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"Right step" in severe asthma- immunological monitoring

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Abstract

Severe asthma is often defined as a separate phenotype of asthma. Different combinations of biological molecules are markers in precise diagnosis of asthma. Type of airway inflammation is the main feature of the disease as well as severity is the main goal in treatment. IgE is produced continuously to maintain constant levels in the blood. Many peripheral blood cells express IgE receptors. Efforts to assess regulation of IgE dependent network among patients treated with biologic therapy may contribute to both better understanding of the disease and choosing right therapy option and dosage regimen.

Keywords: severe asthma monitoring, biological treatment, biomarkers, Ig E network; IgE receptors, eosinophils

Asthma is heterogeneous disease. Many pathways, mediators and systems are involved in inflammatory mechanisms that cause variable airway obstruction in asthmatics. Thus, severe asthma is often defined as a separate phenotype of asthma. Severe asthma is asthma that requires treatment corresponding to steps 4 and 5 according to GINA, high-dose inhaled corticosteroid (ICS) and long-acting β2-agonist (DDBA) to prevent it from becoming

uncontrolled, or asthma that remains uncontrolled despite this treatment. The most complete is definition adopted by the ERS / ATS Task Force on Severe Asthma 2014, taking into account the following criteria:

1. Treatment with high-dose inhaled steroids (ICS) and a second control drug (and / or systemic corticosteroids) to maintain control.

2. Lack of control despite treatment (step 4 or 5).

3. Insufficient control of comorbidities such as sinus diseases or obesity.

The prevalence of severe asthma is 5-10% of asthmatics. On the other hand it is necessary to define difference between asthma under control and non-adherence to therapy, which has been reported up to 56% of asthmatics (1, 4).

Atopy is main feature of 60% of asthmatics and is accompanied by eosinophilic airway inflammation. The mentioned group is characterized by presence of specific immunoglobulin E (IgE) antibody production to various allergens. This phenomenon is proven serologically (*in vitro*) or *in vivo* (by skin prick test) (1, 3). In general, atopy is defined as a tendency to produce IgE antibodies in response to exposure to allergens and subsequent development of diseases such as asthma, rhinoconjunctivitis or atopic dermatitis. In clinical practice, atopy is often equated with the presence of serum allergen-specific IgE antibodies or positive skin allergy tests. However, a positive result is not always associated with clinical manifestation. (2)

Non-atopic asthma tends to develop later in life and is more common in women. Its prevalence is 10–33% of asthmatics. It is associated with a more severe clinical course and lack of atopy (1).

There is no clear rule how to choose biological therapy. Defining the phenotype is the first step towards determining the main biological mechanisms supporting chronic inflammation in asthma. Different combinations of biological molecules are markers in precise classification of asthma. This emphasize the need of specific approach to every single patient.

Type of airway inflammation is the main feature of the disease as well as severity is the main goal in treatment. Inflammation in asthma is heterogeneous. Various cell types, mediators and immune-mediated pathways determine the inflammatory course among asthmatics. Probably the pathways are differ in each patient, varied in time and

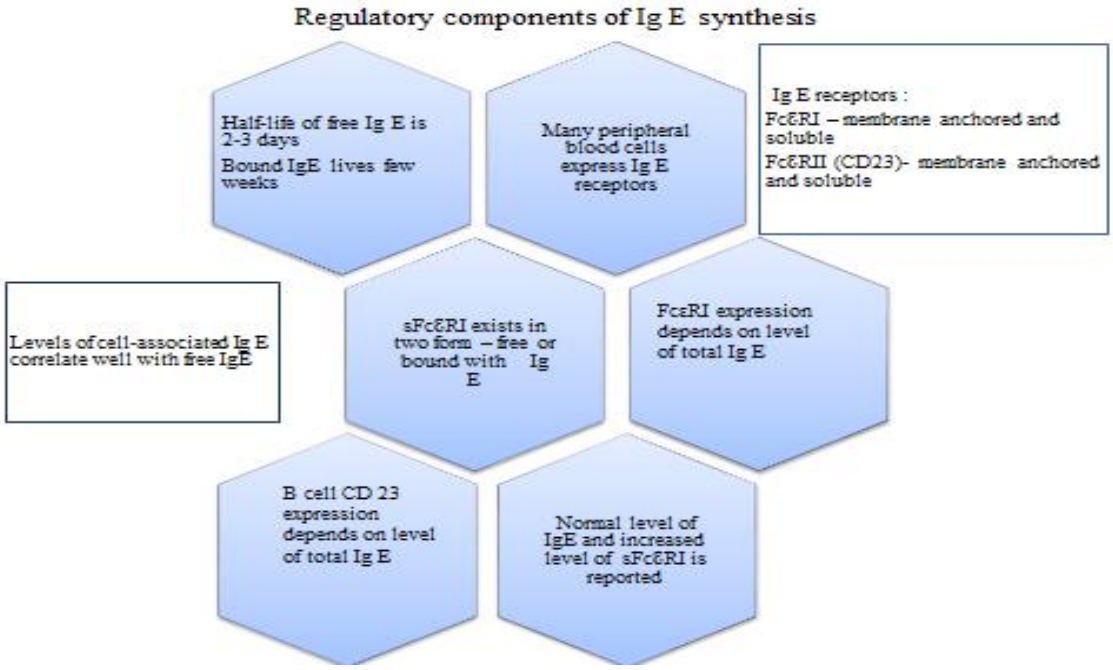
circumstances, and are more complex than simply separated into two main groups: T (Type) 2 and non-T2 inflammation.

