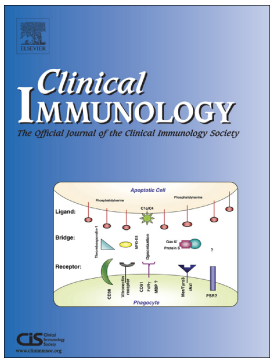

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Treatment of Chronic Spontaneous Urticaria : immunomodulatory approaches.

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Abstract

This paper summarizes and reviews the mechanisms of action and data concerning efficacy of recommended

treatments as well as other treatments that have been tested, independently of the outcomes, in the management of chronic spontaneous urticaria. Due to the central role of mast cells and histamine in the pathophysiology of this disease, H1-antihistamines remain the first-line treatment. However, current knowledge about this complex disease, also recognizes an important role for T lymphocytes, B lymphocytes, and autoantibodies. Implications of these others mediators thus provide further targets for treatment. Indeed, agents previously used to treat other autoimmune and inflammatory diseases, have demonstrated efficacy in chronic spontaneous urticaria and are therefore potential therapeutic alternatives for antihistamine unresponsive patients.

1. Introduction

The main event in pathway of chronic spontaneous urticaria (CSU) is mast cell and basophil degranulation with release of histamine, leukotrienes, prostaglandins and different inflammatory mediators. This is followed by the recruitment of various cells such as neutrophils, eosinophils, macrophages and T-lymphocytes as well as secretion of cytokines, chemokines and proteases. Clinically, it results in the different clinical presentations combining acute (wheals with dermal oedema and pruritus) and sometimes chronic symptoms (1).

Among mediators released by mast cells and basophils, histamine is the most important one. Histamine is a low-molecular-weight amine synthetized from L-histidine exclusively by histidine decarboxylase. It is produced by various cells throughout the body, among which mast cells and basophils, as well as gastric enterochromaffin-like cells and histaminergic neurons.

Due to its very rapid activity on vascular endothelium, bronchial and smooth muscle cells, histamine liberation triggers several acute symptoms, i.e. acute rhinitis, asthma attack, anaphylaxis and urticaria. Moreover, histamine also significantly modulates chronic phase of inflammatory events.

Effects of histamine which possibly act in chronic spontaneous urticaria (CSU) are (2):

- Induction of secretion of cytokines (IL-1a, IL-1b IL-6) and chemokines (RANTES, IL-8) responsible for cell recruitment and inflammatory changes;
- Induction of cell contraction, synthesis of prostacyclin and platelet-activating factor synthesis, Von Willebrand factor and nitric oxide release, resulting in an increase of vascular permeability and edema formation;
- Upregulation of histamine receptors on endothelial cells;
- Enhancement of chemotaxis, increase of adhesion molecules expression such as ICAM-1, VCAM-1 and P-selectin by endothelial cells, causes regulation of granulocytes tissue infiltration;
- Fixation on HR1 and HR4 of non-myelinated C-type fibers (3) responsible for pruritis (3).

Mast cell and basophils activation in CSU can be explained by several non-mutually exclusive hypotheses (4, 5):

- Presence of autoantibodies directed against the α subunit of mast cells high-affinity IgE receptor (FcεRIα). Fixation of these autoantibodies to high-affinity IgE receptor causes activation of mast cells and basophils. Interestingly, the IgG subclasses that appear to be pathogenic are IgG1 and IgG3, both of which being capable of activating complement C5a. However, C5a stimulates skin mast cells by fixation to its receptor. Mast cells in pulmonary or gastrointestinal tract do not express C5a receptor, which may explain why patients with CSU rarely exhibit pulmonary or gastrointestinal involvement (6-8);
- Presence of immunoglobulin E (IgE) against autoantigens. In conventional thinking, the involvement of IgE in mast cell activation requires the cross-linking of FcεRIα-bound IgE by antigen. However, in the absence of antigen, IgE seems to have multiple effects in murine mast cells, including differentiation, proliferation, survival, and mediator and cytokine generation, without especially undergoing mast cells degranulation (9, 10). These IgE are considered highly cytokinergic ones. Interestingly, level of anti-thyroid peroxidase IgE (11) and anti-dsDNA IgE (12) were found higher in CSU population than among healthy subjects. These anti IgE are possibly highly cytokinergic.

- Binding of anti-IgE antibodies (IgG type) to IgE already bound to their receptor on mast cells (13);
- Binding of anaphylatoxins C3a and C5a to their receptor on basophils (14);
- Binding of thrombine and factor VIIa to PAR (proteinase activated receptor) on mast cells (13, 15).

The possibility of one or more circulating histamine-releasing factors being involved in the pathogenesis of CSU was demonstrated, amongst others, by the autologous serum skin test (ASST)(16). Indeed, in a proportion of CSU patients, an urticarial wheal could be elicited locally when autologous serum was re-injected into their skin,

Besides mast cells, basophils and histamine play a crucial role in CSU physiopathology, others inflammatory pathways are implicated as illustrated by patients who are resistant to antihistamines and respond to others anti-inflammatory or immunosuppressive treatments.

2. Treatments of CSU

In view of mast cells, basophils and T-lymphocytes implication in CSU, several treatments have been proposed. Due to the central role of histamine, antihistamines remain the first-line treatment. However, because of the frequent difficulties to treat CSU, many other anti-inflammatory and/or immunomodulator treatments have been tested, whether with positive outcomes or not. Some of them are validated by randomized placebo controlled trials, e.g. H_1-antihistamines, antileukotrienes, cyclosporine and omalizumab. Those treatments are presented in the beginning of the article. Regarding others, efficacy was showed by not placebo controlled trials or by anecdotic case reports. They can be classified into 3 categories: anti-inflammatory, immunosuppressive and other treatments. This paper provides a review of different treatments used in CSU, in regard of their mechanisms of action and efficacy data. Figure 1 summarize the probable immunological targets of those treatments.

2.1 Major treatments of CSU (high level of evidence)

Hereby, only treatments with well-conducted randomized placebo controlled trials are described. Concerning H_1-antihistamines, antileukotrienes, cyclosporine and omalizumab, the conclusions of trials recommend them. Concerning H_2-antihistamines, there is only one randomized placebo controlled trial, which did not recommended them.

2.1.1. H_1-antihistamines:

Mechanisms of action

H_1-antihistamines are inverse agonists of HR1. By binding to their receptors, they stabilize them, and then reduce their activity below the basal level.

It has been shown (2) in asthma that H_1-antihistamines reduce Th2 immune response (with lower secretion of IL-4 and IL-5), prevent production of allergen-specific IgE, reduce eosinophilia infiltration and suppress IL-6 and β-glucuronidase liberation by macrophages.

H_1-antihistamines also inhibit NF-kB in human lymphocytes and monocytes (2, 17).

First-generation H_1-antihistamines (e.g. diphenhydramine, promethazine, chlorphenamine, dexchlorpheniramine, hydroxyzine) have proved their efficacy. However, all of them have a sedative effect, reduce rapid eye movement sleep, alter attention and vigilance, impair learning capacity and reduce work efficiency. Moreover, they are implicated in vehicle accidents. Effects of first-generation H1-antihistamines on the central nervous system (CNS) are similar to those produced by alcohol or other central nervous system-sedatives, such as benzodiazepines (18, 19).

Nowadays, modern second-generation nonsedating H1-antihistamines (e.g. cetirizine, levocetirizine, loratadine, desloratadine, ebastine, rupatadine) are recommended as first line treatment of CU by EAACI/GA^{2}LEN/EDF/WAO Guidelines 2013 and by AAAAI/ACAAI Joint Task Force 2014. They are less or

even not sedative compared to the first generation ones, and are free of anticholinergic effects, have long-lasting antipruritic effects and few interactions with others drugs (20).

Efficacy of H1-antihistamines in chronic spontaneous urticaria

Several randomized (placebo) controlled trials have proved their efficiency in CSU (21). Cetirizine seems to be more effective than fexofenadine (22) and levocetirizine more effective than desloratadine (23). However, rupatadine seems to be more effective than cetirizine (24), whilst levocetirizine seems to be more effective than rupatadine in another study (25).

There are studies showing the benefit and safety of increasing up to 4 times conventional doses of bilastine (20mg), desloratadine (5mg), levocetirizine (5mg), fexofenadine (180mg) in difficult-to-treat CU (26-31). Concerning rupatadine (10mg), one study showed safety of increasing up to 4 times the conventional doses (32) but the real benefit could only be proved in CU when increasing up to 2 times conventional doses (33). Concerning ebastine, one study showed superiority of 20 mg compared to 10 mg in CSU (34). Moreover, ebastine at dose up to five times the recommended therapeutic dose did not cause any clinically relevant change in QTc interval (35).

2.1.2. Antileukotrienes

Mechanisms of action

Leukotrienes are mediators synthetized from arachidonic acid by 5-lipoxygenase.

Zafirlukast and montelukast are antagonists of leukotriene receptors and zileuton is a 5-lipoxygenase inhibitor.

Leukotrienes are potent bioactive mediators known to play important roles in asthma (36), allergic rhinitis (37) and CU (38).

