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Justification for IgE as a therapeutic target in chronic spontaneous urticaria

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Summary
Monoclonal anti-IgE antibodies (omalizumab) are able to induce clinically significant benefits in patients with severe chronic spontaneous urticaria (CS). Those results led clinicians and investigators to reconsider a possible pathogenic role not previously supported for IgE and its receptors in this disease, and to investigate additional approaches for understanding its pathogenesis. IgE antibodies to unknown environmental allergens able to trigger chronic urticaria are not generally regarded as the etiologic factor for the disease. Other proposed mechanisms for the production of wheals and angioedema in CSU include IgG autoantibodies and CD4-positive T cells directed to the high-affinity IgE receptor, autoantibodies to IgE itself, IgE autoantibodies directed to thyroid and nuclear autoantigens, highly cytokinergic IgE, and histamine-releasing factors able to bind to IgE and cause mast cell activation. It is expected that a better knowledge on the mechanisms leading to CSU and the clarification of the immunological effects of anti-IgE will provide novel therapies for this frequent condition.

Introduction

The efficacy of monoclonal anti-immunoglobulin E antibodies (omalizumab) in the treatment of chronic spontaneous urticaria (CSU) has provided a new input for the study of additional pathways leading to the production of symptoms of the disease. IgE-mediated autoimmunity is present in various autoimmune diseases, including systemic lupus erythematosus, rheumatoid arthritis, bullous pemphigoid, and CSU (1).

It has been reported that chronic urticaria is associated with the increase of total and allergen-specific IgE (2-7), basopenia, and basophil phenotypic abnormalities (8-12). Furthermore, a newly described autoimmune mechanism in CSU is based on the demonstration of CD4-positive T cells directed to the high affinity IgE receptor (FcεRI) (13).

In this article, a review of the pathogenesis of CSU and the clinical and experimental findings supporting a pathogenic role for IgE in CSU are presented. Further investigations on the participation of IgE could provide additional clues for the implementation of new diagnostic and therapeutic approaches in this frequent clinical condition.

General concepts on Immunoglobulin E

The role of IgE in the pathogenesis of diseases such as rhinitis, asthma, anaphylaxis, atopic dermatitis, and allergic reactions to foods, drugs and insect venoms has been extensively studied after the paramount discovery of this new immunoglobulin class in 1967 by Ishizaka and Ishizaka (14) and Johansson and Bennich (15). Also, the importance of IgE in the defense against helminths has been demonstrated in multiple studies (16).

The production of specific IgE directed to allergenic molecules is a process finely controlled with the participation of various cellular components of the immune system, including Th2

cells, dendritic cells, and B cells, whereas the binding of IgE antibodies to high affinity receptors (FcεRI) present on the membrane of mast cells and basophils results in the establishment of allergic sensitization. The recognition of allergenic epitopes by IgE bound to its receptors triggers cell activation leading to the release of preformed and newly formed inflammatory mediators, as well as cytokines and chemokines, all of them able to induce tissue responses leading to the clinical manifestations.

The production of allergen-specific IgE is critically regulated by various cytokines. Th2-derived IL-4, IL-13, IL-25, and IL-33 participate in the B-cell isotype switching, whereas TGF-β, IFN-γ, IL-34, and IL-35 inhibit the IgE switch. Products of Th1 lymphocytes (IL-6, IL-17 A/F, IL-21, IL-22, and IL-26) and Treg cells (TGF-β, IL-10, IL-35) decrease IgE synthesis.

IgE is a 190 KDa glycoprotein that does not fix complement, does not cross the placental barrier, and whose half-life is 2 days. It binds its high affinity receptor (FcεRI), and upon allergen binding mast cell and basophil degranulation ensue resulting in the symptoms of immediate hypersensitivity.

Two forms of the high affinity receptor have been described. The tetrameric receptor, composed of α, β, and two γ chains, is present on mast cells and basophils, while the trimeric (α, two β chains) occurs on Langerhans cells, dendritic cells, monocytes, eosinophils and platelets. The low affinity IgE receptor, CD23, is present on B cells, follicular dendritic cells, monocytes, macrophages, eosinophils, and polymorphonuclear leukocytes of the intestinal epithelium (16).

