

Pathogenic Intracellular and Autoimmune Mechanisms in Urticaria and Angioedema

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Abstract Urticaria and angioedema are common disorders. Chronic urticaria is defined as lasting longer than 6 weeks. Causes of chronic urticaria fall into the following categories: physical, allergic, hereditary, autoimmune, and idiopathic. Basophils and mast cells are the primary effector cells responsible for clinical symptoms and signs. These cells produce and secrete a variety of mediators including histamine, leukotrienes, prostaglandins, cytokines, chemokines, and other pro-inflammatory mediators. This leads to vasodilation, fluid exudation, increased vascular permeability, and accumulation of additional secondary inflammatory cells. Two mechanisms have been investigated as possibly contributing to the pathogenesis of chronic urticaria. One is the development of autoantibodies to FcεRI or IgE on mast cells and basophils. This appears to be responsible for 30–50 % of cases. The other is dysregulation of intracellular signaling pathways involving Syk, SHIP-1, or SHIP-2 in basophils and mast cells. The primary treatment for chronic urticaria is to treat the underlying pathology, if any can be identified. Otherwise, in idiopathic cases, H1 antihistamines, H2 antihistamines, antileukotrienes, and corticosteroids constitute the main pharmacologic treatment modalities. In severe and recalcitrant cases of chronic and autoimmune urticaria, immunosuppressive drugs have been used, most commonly

cyclosporin. More recent experimental studies have also suggested that omalizumab, an anti-IgE therapy, may be of benefit. Currently, inhibitors of Syk are also being developed and tested in the laboratory and in animal models. As our understanding of the pathogenesis of idiopathic urticaria increases, development of additional drugs targeting these pathways may provide relief for the significant physical and psychological morbidity experienced by patients with this disorder.

Keywords Angioedema · Autoimmune · Basophil · FcεRI · Histamine · IgE · Leukotriene · Mast cell · Omalizumab · Syk · Urticaria

Introduction

Urticaria (hives) is a disease characterized by superficial wheals and pruritus. It can present anywhere on the skin, but only rarely on mucous membranes. Angioedema presents with deeper dermal or submucosal swelling and itching is much less common. Angioedema generally affects the lips, tongue, periorbital tissues, hands, feet, and genitalia. Temporary attacks are termed acute, while repeating episodes for longer than 6 weeks are termed chronic. These conditions affect 15–30 % of the population [1]. Hives usually resolve in less than 12 h while angioedema is slower to clear, often lasting 24 to 72 h. The prevalence of urticaria is generally twice as high in women as in men and the age group of 20 to 40 years is most commonly affected. Etiologies of urticaria can be separated into physical, allergic, hereditary, autoimmune, and idiopathic. In physical and allergic urticaria, a definitive trigger can usually be determined, but these groups encompass only a small proportion of chronic urticaria cases. Even in these cases, the pathogenic mechanisms are unclear. On the other hand, hereditary angioedema is a serious condition presenting with recurrent

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episodes of angioedema without urticaria, and results from a deficiency in the production or function of a complement component called C1 inhibitor. Autoimmune and idiopathic urticaria are much less well defined. Usually, no inciting agent can be identified, and the mechanism of causation is non-IgE mediated. Autoimmune urticaria results from an IgG antibody to the α subunit of the IgE receptor or to IgE itself. The pathophysiology of chronic idiopathic urticaria is unknown, but there is recent evidence that abnormalities in signal transduction molecules in mast cells and basophils may be involved [2, 3].

Mast Cell and Basophil Biology

Most types of urticaria and angioedema are caused by mast cell and/or basophil mediator release in the skin. The regulation of mast cell and basophil mediator release may play a pivotal role in the pathogenesis of urticaria and angioedema. Mast cells are a class of leukocytes produced in the bone marrow which localize in various tissues of the body. Mature mast cells express a receptor for stem cell factor called c-kit. The interaction of this receptor with its ligand is important in differentiation, proliferation, activation, and survival of mast cells [4]. Type I hypersensitivity reactions are IgE mediated and involve binding of IgE to an antigen and subsequent cross-linking of IgE molecules on the surface of effector cells such as the mast cell. This leads to clinical symptoms and signs of allergic inflammation, which may manifest in the skin and mucous membranes as urticaria or angioedema. The high affinity IgE receptor, Fc ϵ RI, plays an important role in mediating this process [5]. In addition, mast cells also express a low affinity IgE receptor termed Fc ϵ R2 or CD 23, as well as Toll-like receptor (TLR) molecules and complement components such as C3a and C5a receptors [6, 7] (Fig. 1).

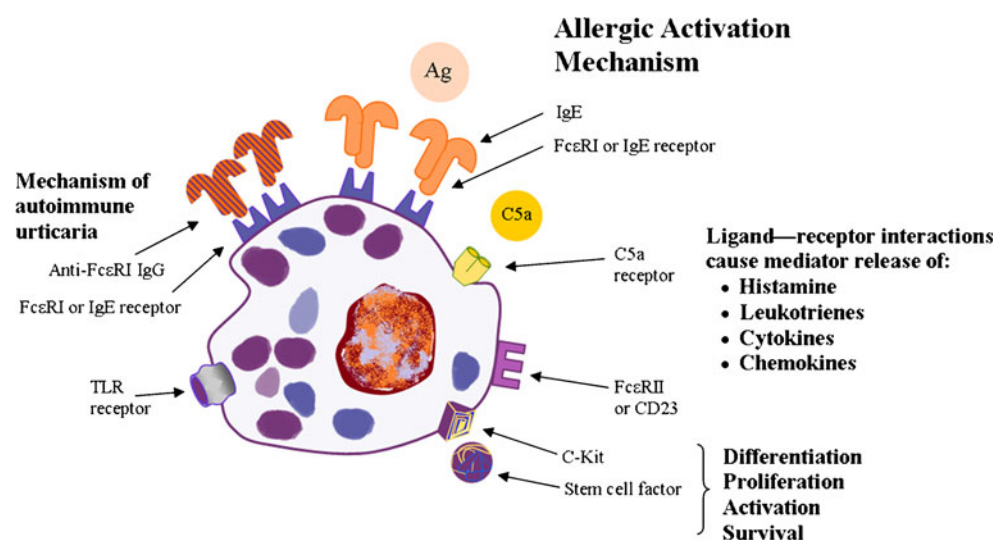
Mast cells are heterogeneous. In man, they are divided into three major categories based on the content of two specific proteases, tryptase and chymase. Mast cells that contain only chymase are called MCsC (MC_C) cells, those with tryptase only are MCsT (MC_T) cells, and those with both of these enzymes as well as carboxypeptidase and cathepsin G are called MCsCT (MC_{CT}) cells. All types of mast cells contain histamine as well as heparin in their granules. In humans and other mammals, mast cells are 9–15 μ m in diameter and long lived with an estimated lifespan of weeks to months [4].

Mast cells are not normally present in the circulation, and generally reside in or near mucosal surfaces of the gastrointestinal and respiratory tracts or in the skin. These organ systems are components of the innate immune defense system, not only providing a physical barrier but also serving an immunological barrier function. The tissues in which mast cells reside are essential in facilitating the interaction between mast cells and invading pathogens, allergens, and toxins [4].

In contrast, basophils are circulating leukocytes with many similarities to mast cells. They are produced in the bone marrow from a granulocyte–monocyte stem cell and exit as mature cells containing many secretory granules [8]. These cells can produce, store, and release numerous mediators, such as histamine, LTC₄, platelet-activating factor, and a variety of chemokines and cytokines including IL-4, IL-5, and IL-13. They are least in numbers of all the granulocytes, making up only 1 % of this class of cells. The estimated lifespan of basophils is 60–70 h [8]. Like mast cells, they have Fc ϵ RI receptors, which can bind IgE, resulting in degranulation and *de novo* production of the many aforementioned mediators [5]. Some studies in other species suggest that mast cells and basophils have a common progenitor cell termed the basophil/mast cell common progenitor, but this remains controversial.

The primary cytokine that stimulates basophil activation, expansion, and survival is IL-3. The primary mechanism of

Fig. 1 Schematic diagram of mast cell/basophil activation. Classic allergic activation involves antigen (Ag) binding to IgE and the IgE receptor. This leads to release of preformed mediators such as histamine and synthesis of other products such as leukotrienes, cytokines, and chemokines. Pathologic activation of the IgE receptor by an IgG to either the IgE receptor or IgE itself is a mechanism of autoimmune urticaria. Stem cell factor binding to c-kit promotes cell differentiation, proliferation, activation, and survival



activation of basophils is through the high affinity IgE receptor Fc ϵ RI. However, these cells can also be activated by IgD, proteases, glycoproteins, TLR molecules, and complement components [8, 9] (Fig. 2).