Leukotrienes are also known to produce local effects on cutaneous blood vessels (39). Soter et al. (40) demonstrated that injection of a leukotriene D_4 agonist in human skin results in an urticarial wheal, due to small blood vessels dilatation and subsequent edema. Studies with leukotriene antagonists in guinea pigs showed suppression of the vascular leakage induced by intradermal injection of leukotriene D_4 agonist (41).

Efficacy of antileukotrienes in chronic spontaneous urticaria

A few randomized double or simple-blind controlled trials were published.

Concerning antileukotrienes separately, Nettis et al. (42) demonstrated that montelukast had better therapeutic effects compared to fexofenadine in CSU patients (majority having a positive ASST). However a double-blind, placebo-controlled study showed that zafirlukast was not more effective than placebo to treat CU (43).

Concerning antileukotrienes in combination with H_1-antihistamines, a randomized, single-blind, placebo-controlled study showed benefit superiority of combining montelukast with H_1-antihistamines compared to placebo with H_1-antihistamines to treat CSU (44). Another randomized, double-blind, placebo-controlled study in CSU patients showed that the combination of desloratadine with montelukast was more effective than

desloratadine with placebo (45).

Finally a double-blinded, placebo-controlled trial comparing cetirizine in combination with zafirlukast, indicates that only CSU patients with a positive ASST might benefit from the addition of zafirlukast to their H_1-antihistamines treatment (46).

Conversely, the combination of desloratadine with montelukast failed to produce substantial advantage for CSU symptoms in comparison with desloratadine administered in monotherapy in a randomized, double-blind placebo-controlled study of 160 CSU patients (47). However, this study only evaluated patients affected by moderate CSU, excluding patients with a positive ASST, patients with intolerance to food additive and/or to acetylsalicylic acid and/or NSAIDs and patients with aggravation of their symptoms through pressure.

Concerning zileuton, they seem effective only in a few case reports (43, 48).

Antileukotrienes are recommended in second line by AAAAI/ACAAI Joint Task Force in 2014, and in third line by EAACI/GA^{2}LEN/EDF/WAO Guidelines 2013 for CSU treatment.

2.1.3. Cyclosporine A

Mechanisms of action

Cyclosporine A (CsA) is an immunosuppressive drug which reduces early and late phases of urticaria.

CsA has been shown to reduce histamine, leukotriene and prostaglandine release by mast cells (49-52) and basophils (53) in vitro as well as and in vivo (11,12). This action on mast cells explains early response of CsA for CSU patients (54). A study showed that pre-incubation of cells with CsA inhibited histamine release, which is normally observed when these cells are stimulated by purified IgG from sera of CSU patients (55).

CsA inhibits the activity of the intracellular enzyme calcineurin phosphatase. This downregulates transcription of a number of cytokine genes (IL2, IL-3, IL-4, IL5, TNF-α and IFN-γ)(56-60). The most significant cytokine is IL-2, which acts as the major T cells activator in numerous immunological processes in interaction with mast cells (61).

CsA also reduces antibody production, i.e. IgG anti-FcεRIα, IgG anti-IgE, IgE against autoantigens (54).

Finally, CsA decreases inflammatory cells recruitment by inhibition of different cell adhesion molecules in humans (51, 53), and by reduction of IgE dependent TNF-α secretion by mast cells in mice (62).

Efficacy of CsA in chronic spontaneous urticaria

Several randomized placebo-controlled trials have shown the efficacy of CsA in CSU. Global response is approximately 60% (54, 63, 64), treatment duration varied from 4 to 16 weeks but in many cases, relapses were observed when CsA was stopped and some patients had to withhold the treatment because of its side effects.

CsA is recommended as third line therapy in CSU by EAACI/GA^{2}LEN/EDF/WAO Guidelines 2013 and by AAAAI/ACAAI Joint Task Force 2014 as fourth line therapy.

2.1.4. Omalizumab

Mechanisms of action

Omalizumab (OmAb) is a recombinant humanized monoclonal anti-IgE antibody that binds to the C epsilon 3 domain of IgE (the site of high-affinity IgE receptor binding).

It was originally approved as a treatment of allergic asthma but it has been shown to be efficacious in the treatment of CSU as well. While the exact cause of CU is not entirely known, a large proportion of patients have autoantibodies which are thought to cause mast cell activation, leading to CSU. Omalizumab is believed to work partially by affecting this pathway and binding free IgE. However, the exact mechanisms are likely more complex and further research is needed to clarify them.

OmAb blocks the binding of IgE to the FcεRI receptor on the surface of target cells, including mast cells, basophils and dendritic cells. Recently, Serrano-Candelas and al. (65) showed that OmAb could also dissociate pre-bound IgE from mast cells and basophils, resulting in a reduction of proximal phosphorylation-mediated signaling events and a decrease in degranulation and leukotrienes synthesis. Thereby, OmAb is expected to decrease mast cells and basophils state of excitability.

OmAb is also able to neutralize free IgE, like highly cytokinergic autoIgE in CSU.

In asthma, it has been suggested that the accumulation of omAb-IgE immune complexes might help to sequester incoming allergen molecules (66). In CSU, accumulation of omAb-IgE immune complexes (67) could possibly trap endogenous autoantigens, such as TPO and dsDNA reacting with IgE.

OmAb induces a depletion of free IgE, which results in a reduction of FcεRI receptor expression by downregulation (68). Metz et al. (69) showed a rapid decrease of FcεRI skin cell numbers in omalizumab-treated CSU patients.

Additionally, OmAb downregulates CD23 (also called FcεRII) on B cells (70). Membrane-bound IgE-expressing B lymphoblasts and memory B cells can also be downregulated, causing a reduction in the continual generation of IgE-secreting plasma cells (71).

OmAb also reduces the release of some inflammatory mediators (72, 73).

Moreover, OmAb has anti-inflammatory activity demonstrated by induction of eosinophil apoptosis and downregulation of the inflammatory cytokines IL-2 and IL-13 (74).

The overall effect of omAb is that the IgE–FcεRI–mast cells axis is down-regulated.

OmAb reinforces mast cells stability by increasing the threshold of activation. Therefore, it causes less mast cell degranulation and smaller amounts of mediators resulting in decrease of urticarial symptoms (50).

Efficacy of omalizumab in chronic spontaneous urticaria

Numerous cases reports and uncontrolled studies have been reported. A systematic review in 2015 had selected 5 randomized, placebo-controlled clinical trials (1117 patients) with 3 different dosages (75mg, 150mg, 300mg). OmAb was clearly more effective than placebo at the dose of 300mg (75, 76).

Three phase III multicenter, randomized, placebo-controlled clinical trials in antihistamines non-responders showed that 52 to 66% of CSU patients presented clinical improvement of their pathology at 12w with an Urticarial Activity Score (UAS) <6 (77). It convincingly established that omalizumab is effective and safe for

treating recalcitrant CSU that cannot be adequately treated with current standard care. Therefore, OmAb is recommended in third line therapy by EAACI/GA^{2}LEN/EDF/WAO Guidelines 2013 and in fourth line therapy by AAAAI/ACAAI Joint Task Force 2014. OmAb is now approved for severe and H_1-antihistamines non-responders CSU patients in many countries.

A recent study suggests that there might be 2 categories of responders to OmAb: those who respond early (before 4 weeks) and those who require more than 3 monthly doses to respond (75). Currently, the reason of an early or late response is not identified. Duration of treatment and risk of relapses when treatment is ended remain unclear (78) (76) .

2.2. Others treatments of CSU

2.2.1. Anti-inflammatory treatments:

2.2.1.1. Corticosteroids

Corticosteroids (CS) are classified as anti-inflammatory agents because in CSU indication, there are not used at immunosuppressive dosages and duration.

Mechanisms of action

It is generally accepted that the anti-inflammatory effect of corticosteroids is primarily based on a complex genomic mechanism leading to the switch-off of many inflammatory genes and to the activation of anti-inflammatory genes encoding for anti-inflammatory proteins (79-81). Nonetheless, theses mechanisms take time and CS such as prednisolone are usually effective in CSU only after 24 hours. Moreover, CS don't exert any effect on cutaneous mast cell degranulation (82) or on complement activation (83). Hence, it has been suggested that the rapid clinical effect of CS observed in CSU is due to the direct inhibition of inflammatory cells (83). A inhibitory effect on the release of mediators from eosinophils (notably, a cell type recently found to be activated in CSU (84, 85)) has also been reported (86). Similarly, an effect on histamine release from basophils has been identified (87). Moreover, vasodilation and vascular permeability inhibition (88) might also be involved in the rapid response to CS in CSU patients.

Efficacy of corticosteroids in chronic spontaneous urticaria

Topical CS were not able to prevent acute experimental urticaria (caused by histamine or codeine) (89).

Conversely, Asero *et al.* (90) have treated 86 H_1-antihistamines resistant CSU patients with oral CS. Nearly half of their patients had an excellent response after a ten-day, gradually-tapered course of prednisone and had subsequent control with H_1-antihistamines only after this treatment. A second course of CS permitted remission in a further 9%.