The binding of IgE to the a chain of FcεRI occurs at the Cε3 domain of the IgE heavy chain, while the β and γ chains are involved in signal transduction for cell activation. An additional function of IgE is antigen presentation via FcεRI.

Overview of the pathogenesis of chronic spontaneous urticaria

The mechanisms for the production of wheals and angioedema occurring in patients with CSU are not completely understood. It seems clear that the clinical picture results from the release of mediators after the activation of mast cells and basophils in the skin. Various stimuli are able to induce such cell activation, and multiple pro-inflammatory substances are involved, including histamine, serotonin, C5a, platelet-activating factor, neuropeptides, and metabolites derived from arachidonic acid (such as PGD2, and the cysteinyl leukotrienes LTC4, D4 and E4).

In turn, those biologically active substances induce vasodilation, increased vascular permeability, and stimulation of sensor nerve endings resulting in erythema, wheals, edema and itch characteristic of urticaria.

Various mechanisms, immunological and non-immunological, can induce mast cell and basophil activation (**table 1**). Among them, the following have been proposed:

1. Autoimmunity mediated by IgE autoantibodies to self-antigens such as thyroid peroxidase, thyroglobulin, or nuclear antigens (for example, dsDNA) (see below). This has been designated as Type 1 autoimmune urticaria.
2. Autoimmunity mediated by IgG autoantibodies to the high-affinity IgE receptor (FcεRI) and/or to IgE itself (17,18). This type is called Type 2 autoimmune urticaria.
3. Autoimmunity mediated by T cells reacting to FceRI (Type 3 autoimmune urticaria).
4. Eosnophils can be activated by autoantibodies against low-affinity IgE receptors (FcεRII, CD23) present in about 70% of patients with chronic urticaria (19), by anti-FcεRI and anti-IgE autoantibodies, or by other unknown factors, including cytokines and chemokines (IL-5, TNF-α, PAF, eotaxin) released by mast cells (20).
5. Activation of the coagulation extrinsic pathway. It has been postulated that the expression of tissue factor by eosinophils would activate the extrinsic pathway of coagulation leading to the release of vasoactive mediators, such as histamine and thrombin, that result in the increase of vascular permeability due to stimulation of the endothelium (21-24). During exacerbations of urticaria and angioedema an increase in thrombin generation, fibrinolysis and levels of inflammatory biomarkers are observed, with those returning to normal values during disease remission (25). Also, mast cell-derived tryptase can induce thrombin generation through direct activation of prothrombin (26).

Table 1 *- Mechanisms of Mast Cell Activation in Chronic Urticaria*

Immunological	Type 1 autoimmunity (anti-thyroid autoantibodies, anti-ds DNA autoantibodies)
	Type 2 autoimmunity (anti-FcεRI, anti-FcεRII, anti-IgE antibodies)
	Type 4 autoimmunity (CD4+ T cells)
	Complement activation
Non immunological	Histamine releasing factors
	Release of eosinophil products leading to activation of the coagulation with thrombin generation

6. Vascular endothelial growth factor (VEGF), a factor that regulates angiogenesis, increases vascular permeability and induces vasodilation which can contribute to the pathophysiology of chronic urticaria (27).
7. Other potential mechanisms include the activation of mast cells by cell to cell contact with T lymphocytes (28), and the interaction of effector cells with histamine-releasing factors (29).

Role of IgE in autoimmune diseases

Increased levels of total IgE in the serum have been observed in various autoimmune diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis. In SLE, serum IgE correlates with disease activity, and consequently a pathogenic role for IgE has been proposed (1,30). IgE autoantibodies to nucleic acids (dsDNA, Sm, SS-A, SS-B) are present in SLE, and anti-double stranded DNA (dsDNA) IgE is associated with disease activity, hypocomplementemia and nephritis (30).
Self-reactive IgE autoantibodies are also present in bullous pemphigoid, CSU and atopic dermatitis. IgE autoantibodies contribute to the direct damage on autoantigen-containing tissues, activation and migration of basophils to the lymph nodes, and induction of type 1 interferon responses from plasmacytoid dendritic cells (1,31).