Mast Cell and Basophil Receptors and Intercellular Signaling Pathways

A substantial amount of data suggests that heightened releasability of mediators either from skin mast cells, basophils, or both cell types is responsible for chronic urticaria [3]. An understanding of the pathways that regulate these processes is important in the development of new modes of therapy for these disorders which are very difficult to treat. These pathways involve intercellular signaling events which occur subsequent to membrane receptor activation.

The first necessary step is membrane receptor interaction with a specific ligand. In the most studied scenario, it is the high affinity IgE receptor Fc ϵ RI on the mast cell or basophil surface, which initiates the process. Studies have shown that typical human basophils require about 2,000 antigen-specific IgE antibodies binding to their receptors to induce a half maximal cellular response such as histamine release [10]. Cross-linking of Fc ϵ RI on the cell surface triggers a complex series of events, which regulates the release of the mediators stored in mast cells and basophils and the synthesis of newly formed biologically active substances.

The first event is phosphorylation of tyrosines in the immunoreceptor tyrosine-based activation motifs (ITAMs), which are associated with the membrane receptor. A kinase called spleen tyrosine kinase (Syk) is then activated and binds to the ITAMs. Activated Syk then initiates a series of subsequent molecular events including phospholipase C (PLC) activation. Active PLC acts in concert with other secondary molecules leading to activation of protein kinase C (PKC) and an increase in intracellular calcium. Calcium stores are lowered in the endoplasmic reticulum, which stimulates an influx of calcium from outside the cell into the cytoplasm. This leads to activation of a series of events leading to upregulation of GTPases including MAP-kinases. This step leads to regulation of transcription factors that drives production of leukotrienes, cytokines, and degranulation, along with subsequent mediator release. Specifically, the increase in cytosolic calcium in participation with a complex of proteins called Soluble NSF Attachment Protein (SNARE) is involved in fusion of cell granules and extracellular release of mediators. NSF is *N*-ethylmaleimide sensitive factor and plays a critical role in the transfer of membrane vesicles among membrane compartments. In parallel, intracellular calcium, through an enzyme calcineurin, dephosphorylates the nuclear factor for T-cell activation (NFAT), which moves to the nucleus and leads to production of a variety of cytokines. Another event resulting from generation of MAP-kinases is activation of phospholipase A2 with release of arachidonic acid and production of prostaglandins and leukotrienes [10–12] (Fig. 3).

Fig. 2 Schematic diagram showing life cycle of the basophil and its surface receptors. The cells develop in the bone marrow and circulate in the blood. Some can accumulate in inflamed tissues such as the skin in chronic urticaria or the respiratory tract in allergic rhinitis and asthma. Basophils like mast cells have an IgE receptor. IL-3 is a primary cytokine stimulating basophil activation, expansion, and survival. Basophils produce and/or store numerous mediators such as LTC₄, PAF, and IL-4, IL-5, and IL-13

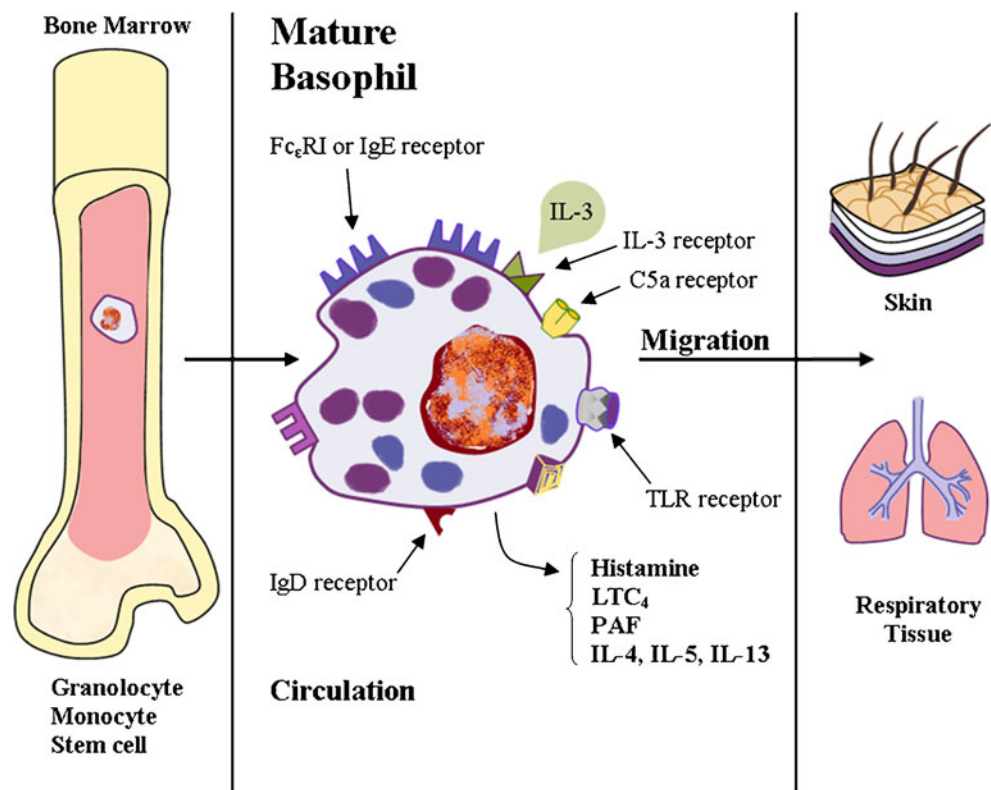
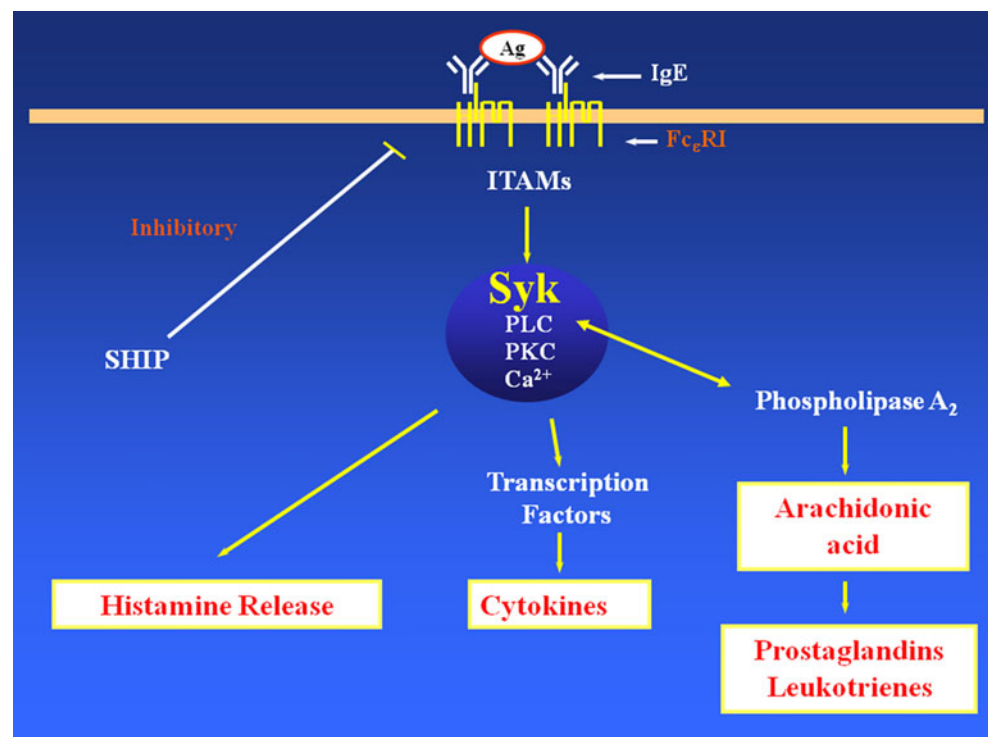


Fig. 3 Schematic pathways of FcεRI-mediated signaling in mast cells. Central regulatory function of Syk in promoting histamine release and cytokine, leukotriene, and prostaglandin synthesis. In contrast, SHIP has inhibitory activity. Modified from Ref. [10]



Aggregation of cell surface receptors also stimulates pathways to turn off mast cell and basophil activation and down regulate inflammatory pathways. These mechanisms are similarly complex and act in opposition to activation of pro-inflammatory pathways. Dysregulation of the balance between mast cell activation and suppression leads to urticaria and angioedema in a manner that is not completely understood.