In fact, airway inflammation is a combination of both T2 pathways and non-T2 inflammation. The process usually begins with airway epithelium activation and subsequent inclusion of a cascade of events that take place in certain patterns of airway inflammation and lead to manifestation of clinically relevant symptoms. T2 model is typical for most asthma patients. Up to 50% of severe asthma patients are characterized as non-T2 type. These patients have low levels of T2 biomarkers and are not candidates for biological T2 therapies. In this case the exact mechanisms underlying the lack of clinical control of the disease is still unclear. (5)

Among all immunoglobulin subclasses, IgE stands out in terms of function, half-life and low serum concentration. Its half-life in serum is 2 days and its long-term removal from the bloodstream is difficult to achieve. IgE is produced continuously to maintain constant levels in the blood. Allergen-specific IgE memory is preserved for years and in the absence of antigenic stimulation. At the same time, seasonal exposure to allergens can cause a rapid increase in allergen-specific IgE levels and increase total IgE levels

Two different processes control IgE production: one that continuously replenishes the IgE pool (long-lived memory cells) and the second one – inducible fraction upon allergen exposure. Activation can be achieved either by repeated contact with an allergen (e.g., seasonal exposure) or by polyclonal activation such as infection. CD23 (low affinity Ig E receptor) determine B-lymphocyte allergen presentation and depends on serum levels of IgE. Free and cell-bound components are involved in regulation of Ig E homeostasis. Figure 1 shows this interactions. (6,7, 10, 11)

Figure 1. Regulation of IgE homeostasis.



Due to high affinity FcεRI receptor , bound IgE , in contrast to free IgE has a relatively long half-life (2-3 weeks).

Mast cells are long-lived tissue cells that differentiate completely in the tissues. They survive there for months. Basophils differentiate completely in bone marrow. Their blood circulation persist only for few days. IgE receptors are two types: FcεRI receptor (high affinity receptor), and low affinity receptor, CD23 (FcεRII) receptor. FcεRI is expressed by mast cells and basophils, dendritic cells, smooth muscle cells, endothelial cells, and eosinophils. High and low affinity Ig E receptors exist in two forms - membrane-fixed and soluble. (7,8)

Positive feedback regulate circulating IgE and expression of FcεRI on mast cells and basophils. The IgE biological network also includes smooth muscle expression of low-affinity IgE receptor (CD23), associated with transport of IgE-allergen complex across the mucosal barrier (6,7,8,9,11).

Although asthma is predominantly Th2-mediated Th1 cells are involved predominantly during induction phase of inflammation. Animal models show that antigen-specific Th1 cells cannot resist to Th2-induced inflamation. Most Th1 inflammatory patterns represent transmural inflammation (patients with Crohn's disease for example), while Th2 model shows superficial inflamation and epithelial hyperplasia (among patients with ulcerative colitis).

After differentiation and migration to peripheral immune organs, CD4 + T cells are naive and functionally immature T cell precursors. Their activation and differentiation requires at least two separate signals. The first one is the T-cell receptor / CD3 complex after its interaction with the antigen in a complex with MHC II. Expression of various costimulatory molecules on APCs surface define the second signal. These molecules interact with their T cell ligands (CD28 / B7-1, CD28 / B7-2, OX40 / OX40L, ICOS / B7H). Cytokines themselves as a third signal play a major role in helper cell polarization. Two major cytokines control Th1 and Th2 differentiation. These are IL-12 and IL-4 respectively. They induce the generation of their own T-helper subtypes and simultaneously inhibit the production of the opposite subtype. IL-18 also modulates the Th1 response. Although IL-18 alone cannot induce Th1 cell differentiation, it strongly enhances IL-12-dependent Th1 cell development, probably due to IL-18-induced increased expression of the IL-12Rβ2 chain of T cells in AP-1- (c-fos / c-jun) dependent activation of the IFN-γ promoter. Another cytokine, IL-13, plays a significant role in the Th2 response. While its functions partially overlap with IL-4, IL-13 and may provoke Th2 development and IgE synthesis by IL-4-independent mechanism in certain situations.