Participation of IgE in the pathogenesis of chronic urticaria

The demonstration of clinical efficacy of monoclonal anti-IgE (omalizumab) in patients with CSU, and its approval by major regulatory authorities (FDA, EMEA) for this indication, has stimulated investigators to further inquire into a possible pathogenic role of IgE in chronic urticaria, a disease which has an important presence of IgE autoantibodies.
Total levels of serum IgE are generally higher in CSU patients than in healthy controls (2,3). Kessel et al observed an association between increased total IgE and CSU severity, duration, and positivity of the autologous serum skin test (ASST) (4). In patients with urticaria and angioedema induced by NSAIDs, a higher frequency of atopy (32) and higher levels of total and mite-specific IgE as compared with healthy controls are present (6), whereas in patients with aspirin / NSAID exacerbated cutaneous disease, an increased prevalence of atopy is observed (7). However, in a study from Taiwan atopy did not influence the severity or duration of CSU, but it was associated with a poor therapeutic response to antihistamines (33). Also, patients with positive ASST and/or positive skin prick tests to house dust mites have more severe urticaria (5). A related investigation has shown that in patients with cholinergic urticaria a higher rate of atopy is associated with higher disease severity and impact on the quality of life (34).
Urticaria and angioedema can be produced by the interaction of allergen with mast cell-bound IgE, a mechanism occurring more often in acute urticaria triggered by foods, drugs, aeroallergens and insect stings.
On the other hand, patients with autoimmune CSU have circulating autoantibodies against the IgE receptor (IgG anti-FcεRI a subunit, 35 to 40% of cases) and/or against IgE (IgG anti-IgE, 5-10% of cases) (35,36). The direct cross-linking of adjacent FcεRI receptors by IgG-anti-FcεRI antibodies results in mast cell or basophil activation and downstream release of inflammatory mediators in the skin, which is augmented by complement activation (C5a fragment) through C5a receptors present on dermal mast cells (37,38). Also, cross-linking of mast cell-bound IgE by anti-IgE antibodies causes mast cell activation, which is followed by the release of histamine and other inflammatory mediators (39).

IgE autoantibodies in patients with chronic spontaneous urticaria

About 50% of patients with CSU have IgG autoantibodies against FcεRI, IgE, or both, which are associated with longer

Table 2 *- Possible Etiologic Factors in Chronic Urticaria*

Allergic	Foods, drugs, aeroallergens, insects
Autoimmune	Anti-FcεRI
	Anti-FcεRII
	Anti-IgE
	CD4 + T cells
	Anti-thyroid autoantibodies
	Anti-ds DNA autoantibodies
Other	Histamine releasing factors
	Highly cytokinergic IgE ?

disease duration and a poor response to antihistamine treatment (40). Anti-dsDNA, anti-thyroglobulin, and anti-thyroid peroxidase IgE autoantibodies have been described in patients with CSU (41-44). Anti-dsDNA IgE has been shown to activate basophils (45) and it has been proposed that mast cell activation through binding of autoantigens released from damaged skin to IgE on FcεRI would be a central mechanism in CSU (1).
Twelve to 24% of patients with CSU also have anti-thyroid antibodies (36,46-9), and CSU is often associated with other autoimmune diseases, including Hashimoto's thyroiditis. Serum of patients with autoantibodies to FcεRI or IgE induce histamine release from basophils of healthy donors *in vitro*, and the injection of autologous serum into the skin produces a wheal and flare local reaction, the so called autologous serum skin test (ASST). The disease is more severe in the autoimmune CSU population (50).
IgE anti-thyroid peroxidase autoantibodies, which could cause mast cell activation, are present in patients with CSU (46). Shin et al have observed IgE antibodies specific for thyroid peroxidase that activate basophils in patients with acute and chronic aspirin intolerant urticaria (51). Furthermore, highly cytokinergic IgE antibodies with polyreactivity to autoantigens, including thyroperoxidase, which could induce mast cell activation, have been demonstrated in the sera from patients with atopic dermatitis (52). The role of non-immunoglobulin histamine releasing factors that can interact with IgE in CSU remains unclear (53).