Two well-described negative regulatory molecules are Src homology 2 (SH2) containing inositol phosphatases (SHIP-1 and SHIP-2). These molecules can dephosphorylate positive signaling mediators and control the activation and degranulation of mast cells and basophils [10]. It is probable that dysregulation at some stage of these biochemical steps is a pathogenic mechanism responsible for some forms of chronic urticaria [13]. However, it must be stated that the understanding of these signaling events has been developed primarily by study of mouse models or malignant mast cell lines which may have essential differences from non-malignant human cells. Also, most studies have used signaling through the FcεRI receptor as a method to study cell activation. However, in chronic idiopathic urticaria there is no evidence of an allergen causing the disease, hence no evidence that IgE receptors are activated through normal immediate type I hypersensitivity pathways. Furthermore, blood basophils and tissue mast cells are distinct cells of different lineages, and it is not clear which cell type is the most important in the pathogenesis of chronic urticaria. Thus, model systems established with one cell type may not be representative of the actual pathologic events causing disease in patients [10].

Mediator Releasability from Mast cells and Basophils in Chronic Urticaria

Since mast cell and basophil mediator synthesis, degranulation, and release are characteristics of urticaria and angioedema, a number of investigators have questioned whether an abnormal intracellular signaling pathway(s) might be one aspect of the pathogenesis of chronic and especially idiopathic urticaria. Saini and co-workers recently studied SHIP-1, SHIP-2, and Syk protein levels in cultured mast cells from patients with chronic urticaria and normals [13]. Twenty-four individuals were studied, six with responsive chronic urticaria (responders), eight with non-responsive chronic urticaria (non-responders), and 10 normal controls. The definition of responsive versus non-responsive was based on greater than or less than 10 % histamine release respectively from mast cells following stimulation with anti-IgE. In this complex study, the investigators isolated basophils and CD 34 positive mast cell progenitors from blood and matured the progenitors with c-kit ligand and other activators. After 5 to 8 weeks in culture, these cells matured into characteristic mast cells and the cells derived from the three patient populations did not differ in phenotypic or cell receptor characteristics [13]. However, measurements of SHIP-1, SHIP-2, and Syk showed significant differences among the cells derived from these three populations of subjects (Fig. 4).

Mast cells from responsive chronic urticaria patients had lowered SHIP-2 and elevated Syk levels compared to the other two populations. SHIP-1 levels were not different

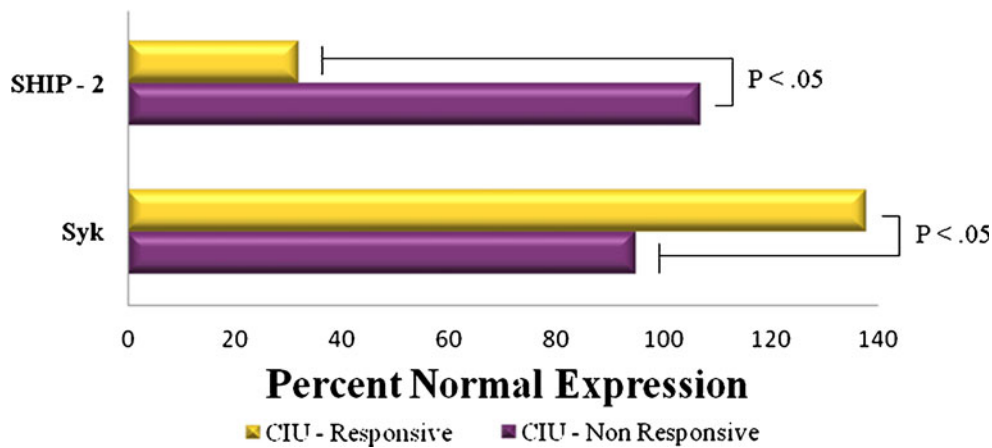


Fig. 4 SHIP-2 and Syk levels in cultured mast cells from chronic urticaria patients. Patients were characterized as either responsive or non-responsive based on mast cell histamine release. Cells from responsive patients had lower SHIP-2 and higher Syk levels. SHIP-1

values did not differ (not shown). These data support the concept that SHIP proteins downregulate and Syk promotes mast cell degranulation and dysregulation of these functions is an underlying mechanism of chronic urticaria. Modified from Ref. (13)

amongst the groups. In addition, Saini et al. showed statistically higher histamine release from cultured mast cells of the chronic urticaria patients versus controls and a trend toward higher spontaneous release from responder patient mast cells versus non-responder patient mast cells [13].

Since SHIP-1 and SHIP-2 downregulate mast cell and basophil activation and degranulation and Syk promotes these events, these findings suggest that abnormalities in intracellular signaling pathways may be an underlying mechanism of chronic urticaria.

In related studies, Vonakis et al. examined histamine release from hyper-releasable human basophils and in parallel measured SHIP, Syk, and another intracellular signal molecule Lyn [14].¹ They found a deficiency in SHIP but not Lyn or Syk and that this defect was specific to basophils and not measurable in lymphocytes or monocytes. Furthermore, they found that mRNA levels for SHIP were normal in the basophils indicating that this was a post transcriptional abnormality. Their data also showed a negative correlation between basophil cellular SHIP levels and in vitro basophil histamine release in response to a histamine-releasing factor.

In an extension of this work to populations of urticaria patients, the same investigative group examined SHIP-1, SHIP-2, and Syk levels in blood basophils from patients with cold urticaria, chronic idiopathic urticaria, and normal donors [15]. In this study, these investigators found that patients with chronic idiopathic urticaria could be divided into two groups based on basophil histamine release in response to anti-IgE. Half of their subjects were non-responders and half responders. The responders had histamine release similar to controls and patients with cold

urticaria. In addition, there were no differences in Syk in the basophils of the different patient populations, but cells from chronic urticaria patients who were non-responders had increased SHIP-2 levels and responder chronic urticaria patients and cold urticaria patients had decreased SHIP-1 levels.

Lastly, this work looked at the presence of serum histamine-releasing factors and anti-FcεRI antibodies in relationship to basophil phenotype and found no correlations. This study, while valuable in describing basophil abnormalities in chronic urticaria, does not provide us with a universal mechanism for understanding of the pathogenesis of this condition, but the authors conclude that signaling pathway abnormalities may cause elevated histamine release in this disease.

In another approach to look for heightened basophil function in chronic urticaria, Vasagar et al. [16] examined surface markers of activation on basophils in patients with this condition compared to allergic and non-allergic subjects without urticaria. They used CD 63, 69, and 203c as specific markers. CD 63 is a member of the transmembrane-4 superfamily and rapidly appears on basophils following stimulation with IL-3, anti-IgE, or other activators. CD 69 is another basophil marker but it is more slowly expressed on these cells after activation. CD 203c is an ectonucleotide pyrophosphatase unique to basophils and mast cells. CD 63 was significantly elevated on cells from chronic urticaria and allergic patients compared to non-allergic controls. CD 69 was variable in expression in chronic urticaria patients and most consistently elevated on cells of allergic subjects. Expression of CD 203c showed no difference amongst the groups. These authors also looked for correlations among serum histamine-releasing factor activity, immunoreactivity to FcεRI, and the CD 63, 69, and CD 203c markers; however, none were found. These investigators concluded that

¹ In this study, the authors did not distinguish between SHIP-1 and SHIP-2 values.

basophil activation markers, in particular CD 63, are elevated in chronic urticaria patients but do not correlate with serum factors implicated by others as a cause of this disease in a large percentage of patients [16].

Autoimmune Urticaria

An extrinsic cause of chronic urticaria is almost never determined. Chronic urticaria and angioedema remain “idiopathic” in over 50 % of cases. The first author to suggest an autoimmune etiology of chronic urticaria/angioedema was Lezhoff [17]. He recognized that there was an unusually frequent association between thyroid disease, the presence of thyroid autoantibodies, and chronic urticaria. Specifically, it was known that thyroglobulin and/or thyroid peroxidase antibodies are present in 3–6 % of the general population but 15–30 % of patients with chronic urticaria/angioedema [17]. Since the presence of thyroid autoantibodies frequently precedes the development of Hashimoto’s thyroiditis or other autoimmune diseases, this led a number of investigators to question whether chronic urticaria was an autoimmune disease in some patients.

