form of treatment involves the subcutaneous or sublingual administration of gradually increasing quantities of allergens until a dose is reached that is effective in inducing immunologic tolerance. The primary objectives of allergen-specific immunotherapy are to decrease the symptoms triggered by allergens and to prevent recurrence of the disease in the long-term. Several mechanisms have been proposed to explain the beneficial effects of immunotherapy. First of all the reduction in specific IgE levels is observed

during long-term therapy, although they can increase temporarily pending the initial phase of SIT. But the inhibition of the recruitment and activation of effector cells including mast cells, eosinophils, and basophils in the allergic respiratory mucosa of the nose and bronchi seems to be more important. Data strongly suggest that these mechanisms are modified as a consequence of altered T-lymphocyte responses following high dose allergen exposure during immunotherapy. Immunotherapy also has been shown to induce a subset of T-regulatory cells with allergen-specific increases in the production of IL-10 and TGFβ. These cytokines inhibit T responses and reverse antibody production in favour of IgG4 and, possibly, IgA synthesis with downregulation of IgE responses. These events are accompanied by suppression of allergen-induced T cell-dependent late responses in the skin and lung and long term disease suppression which is apparent following discontinuation. Immunotherapy is the only treatment that has the potential to modify the course of allergic disease, which is in contrast to usual pharmacotherapy [56]. However, there is some concern about the use of immunotherapy as immunomodulatory treatment in patients with autoimmune disorders- although there is no hard evidence that SIT is actually harmful to these patients. Also, the results of long term observational study do not indicate the increased prevalence of new cases of autoimmune diseases in the group of patients treated with SIT [57].

CONCLUSIONS

Available data indicate the complexity of the allergic inflammation and the possibility of participation of the same components in both allergic and autoimmune diseases. Both types of disorders result from dysregulation of the immune system. Not only genetic factors but also environmental factors (eg, infections) have an impact for their development and course. The imbalance of Th1/Th2 pathways is one of the aspects of pathogenic mechanisms only. Recent studies revealed that the same types of cells (Treg, Breg) regulate both types of inflammation There are involved also similar cytokines, antibodies and mediators. The newest studies have provided additional insight into the roles of Th17 cells, B cells and Treg cells as well as the considerable communication and commonalities between the complex signaling pathways. In addition, external factors may have influence to the immune response. Taking into account pathogenesis mosaic, major task in the future of allergic diseases research should be to identify phenotypes that will ultimately lead to individualized medicine and patient-tailored treatment.

The results of previous in vitro studies and animal models have indicated the promising development of novel compounds targeted at diverse aspects of the inflammatory cascade underlying pathogenesis of allergic diseases such as asthma, atopic dermatitis, chronic urticaria. The development of novel anti-inflammatory therapies for these disorders has proven to be for the most part disappointing; in particular, results from animal-based studies have been very misleading. Despite significant benefit and few adverse effects, the blockade of action of single cytokine or mediator, or receptor often result in partial efficacy only, and does not addresses all allergic population. Future investigations of alternative pathways of inflammation are needed. Moreover identification of specific endotype of disease seems to be essential for adequate treatment. ■

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