In another report, 10 CSU patients were treated with oral mini-pulse therapy (methylprednisolone 16 mg twice a week for 8 weeks) and levocetirizine 5 mg daily. Out of 10 patients, two patients were lost to follow up, one stopped because of side effects and another one had worsening of symptoms after stopping CS. Six patients were still well-controlled 1 month after stopping CS (91).

Short systemic CS treatment could be effective in some CSU refractory patients, but no randomized placebo-controlled trial with long follow-up has been conducted.

In addition to the risk of adverse effects, the other main problem remains CS dependence and rebound after stopping CS treatment, which are well-known phenomena. Moreover, a previous CS treatment seems to be a favoring factor of resistance to H_1-antihistamines (92).

AAAAI/ACAAI Joint Task Force 2014 and EAACI/GA^{2}LEN/EDF/WAO Guidelines 2013 discouraged long-term use of systemic CS for treatment of CSU. They accepted short-term use of oral CS (up to 3 weeks) when they are used to gain a rapid control of the disease, in association with other therapies which take more time to be effective.

2.2.1.2. Dapsone

Mechanisms of action

Dapsone (4-4'-diaminodiphenylsulfone) is a sulfonamide antibiotic which has been shown to inhibit neutrophils chemotaxis (93) and reactive oxygen species production. This explains its efficacy in neutrophilic diseases, such as pyoderma gangrenosum or urticarial vasculitis (94). Dapsone also inhibits 5-lipoxygenase in human polymorphonuclear cells and in rat mast cells (95, 96), therefore reducing leukotrienes production.

Dapsone is also effective in several autoimmune diseases like bullous pemphigoid and IgA dermatosis for which the mechanisms of action remain unclear (94).

Efficacy of dapsone in chronic spontaneous urticaria

Efficacy in CSU was observed in an open-label study with 11 patients (25 mg/d) showing improvement for all of them (97).

In a double-blind placebo-controlled trial with 22 CSU patients, on average 35% had partial resolution of hives and itch and 3 patients showed complete resolution of the disease (98).

A randomized clinical trial (not blinded and without placebo) with 65 CSU patients, comparing dapsone (50 mg/d) associated with H1-antihistamines versus H1-antihistamines alone, showed benefit of adjunction of dapsone (99).

2.2.1.3. Sulfasalazine

Mechanisms of action

Sulfasalazine is commonly used in inflammatory bowel diseases and rheumatoid arthritis. Mechanisms of action are not well known but sulfasalazine reduces antibodies synthesis and influences T cells and cytokines production (4). Some studies have shown an action of sulfasalazine on IgE mediated mast cell histamine release but these results have not been confirmed by others researchers (100-102).

Efficacy of sulfasalazine in chronic spontaneous urticaria

Sulfasalazine has shown efficacy in CSU in 2 retrospective chart trials. A trial reported that 14 out of 19 CSU patients significantly improved their urticaria with sulfasalazine treatment. Among patients who required systemic CS to control their urticaria, all of them were able to reduce or discontinue CS during sulfasalazine therapy. Although, 7 patients had adverse effects (103).

In another study with 39 CSU patients treated by sulfasalazine, approximately 80% of subjects showed an improvement of symptoms within the first 3 months of treatment and 50% became asymptomatic within the first 6 months of treatment. Serious adverse events leading to drug discontinuation occurred in 2 patients (104).

Despite efficacy, side effects seem to limit use of sulfasalazine in CSU.

2.2.1.4. Colchicine

Mechanisms of action

Inhibition of microtubules polymerization and disruption of the cytoskeleton in polymorphonuclear cells and lymphocytes are the main mechanisms of action of colchicine. In this way, colchicine alters chemotactic and phagocytic activity of inflammatory cells and secretion of endogenous mediators such as histamine, leukotrienes, prostaglandins, proteases, cytokines and chemokines. Moreover, colchicine also inhibits immunoglobulin secretion and HLA-DR expression (4, 105-108).

Efficacy of colchicine in chronic spontaneous urticaria

Published data of colchicine efficacy are poor. There are only 2 retrospective chart reviews with 40 to 50% of responders in CSU patients. However, some patients still need oral steroid therapy. (107, 109, 110). No randomized controlled trial has been carried out, indicating low-grade evidence to support its use.

2.2.2. Immunosuppresive treatments:

2.2.2.1. Tacrolimus

Mechanisms of action

Tacrolimus reduces transcription of lymphokine genes involved in T-cell activation and IL2 production. Tacrolimus is also a potent inhibitor of histamine release from basophils and mast cells. Moreover, it inhibits synthesis of leukotriene C4 and prostaglandin D2 by mast cells (111-113).

Efficacy of tacrolimus in chronic spontaneous urticaria

Only one open-label prospective study with 19 CSU patients treated with tacrolimus was conducted. It showed reduction of symptoms in 70% of the patients treated (111). A retrospective study with 36 patients with CU treated with tacrolimus (some of them were also under other urticaria treatments) showed partial/complete

control of the disease for 3/13 patients and remission (at least 3 months after withdrawal) for 8 patients. However, sides effects caused frequent discontinuation of treatment (114).

2.2.2.2. Azathioprine

Mechanisms of action

Azathioprine inhibits purine nucleotide synthesis and causes, amongst others, T cell apoptosis.

Efficacy of azathioprine in chronic spontaneous urticaria

2 patients with severe refractory CU were treated with azathioprine (115). In both patients, a significant clinical improvement was observed with enabling steroid withdrawal.
Only one single-blind randomized control trial with 52 CSU patients has shown superiority of azathioprine versus placebo (both combined with H_1-antihistamines) (116).

2.2.2.3. Cyclophosphamide

Mechanisms of action

Cyclophosphamide is a potent alkylating immunomodulator, which inhibits antibodies production. It also reduces activity of regulatory T cells.

Efficacy of cyclophosphamide in chronic spontaneous urticaria

There are only 2 case reports published showing effectiveness in severe recalcitrant CSU (117, 118).

2.2.2.4. Mycophenolate mofetil

Mechanisms of action

Mycophenolate mofetil acts as a selective antimetabolite by inhibiting inosine monophosphate dehydrogenase, an enzyme involved in the synthesis of purines. By its action, mycophenolate mofetil reduces the number of T and B cells by blocking their proliferation. It also inhibits antibody formation and the generation of cytotoxic T cells. It decreases expression of adhesion molecules and therefore inhibits chemotaxis of lymphocytes (119).

Efficacy of mycophenolate mofetil in chronic spontaneous urticaria

Only a small open-label uncontrolled trial with 9 CSU patients (taking CS and H_1-antihistamines) has shown enough efficacy of mycophenolate mofetil so that all patients were able to withhold CS (119, 120).

2.2.2.5. Methotrexate

Mechanisms of action

Methotrexate (MTX) is another immunomodulatory therapy used in several inflammatory diseases. Its mechanism of action at the doses used in inflammatory diseases is likely related to the release of anti-inflammatory adenosine rather than folates depletion (121). By adenosine increase, MTX inhibits neutrophils recruitment (122-124). In rheumatoid arthritis, MTX reduces leukotriene B_4 neutrophils synthesis (125), modifies cytokines profile (IL-1, IL-6 reduction and IL-2 increase) (126) and alters activity of proteolytic enzymes (127).

Efficacy of methotrexate in chronic spontaneous urticaria

Only case reports were published concerning MTX efficacy in CU. Two patients with recalcitrant disease were treated with 15 to 20 mg MTX weekly in combination with others medications (CS, cyclosporine, H_1-antihistamines). These background medications could be reduced while still improving symptoms. However, the diagnosis of CSU was not quite clear for one patient (128). Another group of 4 CSU patients recalcitrant to H_1-antihistamines were treated with MTX 10 mg weekly for 2 months, with apparent improvement. For 3 patients, after stopping MTX, urticaria was under control with H_1-antihistamines alone (129). Finally 10 CS-dependent CSU patients unresponsive to H_1-antihistamines were treated with methotrexate (5 to 25mg weekly) in addition to CS treatment. 5 patients had considerable benefits and steroid could be stopped or reduced (130). However, the use of MTX is also limited by its side effects.

2.2.2.6. Rituximab

Mechanisms of action

Rituximab is a chimeric monoclonal antibody targeting CD20 on the surface of maturing B cells, but not on stem cells or plasma cells. It causes rapid and sustained reduction in peripheral B cell count and reduces the level of all classes of antibodies, including autoantibodies. It was originally developed for non-Hodgkin's lymphoma but was also used in several autoimmune diseases, i.e. rheumatoid arthritis and pemphigus, as well as atopic dermatitis (131, 132).

The mechanism of action of rituximab in CSU is probably due to his inhibitory effect on autoantibody production.

Efficacy of rituximab in chronic spontaneous urticaria

Only case reports are available. Thanks to rituximab, a pediatric patient suffering from recalcitrant CSU was able to stop CS and to remain free of symptoms with only H_1-antihistamines for one year (133). Two other cases of good efficacy in CSU were reported. One patient took combination of rituximab and CS (134). The other one could stop CS and remained free of symptoms for 10 months (135).