The first authors to detect autoantibodies and propose that the autoantibodies themselves were pathogenic for chronic urticaria or angioedema were Gruber et al. [18]. These investigators looked for evidence of IgG and IgM autoantibodies against IgE in patients with cold urticaria, urticarial vasculitis, and chronic urticaria. They found IgG anti-IgE antibodies in five of nine (55 %) cold urticaria patients, four of eight (50 %) urticarial vasculitis patients and three of six (50 %) chronic urticaria patients. In addition, two of nine cold urticaria patients had IgM anti-IgE antibodies [18]. Several of these sera were also active in producing histamine release in an *in vitro* assay using normal blood basophils. Shortly thereafter, Hide and co-workers studied a group of 26 patients with chronic urticaria and 10 healthy controls [19]. Sera from 17 of the 26 patients induced *in vitro* basophil histamine release; however, in 12 of the 17 they had evidence that the activator of histamine release was not anti-IgE [19]. They went on to identify that the activator in these patients as an IgG autoantibody against FcεRI.

Fiebiger et al. further investigated this autoantibody a few years later [20]. They collected sera from 32 patients with chronic urticaria as well as 20 with atopic dermatitis and 15 healthy subjects. They isolated IgG from sera and performed experiments to detect immunoactivity of the isolated IgG with recombinant FcεRI. They found that 12 of 32 (32 %) of the chronic urticaria patient specimens reacted with FcεRI using Western blot analysis [20]. They confirmed this finding by showing that only immunoblot positive IgG preparations precipitated FcεRI from FcεRIαγ-transfected CHO

cells. In contrast, IgG autoantibodies to FcεRI were not found in the sera of any atopic dermatitis or healthy control patients (Fig. 5). In additional studies, these investigators looked for IgG anti-IgE antibodies and found them present in 69 % of chronic urticaria patients, 73 % of atopic dermatitis patients, and 26 % of normal controls [21]. The authors concluded that the presence of IgG autoantibodies to FcεRI is specific for chronic urticaria patients compared to controls and atopic dermatitis patients, and may indicate a causative role of the disease in some patients (Fig. 5).

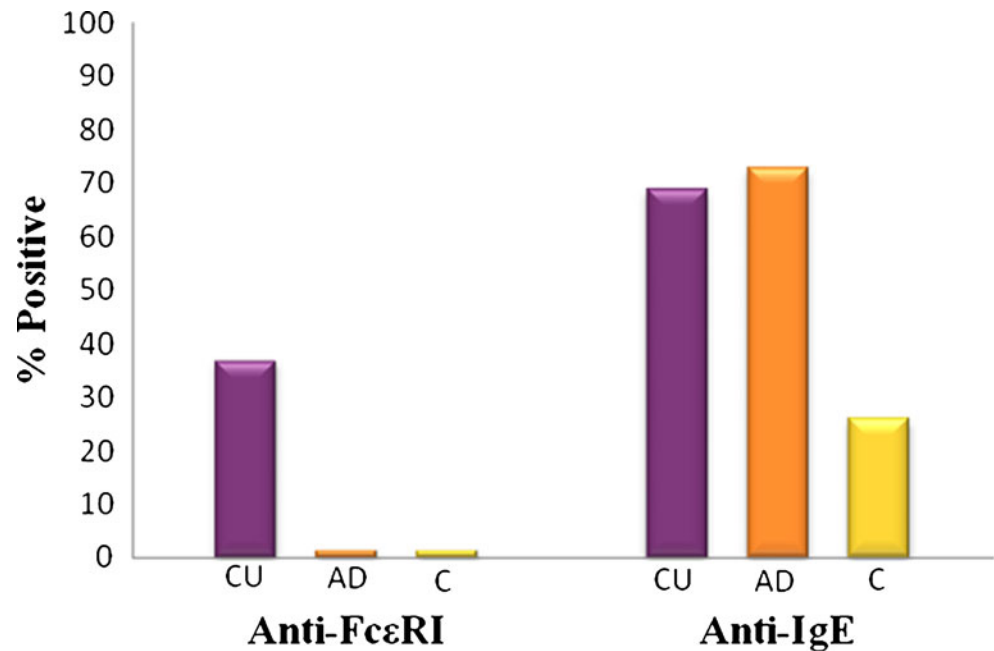
The same authors also point out that not all patients (only 37 % in this study) possess the antibody and in not all patients was the antibody able to stimulate *in vitro* histamine release. They speculated that the isotype of the IgG and its complement fixing ability may be important in the functionality of the autoantibody and hence its ability to produce disease.

In a follow-up paper, the same group of investigators developed an ELISA to measure antibodies to FcεRI in a large group of chronic urticaria patients and individuals with a variety of other immunologic skin diseases [21]. Specifically, they studied 281 patients with chronic urticaria, 32 with atopic dermatitis, 15 with systemic lupus, 30 with psoriasis, 22 with bullous pemphigoid, 45 with dermatomyositis, and 28 with pemphigus vulgaris. They also collected sera from 41 healthy controls. They detected autoantibodies to FcεRI in 106 of 281 (38 %) chronic urticaria patients but not in any atopic dermatitis or healthy control samples [21]. In contrast, however, anti-FcεRI autoantibodies were found in 39 % of pemphigus vulgaris, 36 % of dermatomyositis, 20 % of systemic lupus, and 13 % of bullous pemphigoid patients, again suggesting a role of autoimmunity as a pathogenic mechanism for chronic urticaria.

The authors also noted that the histamine-releasing activity and IgG subclass specificity was different between specimens from chronic urticaria patients and those with the other diseases. In chronic urticaria patients, the autoantibody had histamine-releasing activity and was usually of the complement fixing IgG1 or IgG3 subclass. In contrast, in the other diseases, the patients’ sera had non-complement activating IgG2 or IgG4 subclass antibodies. These authors showed further that C5a receptor blockade of basophils or complement depletion substantially reduced the histamine release function of autoantibody positive sera from chronic urticaria patients. Hence, these data reveal that IgG subclass 1 and 3 complement fixing autoantibodies to FcεRI are specific to chronic urticaria and likely to be causative of the disease in a subset of patients.

Subsequently, a collaborative study between two groups, one in the UK and the other in Austria, examined the relationship between type of antibody and disease severity in chronic urticaria [22]. They studied 28 patients with chronic urticaria, 15 with dermatographism, 10 with cholinergic urticaria, and

Fig. 5 Percentage of patients with chronic urticaria (CU), atopic dermatitis (AD), and normal controls with anti-FcεRI and anti-IgE antibodies. Only patients with CU demonstrated anti-FcεRI antibodies, but all populations had IgG anti-IgE antibodies, indicating that the former antibody was specific to CU and causative of the disease in some patients. Adapted from Ref. (20)



39 healthy controls. Only patients with chronic urticaria had histamine-releasing autoantibodies. Within that group, the investigators defined five characteristics: histamine releasing anti-FcεRI autoantibodies in 26 %, non-histamine releasing anti-FcεRI autoantibodies in 15 %, anti-IgE like autoantibodies in 9 %, a mast cell specific histamine releasing factor in 9 %, and patients with no identifiable factor in 41% [22]. Patients with more severe chronic urticaria had histamine-releasing activity in their sera and positive autologous serum skin tests, which is an in vitro diagnostic test for autoimmune urticaria.

Lastly, in this regard, Mozena and co-workers examined the antibody cross-reactivity between thyroid autoantibodies and anti-FcεRI antibodies in patients with chronic urticaria [23]. The rationale for this study was that 30 % of chronic urticaria patients also have Hashimoto's thyroiditis and others have anti-thyroid antibodies. Because most of these patients are euthyroid, the clinical significance of anti-thyroid antibodies in chronic urticaria is unknown. The authors studied 20 chronic urticaria patients. Twelve of the 20 had anti-FcεRI antibodies, 13 had a positive autologous skin test, nine had either anti-thyroglobulin or anti-thyroid peroxidase antibodies, and six were clinically hypothyroid requiring exogenous thyroid replacement. Further studies examined the sera for cross-reactivity or epitope sharing between anti-FcεRI and thyroid autoantibodies. None was found. Specifically, anti-FcεRI antibodies were depleted with addition of soluble FcεRI but not anti-thyroid peroxidase or thyroglobulin antibodies.

As mentioned above, an in vivo clinically useful test has been developed to look for histamine-releasing autoantibodies in patients with chronic urticaria. It is called the autologous serum skin test (ASST). It is performed by taking a blood

specimen from a subject, allowing the blood to clot, centrifugation to remove the serum, and injection of 50 µl into the epicutaneous layer of the volar forearm. Histamine and saline are used as positive and negative controls, respectively. The test is read at 15 or 30 min and a positive test is defined as an increase in wheal diameter of at least 1.5 or more.