The role of dendritic cells in orchestrating the involvement of naive T cells is crucial. In mice, two subtypes of CD11c + DCs (CD8α + and CD8α– DCs) have been identified and are associated with the induction of different classes of antigen-specific T-cell responses *in vivo*. While CD8α + DCs in the spleen enhance the Th1 response, CD8α-dendritic cells are at the service of the Th2 response. The same is typical to respiratory tract, in which a Th2 cytokine response is preferentially induced (12).

Blood eosinophils express all FcεRI receptor chains. The direct effect of IgE on eosinophils is underlined by the fact that omalizumab induces eosinophilic apoptosis.

Circulating eosinophils have low expression of α chain of FcεRI. Once in the bloodstream, eosinophils are there for 18-24 hours before their migration to tissues. This circulation time may be prolonged in conditions associated with peripheral eosinophilia. Serum IL-5 or GM-CSF levels are often, but not necessary elevated. The bone marrow is the largest eosinophil precursors source. Once eosinophils leave bloodstream and migrate to tissues they do not recycle again. In tissues they are dependent on the local production of cytokines that prevent apoptosis. These include IL-5, GM-CSF, IL-3, TNF-α, IFN-γ, leptin. Eosinophils and their precursors are able to differentiate and survive in tissues for several days.

IL-5 receptor (IL-5R) is a high-affinity receptor expressed on eosinophils, basophils and mast cells and occurs as a heterodimer of IL-5Ra with b subunit common to IL-5, IL-3 and GM-

CSF receptors. IL-5Ra also exists in soluble form (sIL-5Ra). Elevated serum level of sIL-5Ra have been reported in patients with frequent exacerbations of chronic obstructive pulmonary disease and in patients with nasal polyposis. Serum levels of sIL-5Ra are significantly elevated in patients with systemic mastocytosis without eosinophilia. Increased expression of soluble receptor and decreased membrane expression on eosinophils is associated with an increase count in peripheral blood. This is observed in accordance with changes in serum IL-5 and IL-13 levels. (6,7,8.9,10)

To date, there are no strict criteria on how to stop or switch uncontrolled asthmatics to another biological treatment. What is not known is how kinetics of the above mentioned indicators is changing during long-term use of biological therapy. Studying this process will contribute some benefits:

1. Identification of biomarkers applicable at start-up, switching or related to prognostic course of the disease.

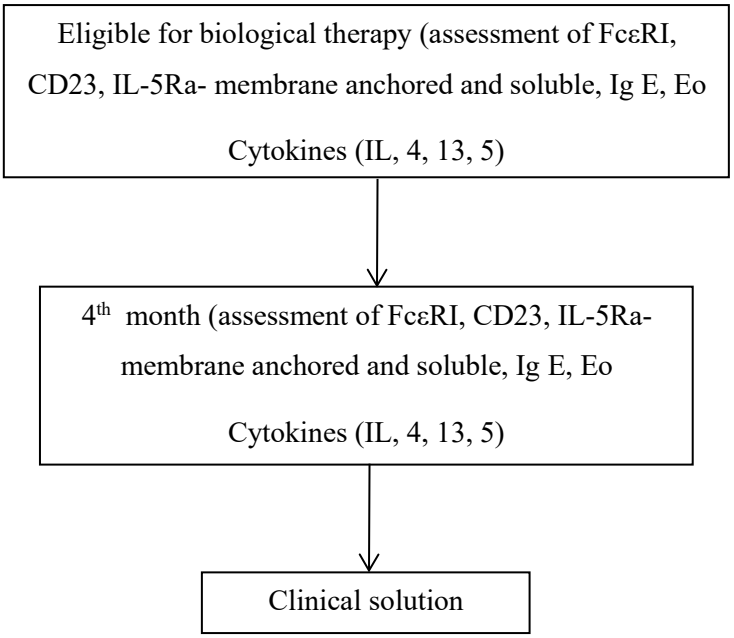
2. Proposes a quantitative method for adjusting the dose regimen after starting therapy.

3. It will contribute to fill gaps in asthma endotypes .

4. This model is applicable various expensive therapies.

Figure 2 shows suitable components for immunological monitoring among severe asthmatics.

Figure 2 Monitoring of free and cell bound components as biomarkers among severe asthmatics



In conclusion , efforts to assess regulation of IgE dependent network among patients treated with biologic therapy may contribute to both better understanding of the disease and choosing right therapy option and dosage regimen.

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