Conversely, a single case report showed no improvement of CSU with rituximab (134).

2.2.2.7. TNF-alpha inhibitors

Mechanisms of action

Three biologic TNF-αinhibitors (namely, etanercept, infliximab, and adalimumab), have been used in the treatment of different types of CU and urticarial vasculitis. This was based on the hypothesis that TNF-α may play an important role in the inflammatory cells recruitment in this pathology.

TNFα expression is indeed important in blood and skin of CSU patients. A quite similar cytokine profile was identified in CSU and rheumatoid arthritis with high level of TNF-α and IL-10 and low level of IL-2 and d'IFN-γ (136, 137).

Efficacy of TNF-α inhibitors in chronic spontaneous urticaria

Only few data about efficacy of TNF-α inhibitors in CSU are available. The efficacy of infliximab was observed in 1 CSU patient (138). Concerning etanercept, the condition of 6 CSU patients was improved by the treatment (138, 139). A group of 14 CSU patients were treated with adalimumab, which was effective in 11 patients but ineffective in 3 patients (139).

The evidence supporting the use of TNF-α blockers in CSU is therefore limited.

2.2.3. Others treatments:

2.2.3.1. H2-antihistamines:

Mechanisms of action

H_2-antihistamines (cimetidine, ranitidine) are inverse agonists of HR2.

Binding of histamine to HR2 receptors seems to have immunosuppressive effects, namely moderate Th1 and Th2 reactions, decrease mast cell and basophils histamine release and reduce granulocyte chemotaxis. This means that H_2-antihistamines block these immunosuppressive effects, which make them a priori not to be effective in urticaria.

Fixation of histamine to HR2 of non-myelinated C-type fibers doesn't cause pruritis. Therefore, H_2-antihistamines don't have any antipruritic properties (140).

Nevertheless, H_2-antihistamines reduce blood vessels vasodilation and vascular permeability induced by HR2 on myocytes and endothelial cells (141).

Efficacy of H2-antihistamines in chronic spontaneous urticaria

Several clinical studies have demonstrated additional benefits by combining H_1-antihistamine with H_2-antihistamine (especially with cimetidine), compared to H_1 antihistamines monotherapy (142-145) in the particular case of dermographism.

Co-administration of hydroxyzine with cimetidine seems to significantly increase serum hydroxyzine

concentrations and enhance wheal and flare suppression. However, there is no effect of cimetidine, either on cetirizine plasma drug concentration-time curve or in wheal and flare suppression (146). Currently, ranitidine is more frequently used than cimetidine.

In 2012 The Cochrane review (147) adopted no clear position about the use of H2-antihistamines for urticaria. H2-antihistamines were still recommended in EAACI/GA^{2}LEN/EDF/WAO Guidelines 2009, yet the evidence was too poor to maintain this as recommendable in Guidelines 2013. In 2014, AAAAI/ACAAI Joint Task Force recommended however H2-antihistamines in CSU in second line therapy.

Nevertheless in 2015, a randomized, double-blind, placebo-controlled trial showed no benefit of adding H2-antihistamines to H1-antihistamines therapy in CU (148)

2.2.3.2. Sodium cromoglicate

Mechanisms of action

Sodium cromoglicate is widely characterized as a "mast cell stabilizer".

However, sodium cromoglicate does not modulate histamine release nor inhibits contact urticaria caused by vegetals, as demonstrated in one study (149). Moreover, skin mast cells seem to be less or unresponsive to sodium cromoglycate compared to mast cells of tonsils or lungs (150).

Sodium cromoglycate seems to reduce pruritus by its action on non-myelinated C-type fibers (151).

Efficacy of sodium cromoglycate in chronic spontaneous urticaria

The only study published is a double-blind cross-over trial which showed no superiority of sodium cromoglycate versus placebo (152).

2.2.3.3. Anticoagulant and antifibrinolytic drugs

Mechanisms of action

Coagulation pathway and inflammation are connected, especially through thrombin, which is a major pro inflammatory mediator.
Thrombin is a serine protease. After binding protease-activated receptor (PAR), which is expressed by numerous inflammatory cells, it activates transcription factors regulating expression of tissue factors, adhesion proteins and cytokines, and directly activates mast cells (13, 15, 153).

Activation of the extrinsic pathway of coagulation seems to be important in CSU physiopathology. Cugno and al. (84) demonstrated that tissue factor is expressed by eosinophils present in the inflammatory infiltrate of CSU skin lesions. They also showed an elevation of the level of plasma D-dimers (marker of fibrin degradation), and

plasma prothrombin fragments F1 and F2 (markers of activation of pro- thrombin to thrombin) (154). Wang et al. (155) also found increased plasma levels of FVIIa (markers of the activation of the tissue factor pathway). The latter, together with elevation of D-dimers and prothrombin fragments F1 and F2, were significantly correlated with CSU disease severity.

However, the exact link between activation of coagulation/fibrinolysis and CSU physiopathology is still to be defined.

Coumarins inhibit vitamin K reductase, thereby preventing carboxylation of various target proteins, including the coagulation factors II, VII, IX and X, which are essential for the production of thrombin. The disruption of thrombin production may explain the therapeutic effect of anticoagulation therapy in urticaria. Coumarins also inhibit carboxylation of other vitamin K- dependent proteins.

Heparin for its part, activates antithrombine III itself blocking thrombine and others factors (156, 157).

Efficacy of anticoagulant and antifibrinolytic drugs in chronic spontaneous urticaria

An open label study reported 6 of 8 CSU patients who responded positively to coumarin (warfarin.) In a double-blind approach, the 3 responders received capsules, identical in appearance, containing either warfarin or placebo. Afterwards, evaluation of their urticaria showed a significant benefit for all of them with warfarine compared to placebo (158).

A study with 5 CSU patients treated with warfarin (associated with CS) showed total/partial response for 2/2 patients (159). A case report of a CSU patient showed improvement both with warfarin and with acenocoumarol (160).

Conversely, published data are very limited concerning heparine and tranexamic acid in CSU. 5 of 8 CSU patients with elevated D-dimers treated with an heparin (nadroparin) and tranexamic acid showed a marked improvement of symptoms (156). A single case report described a CU patient cured by heparin treatment (156, 157).

One limited double-blind study with tranexamic acid alone in CU showed no superiority compared to placebo (161).

2.2.3.4. Phototherapy

Mechanisms of action

Phototherapy targets mast cells. The susceptibility of this type of cells towards UV light however seems to partially depend on the state of cellular activation. Guhl et al. (162) investigated the effects of UV irradiation (UVB, UVA-1, and psoralen plus UVA-1) on purified mast cells from human skin. Immunosuppressive effects predominate in activated mast cells, whereas in the non-activated ones, both stimulatory and inhibitory effects are observed.

Another important aspect of UV immunomodulation concerns the induction of apoptosis in skin infiltrating cells. Guhl et al. (163) also demonstrated that human mast cells undergo apoptosis in response to irradiation with UVB or UVA1.

Efficacy of phototherapy in chronic spontaneous urticaria

A retrospective trial with 88 CSU patients treated with narrowband UVB showed clearance or significant improvement in approximately 50% of cases (164). In a randomized double-blind study, 11 CSU patients were treated with UVA combined with psoralen and 8 CSU patients were treated with UVA and placebo. Both groups showed improvement (7 patients in the first group, 5 in the second one) (165). A randomized controlled trial comparing UVA and psoralen with narrowband-UVB in 24 CSU patients showed comparable improvement in both groups (166). However, no randomized placebo controlled trial has been carried out.

2.2.3.5. Intravenous immunoglobulins

Mechanisms of action

Intravenous immunoglobulins (IVIG) contain pooled immunoglobulin G (IgG) extracted from the plasma of approximately a thousand or more blood donors.

IVIG modulates a number of immune effector pathways, including Fc receptor blockage, neutralization or enhanced clearance of autoantibodies, decrease production of cytokines, blockage of adherence molecules, inhibition of the uptake of complement components on target tissues, modulation of apoptosis, and immune regulation of both B and T-cell immune functions (167). Moreover, IVIG contains anti-idiotypic antibodies (e.g. anti-DNA, anti-intrinsic factor, anti-thyroglobulin, and anti-desmoglein-3 antibodies) (168, 169), which act as immunomodulators against autoantibodies (170) and explain their efficacy in various autoimmune disorders (171).

Efficacy of IVIG in chronic spontaneous urticaria

The efficacy of IVIG in CSU is controversial. Four CSU patients, in a series of six, improved their urticaria after IVIG treatment and stayed free of symptoms for at least one year (172). Among 29 CSU patients treated with IVIG, 26 of them had good response and 20 of them had remission at least 12 months after treatment (173). Another 10 CSU patients were treated with IVIG and showed clinical benefit for 9 patients and prolonged remission for one third of them (3 years after withdrawal) (174).

On the other hand, Asero reported 3 cases of CSU treated with IVIG with less encouraging results, since only one patient had significant urticaria reduction but relapsed after 3 weeks, time corresponding to the half-life of IVIG (175).