Platzer et al using this in vivo assay as a standard compared the results of the ASST with an in vitro basophil histamine release test [24]. They found the histamine release assay had both a specificity and sensitivity of 75 % in patients with chronic urticaria and was negative in control populations of atopic dermatitis patients, pollen allergic patients, and normal controls.

A quite recent paper examined the correlation between the ASST test and chronic urticaria severity in a cohort of 69 patients [25]. In this group, 39 % or 56.5 % of patients were female and 59.4 % tested ASST positive. The patients with positive ASST tests had more severe disease by several measures, including higher daily frequency of hives, higher number of hives, mean size of hives, and disease activity score. In contrast, an earlier paper, which compared ASST positivity and clinical severity, did not detect any correlation [26]. In this study, 85 patients with chronic urticaria were studied, and 21 % or 24.7 % had positive ASST tests. There was no difference in the number or size of wheals, severity or symptoms, or extent of body involvement between ASST positive and negative subgroups.

Treatment

Chronic urticaria and angioedema are very frustrating conditions for physicians and patients alike. Most patients try to

find an explanation from observing the events in their life at the time of an attack. This usually leads to confusion and a usually erroneous implication of various foods, medications, topical contactants (i.e., cosmetics, clothing fabrics, clothing washing products) or environmental factors as presumed causes. In reality, these are almost never the explanation. Yet patients will develop an illogical and extensive list of agents they perceive as the cause of their urticaria or angioedema. The most basic form of treatment and management of all types of urticaria is simply avoidance of exacerbating stimuli such as stress, alcohol ingestion, and use of NSAIDs. Additionally, cooling lotions can help reduce the desire to itch [27]. The most common form of drug treatment for urticaria is H1 antihistamines. This is because the majority of symptoms of urticaria are caused by release of histamine from mast cells and basophils and the stimulation of the H1 receptors in skin [28]. Antihistamines also may act as anti-inflammatory drugs and inhibit basophil and mast cell cytokine release. The effect of antihistamines is dose dependent and therefore higher doses are often needed, compared to use of these drugs to treat other conditions such as allergic rhinitis. This can, however, lead to sedative side effects.

H1 Antihistamines

H1 antihistamines are the first choice and the most common form of treatment for acute and chronic urticaria. The first generation of these drugs causes unintended and undesired central nervous system and anticholinergic side effects, primarily drowsiness and mucosal dryness. The second-generation antihistamines are much less likely to cause these side effects because they have a much greater selectivity for H1 receptors and are less able to cross the blood–brain barrier. The second-generation antihistamines also have a significantly favorable pharmacokinetics, which provides for a less frequent dosing schedule, and potentially better patient compliance [29]. This class of drugs has been proven very effective in treating most patients suffering from acute and chronic urticaria.

Studies of H1 antihistamines in urticaria have generally been of two study designs: either an active drug versus placebo or a comparison of two or more active drugs (head-to-head studies). An example of a placebo-controlled study examined levocetirizine in 166 patients and its effects on symptoms and overall quality of life in adult patients with chronic urticaria. Levocetirizine showed statistically greater reduction of pruritus and a 24 % improvement in quality of life compared to only 8 % with placebo [30]. Another similar study examined once daily levocetirizine versus placebo and compared the effects of these treatments on pruritus, number and size of wheals, and number of urticarial episodes over 6 weeks. This comparison showed a reduction

from baseline for total symptom score of 81 % for the active drug compared to 1 % for placebo over a 6-week period [31]. Similarly designed studies comparing loratadine, desloratadine, and fexofenadine versus placebo have also been performed. In all cases, these studies have shown each drug to be superior to placebo in controlling the physical signs and symptoms of urticaria [29].

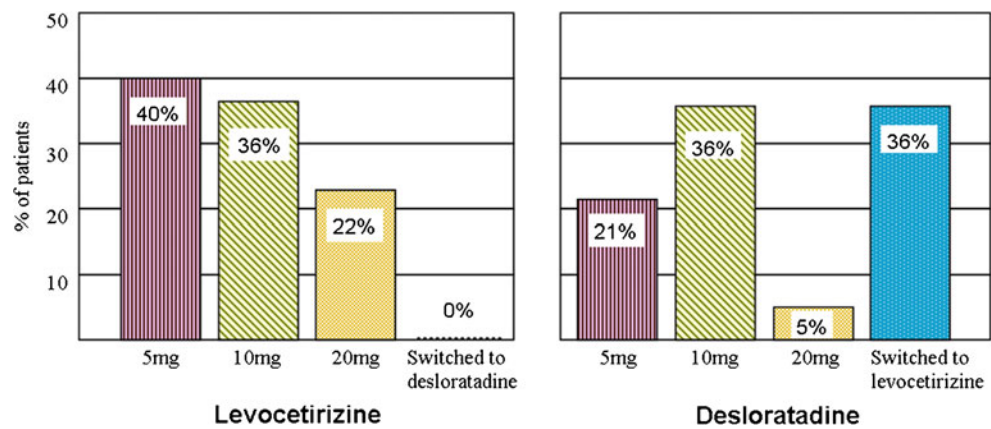
Numerous head-to-head comparison studies of two antihistamines for treating chronic urticaria have also been published. An example of such a study was performed by Staevska et al. who compared levocetirizine and desloratadine [32]. This group also investigated higher than conventional dose treatment up to four times the Federal Drug Administration (FDA) recommended doses of each drug. Eighty patients were enrolled and the subjects were assigned study drugs in a double-blinded protocol. The investigators recorded wheal and pruritus scores, quality of life, patient discomfort, drowsiness, and other side effects. They started treatment at daily doses of 5 mg for each drug and increased as necessary to 20 mg with each agent. Thirteen patients responded well to standard 5 mg doses, but 28 required 10 or 20 mg to become asymptomatic. Overall, this study showed that levocetirizine was the more effective of the two drugs. Seventy-five percent of patients required higher than recommended doses to achieve a response and these higher doses did not increase drowsiness or other side effects (Fig. 6).

Another comparison study was conducted by Hong et al. [33]. These investigators conducted a 6-week double-blind parallel group study comparing the efficacy and safety of levocetirizine and desloratadine in 64 adult patients with chronic urticaria. In this case, conventional 5 mg doses of each drug were given daily. This study showed that levocetirizine produced a better treatment response than desloratadine; however, it also caused higher sleepiness scores for the first 2 weeks of the study. After that point, there was no difference in the sedating effect between the two drugs.

H2 Antihistamines

A limited number of studies have shown H2 antihistamines to be of benefit in acute urticaria. Anecdotal reports suggest that intramuscular cimetidine and famotidine were both effective in resolving itching and cutaneous erythema and swelling in 15 to 30 min with less sedation than treatment with intramuscular diphenhydramine. Subsequently, a prospective, double-blind controlled trial was conducted in 25 patients with urticaria of less than 72-h duration [34]. This study compared a single dose of intramuscular famotidine 20 mg against 50 mg of diphenhydramine. In this double-blinded study, both patient and physician assessments

Fig. 6 Comparison of levocetirizine and desloratadine. This figure shows the percentage of patients whose urticaria was well controlled by each drug at various doses between 5 and 20 mg and the percentage of patients who switched to the alternative drug. Levocetirizine was the more effective drug and no patient required switching to desloratadine. Adapted from Ref. (32)



indicated that famotidine was equivalent to diphenhydramine in reducing pruritus and body surface area affected by hives. Two earlier double-blinded trials reached similar conclusions regarding cimetidine, concluding that it was comparable to diphenhydramine in treatment of acute urticaria [35, 36].

Antileukotrienes

Leukotrienes are lipid mediators derived from arachidonic acid. They have been shown to be important in inflammatory reactions in the respiratory tract especially in asthma; however, it is also likely they are involved in cutaneous inflammatory diseases [37, 38]. Leukotrienes are pro-inflammatory mediators and can increase vascular permeability. Leukotrienes are produced by eosinophils, basophils, and mast cells which are all involved in urticarial reactions. When injected in skin, leukotrienes are able to produce a wheal and flare and stimulate itching with 100-fold greater potency than histamine [37]. Two classes of leukotriene antagonist drugs have been developed. The first class includes the LTD₄ leukotriene receptor antagonists, montelukast and zafirlukast. The second class affects leukotriene synthesis by blocking 5-lipoxygenase. From the second class, there is only one medication, zileuton, approved for use in the USA [38] (Fig. 7).