T cell-mediated autoimmunity directed to FcεRIα in CSU

In addition to the autoantibody response to FcεRI described in patients with CSU, recently Auyeung et al have observed a cell-mediated response directed to this receptor in CSU patients. This cellular response is restricted to CD4 positive T cells while it was not observed in CD8 positive T cells (13). The proposed pathogenic role of IgE and IgE receptors in CSU are summarized in **table 2**.

Therapeutic approaches targeting IgE in CSU

International Guidelines for the management of urticaria recommend second generation H1 antihistamines as a first-line symptomatic treatment. For second-line therapy, if symptoms persist after 2 weeks, up-dosing of H1 antihistamines (up to 4 times the licensed dose) is recommended. In patients with refractory urticaria after 1-4 weeks, omalizumab, cyclosporine A or leukotriene receptor antagonists are added to the antihistamine (54).
The efficacy and safety of monoclonal anti-IgE (omalizumab) was clearly established in double-blind placebo-controlled studies such as ASTERIA I, ASTERIA II, and GLACIAL (55-7), and has been confirmed by a meta-analysis recently published by Zhao et al, where omalizumab was superior to placebo for improvement of itch and wheal scores, and rates of complete responses. The profile of adverse events was similar to the one observed in placebo-treated patients (58).
Omalizumab binds to IgE at the Cε3 domain, the same site of IgE interaction with its FcεRI receptor, interfering with the union to its high affinity receptor (59). The mechanisms of action of omalizumab in CSU are not completely understood. A number of possible effects mediating the benefits of omalizumab are summarized in **table 3**.
Although the demonstration of a clinical benefit induced by omalizumab in patients with severe CSU has encouraged further research on the pathogenic mechanisms of the disease, there are a number of issues that deserve additional consideration:
1. The cost of the medication prevents its use in many patients whose health systems are not prepared to assume the burden of more sophisticated and costly therapies.
2. The mechanisms of action of omalizumab in CSU have not been clarified.
3. The optimal duration of the treatment and its long-term safety have not been established.
In the future, the effects of additional anti-IgE monoclonal antibodies, for example Ligelizumab, which show greater affinity for IgE than omalizumab, will be investigated in patients with chronic urticaria (60).
A recent trial with Quilizumab, a humanized, afucosylated monoclonal IgG_1 antibody that binds membrane IgE at the M1-prime segment, which is absent in soluble IgE, has been published. Whereas a reduction (approximately 30%) of total and specific IgE was observed, which was sustained for 6 months, no significant improvements in itch scores or urticaria activity score were found (61). Since Quilizumab targets IgE switching and blocks newly produced specific IgE, the authors hypothesized that remaining serum IgE that mediates CSU pathology is produced by long-lived IgE plasma cells that are not targeted by Quilizumab because of their lack of membrane IgE.

Table 3 *- Mechanisms of action of omalizumab in Chronic spontaneous urticaria.*

Sequestration of autoallergens by IgE-anti-IgE complexes
Reduction of IgE bound to mast cells and basophils
Decrease of FcεRI on mast cells, basophils and dendritic cells
Decrease of low affinity IgE receptors (CD23)
Reduction of IgE-expressing B cells
Prevention of inflammatory mediator release resulting from the decrease of IgE binding

Conclusions

The efficacy of omalizumab in the improvement of symptoms and quality of life of patients with severe CSU opened new approaches for understanding the pathogenesis of this disease. Contrary to the previously proposed theories stating that IgE had no role in the production of chronic urticaria, new investigations have encouraged the search for additional pathogenic pathways of the disease. A better knowledge on the mechanisms leading to CSU will provide novel therapies for this puzzling and sometimes vexing condition.

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