2.2.3.6. Plasmapheresis

Mechanisms of action

Plasmapheresis is a treatment based on removal from blood of small blood molecules (such as antibodies). After filtration, medium and large components e.g. cells, are reinjected to the patient (176).
In view of the role of autoantibody in CSU, plasmapheresis could theoretically be effective. However, from a practical point of view, this treatment removes antibodies but does not inhibit their production.

Efficacy of plasmapheresis in chronic spontaneous urticaria

Few published data are available about plasmapheresis in CSU. Efficacy is however demonstrated in a case report in association with CS, which clearly reduces the objectivity of the result (176). In another study, among 8 CSU patients treated with plasmapheresis (alone or together with antihistamines) efficacy was observed in 5 patients (177).

3. Conclusion

CU remains a challenge to treat in some cases. One difficulty in providing treatment guidance for severe CU is the lack of double-blind, randomized placebo controlled trials for many treatments, which are considered as the best in reliability. Many immunomodulatory drugs are used, although evidence for their efficacy is mostly limited to case reports, small case series, and open-label experiences. Double-blind, randomized placebo controlled trials are only available for H_1-antihistamines, antileukotrienes, cyclosporine and omalizumab. Therefore, these four treatments are the only ones recommended with high level of scientific evidence. However, some molecules could be useful in refractory cases to these therapies, for example dapsone, sulfazalazine, MTX and azathioprine. Nonetheless, these drugs have significant side effects and more published data, especially double-blind, randomized placebo controlled trials, are needed.

It is hoped that better understanding of the disease, possibly in an autoimmune disease context, will enable the development of more specific therapies beyond terminal mediator blockade.

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Bibliography

1. Kaplan AP, Greaves M. Pathogenesis of chronic urticaria. Clinical & Experimental Allergy. 2009; 39:777-87.
2. Jutel M, Akdis M, Akdis CA. Histamine, histamine receptors and their role in immune pathology. Clinical & Experimental Allergy. 2009; 39:1786-800.
3. Gaudenzio N. Étude de l'interaction entre les mastocytes et les lymphocytes T Helper: INSERM U1043, Université de Toulouse; 2012.
4. Bingham C. Immunomodulatory approaches to the management of chronic urticaria: An immune-mediated inflammatory disease. Curr Allergy Asthma Rep. 2008; 8:277-87.
5. Nosbaum A, Augey F, Nicolas JF, *et al*. Physiopathologie de l'urticaire et approches thérapeutiques. La Revue de Médecine Interne. 2010; 31:18-22.
6. Benyon RC. The human skin mast cell. Clinical & Experimental Allergy. 1989; 19:375-87.
7. Soundararajan S, Kikuchi Y, Joseph K, *et al*. Functional assessment of pathogenic IgG subclasses in chronic autoimmune urticaria. Journal of Allergy and Clinical Immunology. 2005; 115:815-21.
8. Füreder W, Agis H, Willheim M, *et al*. Differential expression of complement receptors on human basophils and mast cells. Evidence for mast cell heterogeneity and CD88/C5aR expression on skin mast cells. J Immunol. 1995; 155:3152–60.
9. Asai K, Kitaura J, Kawakami Y, *et al*. Regulation of Mast Cell Survival by IgE. Immunity. 2001; 14:791-800.
10. Kalesnikoff J, Huber M, Lam V, *et al*. Monomeric IgE Stimulates Signaling Pathways in Mast Cells that Lead to Cytokine Production and Cell Survival. Immunity. 2001; 14:801-11.
11. Altrichter S, Peter H-J, Pisarevskaja D, *et al*. IgE Mediated Autoallergy against Thyroid Peroxidase – A Novel Pathomechanism of Chronic Spontaneous Urticaria? PLoS ONE. 2011; 6:e14794.
12. Hatada Y, Kashiwakura J, Hayama K, *et al*. Significantly high levels of anti-dsDNA immunoglobulin E in sera and the ability of dsDNA to induce the degranulation of basophils from chronic urticaria patients. Int Arch Allergy Immunol. 2013; 161 Suppl 2:154-8.
13. Vliagoftis H. Thrombin induces mast cell adhesion to fibronectin: evidence for involvement of protease-activated receptor-1. J Immunol. 2002; 169:4551-8.
14. Kikuchi Y, Kaplan AP. A role for C5a in augmenting IgG-dependent histamine release from basophils in chronic urticaria. Journal of Allergy and Clinical Immunology. 2002; 109:114-8.
15. Razin E, Marx G. Thrombin-induced degranulation of cultured bone marrow-derived mast cells. J Immunol. 1984; 133:3282-5.
16. Grattan CE, Wallington TB, Warin RP, *et al*. A serological mediator in chronic idiopathic urticaria—a clinical, immunological and histological evaluation. British Journal of Dermatology. 1986; 114:583-90.
17. Yoneda K, Yamamoto T, Ueta E, *et al*. Suppression by azelastine hydrochloride of NF-kappa B activation involved in generation of cytokines and nitric oxide.
18. Church MK, Maurer M, Simons FER, *et al*. Risk of first-generation H1-antihistamines: a GA2LEN position paper. Allergy. 2010; 65:459-66.
19. Juniper E, Stahl E, Doty R, *et al*. Clinical outcomes and adverse effect monitoring in allergic rhinitis. Journal of Allergy and Clinical Immunology. 115:390-413.
20. Zuberbier T, Asero R, Bindslev-Jensen C, *et al*. EAACI/GA2LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria. Allergy. 2009; 64:1417-26.
21. Zuberbier T. Pharmacological rationale for the treatment of chronic urticaria with second-generation non-sedating antihistamines at higher-than-standard doses. Journal of the European Academy of Dermatology and Venereology. 2012; 26:9-18.
22. Handa S, Dogra S, Kumar B. Comparative efficacy of cetirizine and fexofenadine in the treatment of chronic idiopathic urticaria. The Journal of Dermatological Treatment. 2004; 15:55-7.
23. Hong J-B, Lee H-C, Hu F-C, *et al*. A randomized, double-blind, active-controlled, parallel-group pilot study to compare the efficacy and sedative effects of desloratadine 5 mg with levocetirizine 5 mg in the treatment of chronic idiopathic urticaria. Journal of the American Academy of Dermatology. 2010; 63:100-2.
24. Dakhale G, Shinde A, Mahatme M, *et al*. Clinical effectiveness and safety of cetirizine versus rupatadine in chronic spontaneous urticaria: a randomized, double-blind, 6-week trial. International Journal of Dermatology. 2014; 53:643-9.
25. Johnson M, Kwatra G, Badyal D, *et al*. Levocetirizine and rupatadine in chronic idiopathic urticaria.
26. Staevska M, Popov TA, Kralimarkova T, *et al*. The effectiveness of levocetirizine and desloratadine in up to 4 times conventional doses in difficult-to-treat urticaria. J Allergy Clin Immunol. 2010; 125:676-82.
27. Godse K, Nadkarni N, Jani G, *et al*. Fexofenadine in higher doses in chronic spontaneous urticaria. Indian Dermatology Online Journal. 2010; 1:45-6.