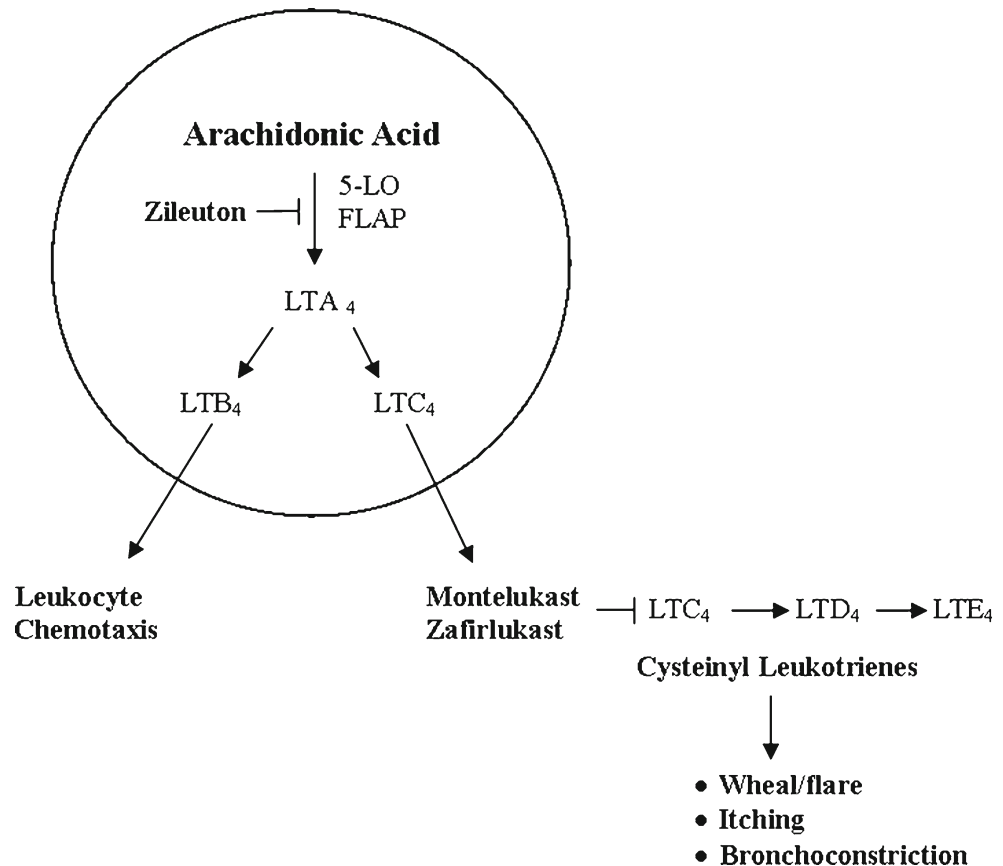
A number of studies have investigated the effectiveness of leukotriene antagonists in treating urticaria. Some have looked at these drugs as solo treatment compared to H1 antihistamines and others investigated antileukotriene drugs in combination with antihistamines. A group of researchers in Italy conducted a double-blind placebo-controlled study comparing the effects of montelukast and cetirizine. A total of 51 patients were evaluated, all suffering from chronic urticaria. These researchers found that the montelukast treated group had a higher percentage of symptom-free days than those in the placebo and cetirizine groups. The patients receiving montelukast also had lower disruption of sleep

due to attacks [39]. Another group of researchers performed a double-blind study with 27 patients. Fifteen patients were randomized to the montelukast group and 12 to the fexofenadine group. These individuals were observed over 30 days and the patients on fexofenadine recorded worse average scores than those receiving montelukast [40]. One further study was a single-blind placebo-controlled, crossover trial looking at the effects of montelukast. A total of 30 patients were enrolled all of whom had responded poorly to antihistamines or combined therapy with corticosteroids or cyclosporin. They were divided into two groups, one receiving 10 mg montelukast and the other receiving 10 mg placebo and an H1 antihistamine as needed. Results of this study indicated that patients responded to montelukast and 18 of 30 subjects were totally free of symptoms with no antihistamines requirement [41]. In all of these studies, no adverse reactions were observed with montelukast therapy. Since antileukotrienes do not affect the action of histamine these findings suggest that there are other mediators besides histamine that are involved in the pathogenesis of urticaria.

In addition to the above studies on the effects of antileukotriene monotherapy, several studies have been conducted to observe the efficacy of combination therapy. One group performed a double-blinded, placebo-controlled study in which 81 patients were enrolled and divided into three groups. One group received placebo only, the second received desloratadine and placebo, and the third group received desloratadine and montelukast. These researchers found that groups two and three had significant improvements in overall symptoms compared to the placebo group. Furthermore, the group receiving combination active therapy reported significantly greater improvement compared to those receiving desloratadine alone [42]. In contrast, however, another larger study came to a different conclusion. These investigators recruited 160 patients and divided them into four groups. The groups were defined by the following treatments: (1) 5 mg desloratadine in the morning and placebo in the evening; (2) 5 mg desloratadine in the morning

Fig. 7 Schematic pathways of leukotriene biology. Leukotrienes are synthesized from arachidonic acid in eosinophils, basophils, and mast cells. The enzyme 5-lipoxygenase (5-LO) and 5-lipoxygenase-activating protein (FLAP) led to the generation of two products LTB₄ and LTC₄. LTB₄ is primarily a leukocyte chemotactic factor. LTC₄ is sequentially converted into LTD₄ and LTE₄. These are collectively termed cysteinyl leukotrienes. These molecules can produce itching and a wheal and flare in skin and bronchoconstriction in the lungs. Zileuton is a 5-LO inhibitor and blocks production of all leukotrienes, while montelukast and zafirlukast block the actions of cysteinyl leukotrienes at the receptor

Eosinophil, Basophil, or Mast Cell



and 10 mg montelukast in the evening; (3) placebo in the morning and 10 mg montelukast in the evening; (4) placebo in both morning and evening. Of the four groups, only those receiving desloratadine as monotherapy or in combination completed the study. Twenty-seven of 40 patients in the montelukast group and 35 of 40 patients in the placebo group discontinued treatment before the end of the 6-week study period due to uncontrolled symptoms. The primary endpoints of this study were daily cutaneous symptom scores. The researchers also recorded instantaneous evaluation, interference with sleep and daily activities, and the need of rescue medication. These investigators found that treatment with desloratadine was effective; however, they observed no difference between those receiving it as monotherapy or in combination with montelukast. They concluded that desloratadine is more effective than montelukast in treating urticaria and combination therapy did not prove to have any significant added advantage [43]. Again, in these studies no or only minor adverse effects were observed. The contradictory conclusions in these studies illustrate the problems associated with evaluation of efficacy of various drugs in urticaria, which is often complicated by a significant placebo effect.

Corticosteroids

For some patients with chronic urticaria, H1 and H2 antihistamines and/or antileukotriene drugs are insufficient to provide adequate relief of symptoms. Corticosteroids are frequently the next medication prescribed to patients. Although this is a common practice, there are few studies to evaluate the benefit of this treatment.

Recently, Asero and Tedeschi carried out a retrospective analysis of 750 patients with chronic urticaria [44]. Six hundred and sixty (660) or 88 % responded adequately to antihistamine treatment. The remaining patients were treated with a tapering course of oral prednisone, on a schedule of 25 mg daily for 3 days, followed by 12.5 mg daily for 3 days and finally 6.25 mg daily for another 4 days. In 40 of 86 patients, this treatment induced a remission of the urticaria such that continued control was possible with standard doses of antihistamines. However, in 35 patients only a transient remission was induced and antihistamine control was again insufficient. Twenty-three of these 35 transient responders agreed to a second prednisone course, and in eight of the 23 patients, long-term remission was induced. The authors concluded that almost 50 % of chronic urticaria

patients could be induced into remission after a 10-day tapering course of prednisone and another 9 % after a second identical treatment. Corticosteroids should be avoided for long-term treatment because at high dosage they can lead to many side effects, including but not limited to bone demineralization, osteonecrosis, hypertension, diabetes, cataracts, and glaucoma. A list of adverse effects of chronic corticosteroid use is shown in Table 1.

Immunosuppressive Treatments

Besides corticosteroids, other immunosuppressive regimens may be indicated in patients suffering from autoimmune and recalcitrant chronic urticaria. These patients are often unresponsive to antihistamines even at substantially higher than recommended doses. Immunosuppressive agents used to treat chronic urticaria include cyclosporin, methotrexate, hydroxy-chloroquine, and sulfasalazine.

The drug with which there is the greatest amount of experience in the treatment of autoimmune or recalcitrant urticaria is cyclosporine. This drug is able to downregulate Th1 cells and T-cell-dependent antibody formation. It is also able to inhibit anti-IgE stimulated histamine release from basophils and mast cells. A double-blind study performed in the UK evaluated the potential therapeutic effects of cyclosporine on 30 subjects with chronic urticaria [45]. The authors assessed clinical severity by recording daily urticaria activity score of wheals and itching and investigated in vitro response by measuring histamine releasing activity of patient sera using a basophil histamine release assay. Patients either received daily cyclosporin or placebo over 4 weeks and were followed for up to 20 weeks. By week 4, eight of the 19 patients receiving active treatment responded to cyclosporine, whereas no placebo-treated patients responded. The mean histamine-releasing activity in the treatment group dropped from 36 % at baseline to 5 % after

treatment [44]. The researchers concluded that these findings were significant and that cyclosporin is an effective form of treatment for chronic urticaria [45].

An earlier, uncontrolled study enlisted 12 patients with chronic urticaria who did not respond to antihistamines or corticosteroids [46]. These patients were treated with low dose cyclosporin over 4 weeks. Nine of the patients experienced improvement with full resolution of symptoms. Seven of the nine reported that the benefit lasted for at least a month after stopping therapy. The remaining three patients experienced no benefit. Another study recruited 35 patients with chronic urticaria who experienced attacks almost daily and were unresponsive to H1 antihistamines solely or in combination with H2 drugs [47]. Twenty-five of the 35 patients were randomly selected to receive active treatment, while 10 were a control group. Patients were graded on an urticaria score as follows: 0=no symptoms; 1=mild urticaria; 2=moderate urticaria; 3=severe urticaria. Of the 25 patients receiving cyclosporin, two dropped out due to unrelated issues and four showed no benefit. The remaining 19 were followed for 6 months and showed rapid recovery while on cyclosporin. The investigators observed significant improvement in symptoms [46]. All of the patients dropped their urticaria scores from 3 on a maximum scale of 4, to 0–1 by the end of week 1. These patients were able to discontinue use of other medications. By week 4, some urticaria symptoms resurfaced; however, patients were able to control these by the addition of antihistamines [47].

Researchers have also looked into using cyclosporin as treatment of chronic urticaria in pediatric patients. One recent study evaluated 54 children with chronic urticaria [48]. They found that seven of these patients did not respond to antihistamines and were thus put on cyclosporin, receiving two doses daily for varying periods up to 2 years. All seven patients had reduced symptoms after treatment and no side effects. These researchers concluded that cyclosporin is an effective form of treatment in pediatric and adolescent age groups [48].

Methotrexate has also been studied as a treatment for chronic urticaria. Methotrexate acts by inhibiting folic acid from being converted to folinic acid by dihydrofolate reductase in dividing cells. It therefore acts as an immunosuppressant by inhibiting lymphocytes [49]. A retrospective case review study of 16 patients with steroid-dependent chronic urticaria was performed. These patients had been unresponsive to H1 and H2 antihistamines and a variety of other drugs including montelukast, cyclosporin, and various other unconventional therapies [49]. Tests for autoimmunity by either ASST or in vitro basophil histamine release had been performed in 11 of the 16 and were positive in seven of these. Therefore, some had confirmed autoimmune chronic urticaria, while others chronic idiopathic urticaria. The 16 patients were treated with methotrexate and scored on a scale of (1) no benefit, (2) some benefit (reduction in number

Table 1 Commons side effects of corticosteroids

Rapid onset
Mood change—anxiety, depression, paranoia
Insomnia
Fluid retention
Bruising
Oral thrush
Delayed
Cataracts
Glaucoma
Osteopenia, osteoporosis
Growth retardation—children
HPA axis suppression

of wheals and symptoms but no reduction of steroid dose), (3) considerable benefit (reduction in number of wheals and symptoms with reduction of steroid dose), and (4) clear (no further wheals, off steroid, but on antihistamines) [48]. The researchers found that 12 of the patients responded to the therapy. Seven of these 12 were able to reduce their steroid dose, in other words experiences a stage 3 response. Two were able to stop steroids completely, i.e., a stage 4 response. Researchers found the best dosage was once weekly administration of 10–15 mg of methotrexate [48]. Methotrexate was effective in patients whether or not they had evidence of autoantibodies. Therefore, these researchers concluded that the presence of autoantibodies does not predict a response. They did, however, conclude that methotrexate can be an effective form of therapy in steroid-dependent patients with chronic urticaria that does not respond to antihistamines or a variety of other agents [49].

Sulfasalazine has been studied via a retrospective chart review of 19 patients with chronic urticaria. [50]. All 19 patients had tried different antihistamines and were still unable to control their symptoms. Fourteen of the 19 (74 %) reported significant improvement after starting therapy with sulfasalazine. Four (21 %) reported non-significant improvement and one patient (5 %) reported the symptoms worsening. Six patients were able to terminate other therapy. Seven patients (37 %), however, reported experiencing unintended side effects such as headaches and gastrointestinal discomfort [50].

Hydroxychloroquine has also been investigated in treating chronic urticaria. A group of Australian investigators recruited 21 patients with chronic urticaria [50]. They were randomly divided to receive treatment with standard therapies (corticosteroids or H1 or H2 antihistamines) with or without hydroxychloroquine. Urticaria control was measured at baseline and at 12 weeks by assessing urticaria score, quality of life, and medication use. The researchers found that the group receiving hydroxychloroquine had significant improvement in quality of life, although there was no significant change in medication or urticaria score [51].

An Algorithm for the Treatment of Chronic Urticaria

Because of the potential side effects of chronic corticosteroids, it is best to exhaust all other less “dangerous” treatments before embarking on this mode of therapy. The basic principal of treating chronic urticaria falls under the age old adage, “First, do no harm”. For this reason, we recommend the use of second- or third-generation antihistamines as a first line therapy. The dose may be increased beyond what is customarily used for allergic rhinitis. Most people do not experience sedation even at these higher doses. The next

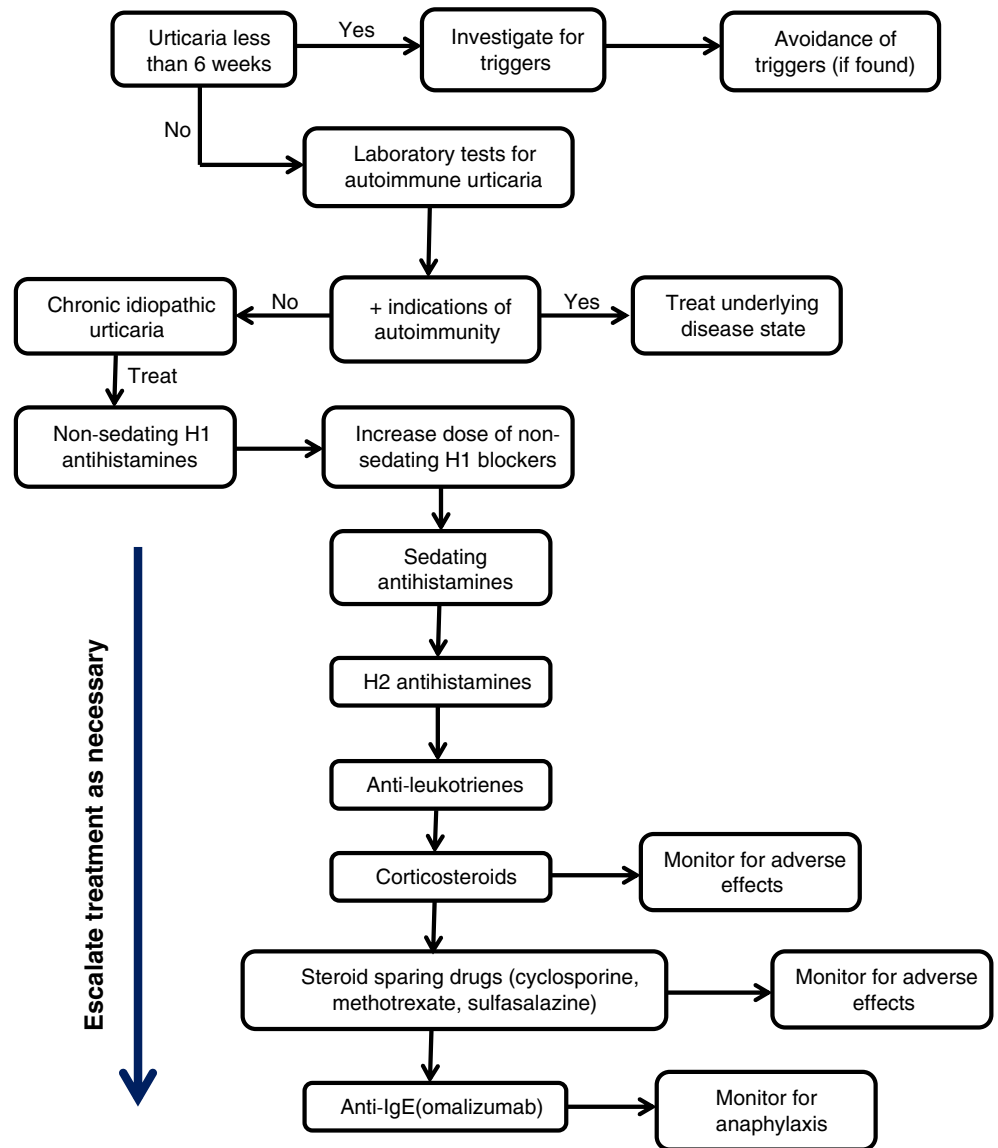
step is to add either an H2 blocker or to use a sedating antihistamine or both. People on regular sedating antihistamines frequently report a resolution of the sedative side effects after a few days. H2 blockers, while not found to be the most effective agents, are relatively harmless and may have the potential of providing slight additive benefit to H1 blockers. After the use of antihistamines has been maximized (or optimized), then if the patient is still experiencing symptoms, we will add the use of anti-leukotriene pathway agents, such as montelukast. If all this fails, only then will we resort to second tier drugs such as immunosuppressives, including corticosteroids, cyclosporine, or methotrexate. Greater vigilance to clinical side effects and abnormal laboratory tests must be conducted in these cases (Fig. 8).