28. Krause K, Spohr A, Zuberbier T, *et al*. Up-dosing with bilastine results in improved effectiveness in cold contact urticaria.
29. Sharma VK, Gupta V, Pathak M, *et al*. An open-label prospective clinical study to assess the efficacy of increasing levocetirizine dose up-to four times in chronic spontaneous urticaria not controlled with standard dose. Journal of Dermatological Treatment. 2016:1-17.
30. Pratt CM, Mason J, Russell T, *et al*. Cardiovascular safety of fexofenadine HCl.
31. Banfield C, Padhi D, Herron JM, *et al*. Electrocardiographic effects of multiple high doses of desloratadine. Journal of Allergy and Clinical Immunology. 105:S383.
32. Abajian M, Curto-Barredo L, Krause K, *et al*. Rupatadine 20 mg and 40 mg are Effective in Reducing the Symptoms of Chronic Cold Urticaria.
33. Gimenez-Arnau A, Izquierdo I, Maurer M. The use of a responder analysis to identify clinically meaningful differences in chronic urticaria patients following placebo-controlled treatment with rupatadine 10 and 20 mg.
34. Godse K. Ebastine in chronic spontaneous urticaria in higher doses. Indian Journal of Dermatology. 2011; 56:597-8.
35. Gillen MS, Miller B, Chaikin P, *et al*. Effects of supratherapeutic doses of ebastine and terfenadine on the QT interval.
36. Wardlaw AJ, Hay H, Cromwell O, *et al*. Leukotrienes, LTC4 and LTB4, in bronchoalveolar lavage in bronchial asthma and other respiratory diseases. J Allergy Clin Immunol. 1989; 84:19-26.
37. Shirasaki H, Kanaizumi E, Watanabe K, *et al*. Expression and localization of the cysteinyl leukotriene 1 receptor in human nasal mucosa. Clin Exp Allergy. 2002; 32:1007-12.
38. Ferrer M, Luquin E, Sanchez-Ibarrola A, *et al*. Secretion of cytokines, histamine and leukotrienes in chronic urticaria. Int Arch Allergy Immunol. 2002; 129:254-60.
39. Bisgaard H. Vascular effects of leukotriene D4 in human skin. J Invest Dermatol 1987; 88:109-14.
40. Soter N, Lewis RA, Corey EJ, *et al*. Local effects of synthetic leukotrienes (LTC4, LTD4, LTE4, and LTB4) in human skin. J Invest Dermatol 1983; 80:115-9.
41. Rinkema L, Bemis K, Fleisch JH. Production and antagonism of cutaneous vascular permeability in the guinea pig in response to histamine, leukotrienes and A23187. J Pharmacol Exp Ther 1984; 230:550-7.
42. Nettis E, Dambra P, D'Oronzio L, *et al*. Comparison of montelukast and fexofenadine for chronic idiopathic urticaria. Arch Dermatol. 2001; 137:99-100.
43. Reimers A, Pichler C, Helbling A, *et al*. Zafirlukast has no beneficial effects in the treatment of chronic urticaria. Clinical & Experimental Allergy. 2002; 32:1763-8.
44. Erbagci Z. The leukotriene receptor antagonist montelukast in the treatment of chronic idiopathic urticaria: a single-blind, placebo-controlled, crossover clinical study. J Allergy Clin Immunol. 2002; 110:484-8.
45. Nettis E, Colanardi MC, Paradiso MT, *et al*. Desloratadine in combination with montelukast in the treatment of chronic urticaria: a randomized, double-blind, placebo-controlled study. Clinical & Experimental Allergy. 2004; 34:1401-7.
46. Bagenstose SE, Levin L, Bernstein JA. The addition of zafirlukast to cetirizine improves the treatment of chronic urticaria in patients with positive autologous serum skin test results. Journal of Allergy and Clinical Immunology. 2004; 113:134-40.
47. Di Lorenzo G, Luisa Pacor M, Mansueto P, *et al*. Randomized placebo-controlled trial comparing desloratadine and montelukast in monotherapy and desloratadine plus montelukast in combined therapy for chronic idiopathic urticaria. Journal of Allergy and Clinical Immunology. 2004; 114:619-25.
48. Di Lorenzo G, Pacor ML, Mansueto P, *et al*. Is there a role for antileukotrienes in urticaria? Clinical and Experimental Dermatology. 2006; 31:327-34.
49. Kashiwakura J, Hayama K, Fujisawa D, *et al*. Significantly High Levels of Anti-dsDNA Immunoglobulin E in Sera and the Ability of dsDNA to Induce the Degranulation of Basophils from Chronic Urticaria Patients. International Archives of Allergy and Immunology. 2013; 161:154-8.
50. Chang TW, Chen C, Lin C-J, *et al*. The potential pharmacologic mechanisms of omalizumab in patients with chronic spontaneous urticaria. Journal of Allergy and Clinical Immunology. 2015; 135:337-42.
51. Stellato C, de Paulis A, Ciccarelli A, *et al*. Anti-inflammatory effect of cyclosporin A on human skin mast cells. J Invest Dermatol. 1992; 98:800-4.
52. Casolaro V, Spadaro G, Patella V, *et al*. In vivo characterization of the anti-inflammatory effect of cyclosporin A on human basophils. J Immunol 1993 151:5563-73.
53. Cirillo R, Triggiani M, Siri L, *et al*. Cyclosporin A rapidly inhibits mediator release from human basophils presumably by interacting with cyclophilin. J Immunol. 1990; 15:3891-7.
54. Grattan CEH, O'Donnell BF, Francis DM, *et al*. Randomized double-blind study of cyclosporin in chronic 'idiopathic' urticaria. British Journal of Dermatology. 2000; 143:365-72.
55. Marsland AM, Soundararajan S, Joseph K, *et al*. Effects of calcineurin inhibitors on an in vitro assay for chronic urticaria. Clin Exp Allergy. 2005; 35:554-9.

56. Andersson J, Nagy S, Groth CG, *et al*. Effects of FK506 and cyclosporin A on cytokine production studied in vitro at a single-cell level. Immunology. 1992; 75:136-42.
57. Dokter WH, Esselink MT, Sierdsema SJ, *et al*. Transcriptional and posttranscriptional regulation of the interleukin-4 and interleukin-3 genes in human T cells. Blood. 1993; 81:35-40.
58. Mori A, Suko M, Nishizaki Y, *et al*. Regulation of interleukin-5 production by peripheral blood mononuclear cells from atopic patients with FK506, cyclosporin A and glucocorticoid. Int Arch Allergy Immunol. 1994; 104:32-5.
59. Ishii E YS, Sakai R, Hamasaki Y, Miyazaki S. Production of interleukin-5 and the suppressive effect of cyclosporin A in childhood severe atopic dermatitis. J Pediatr. 1996; 128:152-5.
60. Tokura Y, Röcken M, Clark R, *et al*. What are the most promising strategies for the therapeutic immunomodulation of allergic diseases?Note. Experimental Dermatology. 2001; 10:128-40.
61. Serhat Inaloz H, Ozturk S, Akcali C, *et al*. Low-dose and short-term cyclosporine treatment in patients with chronic idiopathic urticaria: A clinical and immunological evaluation. The Journal of Dermatology. 2008; 35:276-82.
62. Wershil BK, Furuta GT, Lavigne JA, *et al*. Dexamethasone and cyclosporin A suppress mast cell-leukocyte cytokine cascades by multiple mechanisms. Int Arch Allergy Immunol. 1995; 107:323-4.
63. Vena GA, Cassano N, Colombo D, *et al*. Cyclosporine in chronic idiopathic urticaria: A double-blind, randomized, placebo-controlled trial. Journal of the American Academy of Dermatology. 2006; 55:705-9.
64. Kessel A, Toubi E. Cyclosporine-A in severe chronic urticaria: the option for long-term therapy. Allergy. 2010; 65:1478-82.
65. Serrano-Candelas E, Martinez-Aranguren R, Valero A, *et al*. Comparable actions of omalizumab on mast cells and basophils. Clinical & Experimental Allergy. 2016; 46:92-102.
66. Hsu C-L, Shiung Y-Y, Lin B-L, *et al*. Accumulated immune complexes of IgE and omalizumab trap allergens in an in vitro model. International Immunopharmacology. 2010; 10:533-9.
67. Chang TW. The pharmacological basis of anti-IgE therapy. Nat Biotech. 2000; 18:157-62.
68. Gomez G, Jogie-Brahim S, Shima M, *et al*. Omalizumab Reverses the Phenotypic and Functional Effects of IgE-Enhanced FcεRI on Human Skin Mast Cells. Journal of immunology. 2007; 179:1353-61.
69. Metz M, Staubach P, Bauer A, *et al*. Omalizumab normalizes levels of high affinity immunoglobulin E receptor- positive skin mast cells in patients with chronic spontaneous urticaria: a random- ized, double-blind, placebo-controlled study. J Invest Dermatol 2014; 134:30-8.
70. Stämpfli MR, Miescher S, Aebischer I, *et al*. Inhibition of human IgE synthesis by anti-IgE antibodies requires divalent recognition. European Journal of Immunology. 1994; 24:2161-7.
71. Davis FM, Gossett L, Pinkston KL, *et al*. Can anti-IgE be used to treat allergy? Springer Semin Immunopathol 1993; 15:51-73.
72. Oliver JM, Tarleton CA, Gilmartin L, *et al*. Reduced Fc∈RI-Mediated Release of Asthma-Promoting Cytokines and Chemokines from Human Basophils during Omalizumab Therapy. International Archives of Allergy and Immunology. 2010; 151:275-84.
73. Beck L, Marcotte G, MacGlashan D, *et al*. Omalizumab-induced reductions in mast cell FcεRI expression and function. Journal of Allergy and Clinical Immunology. 2004; 114:527-30.
74. Noga O, Hanf G, Brachmann I, *et al*. Effect of omalizumab treatment on peripheral eosinophil and T-lymphocyte function in patients with allergic asthma. Journal of Allergy and Clinical Immunology. 2006; 117:1493-9.
75. Kaplan A, Ferrer M, Bernstein JA, *et al*. Timing and duration of omalizumab response in patients with chronic idiopathic/spontaneous urticaria. Journal of Allergy and Clinical Immunology. 2016; 137:474-81.
76. Urgert MC, van den Elzen MT, Knulst AC, *et al*. Omalizumab in patients with chronic spontaneous urticaria: a systematic review and GRADE assessment. British Journal of Dermatology. 2015; 173:404-15.
77. Maurer M, Church MK, Gonçalo M, *et al*. Management and treatment of chronic urticaria (CU). Journal of the European Academy of Dermatology and Venereology. 2015; 29:16-32.
78. Carrillo DC, Borges MS, García E, *et al*. Omalizumab vs. placebo in the management of chronic idiopathic urticaria: a systematic review. The World Allergy Organization Journal. 2014; 7:72.
79. Stahn C, Lowenberg M, Hommes D, *et al*. Molecular mechanisms of glucocorticoid action and selective glucocorticoid receptor agonists. Immunol Allergy Clin North Am. 2005; 25::451-68.
80. Barnes PJ. Molecular mechanisms and cellular effects of glucocorticosteroids.
81. Stahn C, Buttgereit F. Genomic and nongenomic effects of glucocorticoids.
82. Cohan VL, Undem B, Fox C, *et al*. Dexamethasone does not inhibit the release of mediators from human mast cells residing in airway, intestine, or skin. Am Rev Respir Dis 1989; 140:951-4.
83. Kaplan A. Chronic urticaria: Pathogenesis and treatment. Journal of Allergy and Clinical Immunology. 2004; 114:465-74.
84. Cugno M, Marzano AV, Tedeschi A, *et al*. Expression of Tissue Factor by Eosinophils in Patients with Chronic Urticaria. International Archives of Allergy and Immunology. 2009; 148:170-4.