New and Developing Treatments for Chronic Urticaria

Omalizumab is a humanized mouse monoclonal antibody against IgE. It is approved for use in severe, poorly controlled asthma. However, it has been used off label and in phase II research for treating severe chronic idiopathic urticaria. Anti-IgE targets the apparent abnormality in idiopathic or autoimmune urticaria, which is pathologic development of an autoantibody to the IgE receptor, FcεRI or IgE itself. Omalizumab has also been shown to be associated with a reduction of tissue eosinophil accumulation and downregulation of FcεRI expression on mast cells and basophils. It is presumed that omalizumab works in treating chronic urticaria by a competitive binding mechanism, so that the pathologic autoantibody has fewer receptors or IgE molecules with which to interact.

Twelve patients with autoimmune urticaria who presented with symptoms and did not respond to antihistamines were recruited into a study on the efficacy of omalizumab. They were initially treated with a placebo for 4 weeks and then omalizumab every 2 or 4 weeks over a total duration of 16 weeks. The researchers recorded change from baseline to the final 4 weeks of treatment with omalizumab by mean urticaria activity score and noted changes in use of rescue medications and quality of life. They found a significant improvement in quality of life and a decline in urticaria activity score and need of rescue medications. In fact, seven patients had their symptoms resolve completely [52]. Another group reported on three different patients that did not respond to antihistamines, both H1 and H2, and antileukotrienes. These individuals were treated with omalizumab every 2 weeks. Two of the patients were completely symptom free after starting therapy [53]. One additional case report discusses a 51-year-old woman who suffered from chronic urticaria. She did not respond to antihistamines or combination therapy with montelukast. Prior to treatment with omalizumab, she had a five-fold greater level of the IgE receptors compared to a healthy control subject. After

Fig. 8 Algorithm for the diagnosis and treatment of chronic idiopathic urticaria



14 days and just the first treatment this level decreased by 80 % and was maintained at this reduced level for the year of treatment[54].

Summary

Although extensive time and effort has been invested by numerous investigators to elucidate the causes of chronic urticaria, at least 80 % of cases remain unexplained or idiopathic. Two lines of evidence indicate that abnormalities of signal transduction in mast cells and basophils and development of autoantibodies to FcεRI or to IgE on these

cells are mechanistic causes of this disease. Recent experimental evidence showing that omalizumab is highly effective in treating patients with chronic urticaria suggests a previously unrecognized indication for this drug. This has further spawned novel concepts about the pathophysiology of chronic urticaria. Omalizumab was developed to remove circulating IgE and is very effective in this regard. However, there is no evidence of antigen–IgE interaction on mast cells or basophils in chronic idiopathic or autoimmune urticaria. What may be occurring is that as a consequence of removing IgE from the circulation, FcεRI is downregulated on mast cells and basophils, and this may be one effective mechanism of disease amelioration as shown by Saavedra

and Sur [54]. It is also possible that further consequences of omalizumab treatment may include either downregulation of Syk or upregulation of SHIP-1 or SHIP-2, which in either case would reduce mast cell and basophil degranulation, histamine release, leukotriene, and cytokine production. The net effect would be reduction of vasodilation, eosinophil and lymphocyte infiltration, and would lead to reduction of hives and angioedema.

This hypothesis leads to a suggestion for future drug development. If omalizumab works by the mechanism postulated above, it is an unintended benefit of a drug created to treat another disease, asthma, by a mechanism not thought of as relevant to chronic urticaria at the time it was developed. In contrast, development of drugs engineered to decrease Syk or increase SHIP-1 or SHIP-2 might be more effective and specific because they would target the critical intracellular abnormality of the disease.

While it is just speculation that omalizumab may be efficacious in treating chronic urticaria by inhibiting Syk, research is underway to develop drugs which specifically inhibit this cytoplasmic kinase. Syk is present not only in mast cells and basophils but also in T and B cells, other classes of leukocytes, and many other tissues. As such, drugs to inhibit this enzyme have the potential to treat a wide array of diseases and to date most of the preliminary work has been focused on rheumatoid arthritis. In this disease, a drug called fostamatinib or R-788 has already shown efficacy in phase II human studies and a phase III study is underway [55, 56]. In the field of allergy, Syk inhibitor drug development is not as advanced and there appear to be no ongoing clinical trials of Syk inhibitor drugs to treat acute or chronic urticaria. However, a Syk inhibitor named BA9 61-3606 has proven capable of blocking lung inflammation in a rat model of asthma, and a different Syk inhibitor R-112 has been tested in humans. This drug, when given intranasally, blocked symptoms of seasonal allergic rhinitis more effectively than placebo [57].

Using another approach, a group from France performed a virtual screening of 500,000 molecules to find those which block the interaction of Syk with other signal transduction molecules, but do not affect the catalytic site on Syk [58, 59]. They found a number of compounds with such activity and the most potent is called C-13. Further, they have shown that this compound can block in vitro degranulation of mast cells triggered through FC ϵ RI and anaphylactic shock in a mouse model. Of further therapeutic interest, C-13 was active in vivo when administered orally, increasing the possibility of drug development and clinical relevance. Collectively, these experimental studies suggest that developing drugs to block Syk activity is a potential new direction of therapy for allergic and inflammatory diseases including chronic urticaria.

Until these new and exciting developments come to fruition, however, the treatment of chronic urticaria is limited to the use of “conventional” medications. It is important for

physicians and other caregivers to always embrace the dictum “first do no harm”. And while anti-histamines are not always successful in treating chronic urticaria, these are probably the class of medications with the least propensity for adverse effects associated with long-term use of the other medications described above. Therefore, before moving towards corticosteroids and other immunosuppressive agents, it is always important to maximize dosages of antihistaminic therapy when treating chronic urticaria.

In the end, the pathways that are being studied as potential etiologic mechanisms for chronic and autoimmune urticarial may play a role in other allergic and immunologic skin diseases, such as atopic dermatitis [60–62]. The paradigm of Gell and Coombs hypersensitivity reactions may ultimately need to be re-formulated, as the mechanistic pathways for each of the types of hypersensitivity reactions may be found to overlap and interact with one another. Discovering the point at which the signaling pathways involved converge may prove to be the “holy grail” for development of new more effective and safer drugs for the treatment of a wide range of allergic and immunological diseases. The mechanisms outlined in this article also raise the possibility that chronic idiopathic urticaria and angioedema are, indeed, autoimmune diseases [63]. Classical immunosuppressive agents such as cyclosporin have already been used successfully in the treatment of chronic idiopathic urticarial, but may other newer biological modulators used in other rheumatologic diseases such as systemic lupus erythematosus also play a role? Further studies are needed to investigate the efficacy and safety of these potential treatment modalities in chronic and autoimmune urticaria.

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