85. Tedeschi A, Asero R, Marzano AV, *et al*. Plasma levels and skin-eosinophil-expression of vascular endothelial growth factor in patients with chronic urticaria. Allergy. 2009; 64:1616-22.
86. Kita H, Abu-Ghazaleh R, Sanderson CJ, *et al*. Effect of steroids on immunoglobulin-induced eosinophil degranulation. J Allergy Clin Immunol. 1991; 87:70-7.
87. Schleimer R, Lichtenstein LM, Gillespie E. Inhibition of basophil histamine release by anti-inflammatory steroids. Nature. 1982; 292:454-5.
88. Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids--new mechanisms for old drugs. N Engl J Med 2005; 353:1711-23.
89. Nancey S, Freymond N, Catelain A, *et al*. Effects of local corticosteroids on acute experimental urticaria. Eur J Dermatol. 2004; 14:323-6.
90. Asero R, Tedeschi A. Usefulness of a short course of oral prednisone in antihistamine-resistant chronic urticaria: a retrospective analysis. J Investig Allergol Clin Immunol 2010; 20:386-90.
91. Godse K. Severe chronic urticaria treated with oral mini-pulse steroid therapy Indian Journal of Dermatology. 2010; 55:402-3.
92. Augey F, Guillot-Pouget I, Gunera-Saad N, *et al*. Impact of corticosteroid withdrawal in chronic urticaria: a prospective study of 17 patients. Ann Dermatol Venereol. 2008; 135:21-5.
93. Maloff BL, Fox D, Bruin E, *et al*. Dapsone inhibits LTB4 binding and bioresponse at the cellular and physiologic levels. European Journal of Pharmacology. 1988; 158:85-9.
94. Zhu YI, Stiller MJ. Dapsone and sulfones in dermatology: Overview and update. Journal of the American Academy of Dermatology. 2001; 45:420-34.
95. Wozel G, Lehmann B. Dapsone Inhibits the Generation of 5-Lipoxygenase Products in Human Polymorphonuclear Leukocytes. Skin Pharmacology and Physiology. 1995; 8:196-202.
96. Ruzicka T, Wasserman SI, Soter NA, *et al*. Inhibition of rat mast cell arachidonic acid cyclooxygenase by dapsone. Journal of Allergy and Clinical Immunology. 1983; 72:365-70.
97. Cassano N, D'Argento V, Filotico R, *et al*. Low-dose dapsone in chronic idiopathic urticaria: preliminary results of an open study. Acta Derm Venereol. 2005; 85:254-5.
98. Morgan M, Cooke A, Rogers L, *et al*. Double-Blind Placebo-Controlled Trial of Dapsone in Antihistamine Refractory Chronic Idiopathic Urticaria. The Journal of Allergy and Clinical Immunology: In Practice. 2014; 2:601-6.
99. Engin B, Özdemir M. Prospective randomized non-blinded clinical trial on the use of dapsone plus antihistamine vs. antihistamine in patients with chronic idiopathic urticaria. Journal of the European Academy of Dermatology and Venereology. 2008; 22:481-6.
100. Fox C, Moore W, Lichtenstein L. Modulation of mediator release from human intestinal mast cells by sulfasalazine and 5-aminosalicylic acid. Digest Dis Sci. 1991; 36:179-84.
101. Lee EH, Kim HM. Inhibition of anaphylaxis by sulfasalazine in rats. Pharmacology. 1998; 56:223-9.
102. Barrett K, Tashof T, Metcalfe D. Inhibition of IgE-mediated mast cell degranulation by sulphasalazine. European Journal of Pharmacology. 1985; 107:279-81.
103. McGirt L, Vasagar K, Gober L, *et al*. Successful treatment of recalcitrant chronic idiopathic urticaria with sulfasalazine. Arch Dermatol. 2006; 142.
104. Orden RA, Timble H, Saini SS. Efficacy and safety of sulfasalazine in patients with chronic idiopathic urticaria. Ann Allergy Asthma Immunol. 2014; 112.
105. Mekori YA, Chowers Y, Ducker I, *et al*. Inhibition of delayed hypersensitivity reactions by colchicine. II. Colchicine inhibits interferon-gamma induced expression of HLA-DR on gut epithelial cell line. Clinical and Experimental Immunology. 1989; 78:230-2.
106. Antoine J, Maurice M, Feldmann G, *et al*. In vivo and in vitro effects of colchicine and vinblastine on the secretory process of antibody-producing cells. J Immunol 1980; 125:1939-49.
107. Pho L, Eliason M, Regruto M, *et al*. Treatment of chronic urticaria with colchicine. J Drugs Dermatol. 2011; 10:1423-8.
108. Ben-Chetrit E, Levy M. Colchicine: 1998 update.
109. Pho L, Hull C, Powell D, *et al*. A retrospective review of the use of colchicine in chronic idiopathic urticaria. Journal of the American Academy of Dermatology. 2010; 62:AB27.
110. Georgy MS, Grammer LC, Greenberger PA, *et al*. A Retrospective Chart Review of the Use of Colchicine for the Treatment of Refractory Chronic Idiopathic Urticaria. Journal of Allergy and Clinical Immunology. 2010; 125:AB96.
111. Kessel A, Bamberger E, Toubi E. Tacrolimus in the treatment of severe chronic idiopathic urticaria: an open-label prospective study. J Am Acad Dermatol. 2005; 52:145-8.
112. de Paulis A, Cirillo R, Ciccarelli A, *et al*. FK-506, a potent novel inhibitor of the release of proinflammatory mediators from human Fc epsilon RI+ cells. J Immunol. 1991; 146:2374-81.
113. de Paulis A, Cirillo R, Ciccarelli A, *et al*. Characterization of the anti-inflammatory effect of FK-506 on human mast cells. J Immunol. 1991; 147:4278-85.

114. Seth S, Khan DA. The Comparative Safety of Multiple Alternative Agents in Refractory Chronic Urticaria Patients. J Allergy Clin Immunol Pract 2017; 5:165-70.
115. Tal Y, Toker O, Agmon-Levin N, *et al*. Azathioprine as a therapeutic alternative for refractory chronic urticaria. International Journal of Dermatology. 2015; 54:367-9.
116. Bhanja DC, Ghoshal L, Das S, *et al*. Azathioprine in autologous serum skin test positive chronic urticaria: A case–control study in a tertiary care hospital of eastern India. Indian Dermatology Online Journal. 2015; 6:185-8.
117. Asero R. Oral cyclophosphamide in a case of cyclosporin and steroid-resistant chronic urticaria showing autoreactivity on autologous serum skin testing. Clinical and Experimental Dermatology. 2005; 30:582-3.
118. Bernstein JA, Garramone SM, Lower EG. Successful treatment of autoimmune chronic idiopathic urticaria with intravenous cyclophosphamide. Annals of Allergy, Asthma & Immunology. 89:212-4.
119. Moder KG. Mycophenolate mofetil: new applications for this immunosuppressant. Annals of Allergy, Asthma & Immunology. 2003; 90:15-20.
120. Shahar E, Bergman R, Guttman-Yassky E, *et al*. Treatment of severe chronic idiopathic urticaria with oral mycophenolate mofetil in patients not responding to antihistamines and/or corticosteroids. International Journal of Dermatology. 2006; 45:1224-7.
121. Tian H, Cronstein BN. Understanding the mechanisms of action of methotrexate: implications for the treatment of rheumatoid arthritis. Bull NYU Hosp Jt Dis 2007; 65:168-73.
122. Cronstein BN. The antirheumatic agents sulphasalazine and methotrexate share an anti-inflammatory mechanism. Br J Rheumatol. 1995; 34:30-2.
123. Cream J, Pole D. The effect of methotrexate and hydroxyurea on neutrophil chemotaxis. Br J Dermatol. 1080; 102:557-63.
124. Tian H, Cronstein BN. Understanding the mechanisms of action of methotrexate: implications for the treatment of rheumatoid arthritis. Bull NYU Hosp Jt Dis. 2007; 65:168-73.
125. Sperling R, Benincaso A, Anderson R, *et al*. Acute and chronic suppression of leukotriene B4 synthesis ex vivo in neutrophils from patients with rheumatoid arthritis beginning treatment with methotrexate. Arthritis Rheum. 1992; 35:376-84.
126. Kremer JM. The mechanism of action of methotrexate in rheumatoid arthritis: the search continues. J Rheumatol. 1994; 21:1-5.
127. Bannwart B, Labat L, Moride Y, *et al*. Methotrexate in rheumatoid arthritis. An update. Drugs. 1994; 47:25-50.
128. Gach JE, Sabroe RA, Greaves MW, *et al*. Methotrexate-responsive chronic idiopathic urticaria: a report of two cases. British Journal of Dermatology. 2001; 145:340-3.
129. Godse K. Methotrexate in autoimmune urticaria. Indian Journal of Dermatology, Venereology, and Leprology. 2004; 70:377.
130. Perez A, Woods A, Grattan C. Methotrexate: a useful steroid-sparing agent in recalcitrant chronic urticaria. British Journal of Dermatology. 2010; 162:191-4.
131. Currimbhoy S, Zhu V, Dominguez AR, *et al*. Rituximab in the treatment of 38 patients with Pemphigus with long-term follow-up. Journal of the European Academy of Dermatology and Venereology. 2016; 30:1050-2.
132. Simon D, Hösli S, Kostylina G, *et al*. Anti-CD20 (rituximab) treatment improves atopic eczema. Journal of Allergy and Clinical Immunology. 121:122-8.
133. Arkwright PD. Anti-CD20 or anti-IgE therapy for severe chronic autoimmune urticaria. Journal of Allergy and Clinical Immunology. 2009; 123:510-1.
134. Chakravarty SD, Yee AF, Paget SA. Rituximab successfully treats refractory chronic autoimmune urticaria caused by IgE receptor autoantibodies. Journal of Allergy and Clinical Immunology. 2011; 128:1354-5.
135. Steinweg S, Gaspari A. Rituximab for the Treatment of Recalcitrant Chronic Autoimmune Urticaria. J Drugs Dermatol. 2015; 14:1387.
136. Piconi S, Trabattoni D, Iemoli E, *et al*. Immune Profiles of Patients with Chronic Idiopathic Urticaria. International Archives of Allergy and Immunology. 2002; 128:59-66.
137. Hermes B, Prochazka AK, Haas N, *et al*. Upregulation of TNF-α and IL-3 expression in lesional and uninvolved skin in different types of urticaria. Journal of Allergy and Clinical Immunology. 1999; 103:307-14.
138. Wilson LH, Eliason MJ, Leiferman KM, *et al*. Treatment of refractory chronic urticaria with tumor necrosis factor–alfa inhibitors. Journal of the American Academy of Dermatology. 2011; 64:1221-2.
139. Sand F, Thomsen S. TNF-Alpha Inhibitors for Chronic Urticaria: Experience in 20 Patients. Journal of Allergy. 2013:130905.
140. Shim WS, Oh U. Histamine-induced itch and its relationship with pain. Mol Pain. 2008 4:29.
141. Hardman J, Limbird L, Molinoff P, *et al*. Goodman and Gilman's the pharmacological basis of therapeutics. 9th edition. McGraw-Hill ed1996. 1905 p.

142. Bleehen S, Thomas S, M.W. G, *et al*. Cimetidine and chlorpheniramine in the treatment of chronic idiopathic urticaria: a multi-centre randomized double-blind study. The British Journal of Dermatology. 1987; 117:81-8.
143. Matthews CN, Boss JM, Warin RP, *et al*. The effect of H1 and H2 histamine antagonists on symptomatic dermographism. Br J Dermatol. 1979; 10:57-61.
144. Kaur S, Greaves M, Eftekhari N. Factitious urticaria (dermographism): treatment by cimetidine and chlorpheniramine in a randomized double-blind study. Br J Dermatol. 1981; 104:185-90.
145. Mansfield L, Smith J, Nelson H. Greater inhibition of dermographia with a combination of H1 and H2 antagonists. Ann Allergy 1983; 50(4):264-5.
146. Simons F, Sussman G, Simons K. Effect of the H2-antagonist cimetidine on the pharmacokinetics and pharmacodynamics of the H1-antagonists hydroxyzine and cetirizine in patients with chronic urticaria. The Journal of Allergy and Clinical Immunology. 1995; 95:685-93.
147. Fedorowicz Z, van Zuuren E, Hu N. Histamine H2-receptor antagonists for urticaria. Cochrane Database Syst Rev. 2012; 14.
148. Guevara-Gutierrez E, Bonilla-Lopez S, Hernández-Arana S, *et al*. Safety and efficacy of cetirizine versus cetirizine plus ranitidine in chronic urticaria: Double-blind randomized placebo-controlled study. Journal of Dermatological Treatment. 2015; 26:548-50.
149. Ting S, Zweima B, Lavker RM. Cromolyn does not modulate human allergic skin reactions in vivo. J Allergy Clin Immunol. 1983; 71:12-7.
150. Okayama Y, R B, Rees P, *et al*. Inhibition profiles of sodium cromoglycate and nedocromil sodium on mediator release from mast cells of human skin, lung, tonsil, adenoid and intestine. Clin Exp Allergy. 1992; 22:401-9.
151. Ahluwalia P, McGill J, Church M. Nedocromil sodium inhibits histamine-induced itch and flare in human skin. Br J Pharmacol. 2001; 132:613-6.
152. Thormann J, Laurberg G, Zachariae H. Oral Sodium Cromoglycate in Chronic Urticaria. Allergy. 1980; 35:139-41.
153. Coughlin SR. Thrombin signalling and protease-activated receptors. Nature. 2000; 407:258-64.
154. Asero R, Tedeschi A, Riboldi P, *et al*. Severe chronic urticaria is associated with elevated plasma levels of D-dimer. Allergy. 2008; 63:176-80.
155. Wang D, Tang H, Shen Y, *et al*. Activation of the blood coagulation system in patients with chronic spontaneous Urticaria. Clinical Laboratory. 2015; 61:1283-8.
156. Asero R, Tedeschi A, Cugno M. Heparin and tranexamic Acid therapy may be effective in treatment-resistant chronic urticaria with elevated d-dimer: a pilot study. Int Arch Allergy Immunol. 2010; 152:384-9.
157. Chua S, Gibbs S. Chronic urticaria responding to subcutaneous heparin sodium. Br J Dermatol. 2005; 153:216-7.
158. Parslew R, Pryce D, Ashworth J, *et al*. Warfarin treatment of chronic idiopathic urticaria and angio-oedema. Clin Exp Allergy. 2000 30:1161-5.
159. Mahesh P, Pudupakkam V, Holla A, *et al*. Effect of warfarin on chronic idiopathic urticaria. Indian J Dermatol Venereol Leprol. 2009; 75:187-9.
160. Samarasinghe V, Marsland AM. Class action of oral coumarins in the treatment of a patient with chronic spontaneous urticaria and delayed-pressure urticaria. Clinical and Experimental Dermatology. 2012; 37:741-3.
161. Laurberg G. Tranexamic acid (Cyklokapron) in chronic urticaria: a double-blind study. Acta Derm Venereol. 1977; 57:369-70.
162. Guhl S, Stefaniak R, Strathmann M, *et al*. Bivalent Effect of UV Light on Human Skin Mast Cells-Low-Level Mediator Release at Baseline but Potent Suppression Upon Mast Cell Triggering. Journal of Investigative Dermatology. 124:453-6.
163. Guhl S, Tapkenhinrichs S, Smorodchenko A, *et al*. Ultraviolet Irradiation Induces Apoptosis in Human Immature, But Not in Skin Mast Cells. Journal of Investigative Dermatology. 121:837-44.
164. Berroeta L, Clark C, Ibbotson SH, *et al*. Narrow-band (TL-01) ultraviolet B phototherapy for chronic urticaria. Clinical and Experimental Dermatology. 2004; 29:97-8.
165. Olafsson J, Larko O, Roupe G, *et al*. Treatment of chronic urticaria with PUVA or UVA plus placebo: a double-blind study. Arch Dermatol Res. 1986; 278:228-31.
166. Khafagy NH, Salem SAM, Ghaly EG. Comparative study of systemic psoralen and ultraviolet A and narrowband ultraviolet B in treatment of chronic urticaria. Photodermatology, Photoimmunology & Photomedicine. 2013; 29:12-7.
167. Ballow M. The IgG molecule as a biological immune response modifier: Mechanisms of action of intravenous immune serum globulin in autoimmune and inflammatory disorders. Journal of Allergy and Clinical Immunology. 127:315-23.

168. Mimouni D, Blank M, Ashkenazi L, *et al*. Protective effect of intravenous immunoglobulin (IVIG) in an experimental model of pemphigus vulgaris. Clinical and Experimental Immunology. 2005; 142:426-32.
169. Rossi F, Kazatchkine MD. Antiidiotypes against autoantibodies in pooled normal human polyspecific Ig. J Immunol. 1989; 143:4104-9.
170. Dietrich G, Kaveri SV, Kazatchkine MD. Modulation of autoimmunity by intravenous immune globulin through interaction with the function of the immune/idiotypic network. Clinical immunology and immunopathology. 1992; 62:73-81.
171. Kazatchkine MD, Kaveri SV. Immunomodulation of Autoimmune and Inflammatory Diseases with Intravenous Immune Globulin. New England Journal of Medicine. 2001; 345:747-55.
172. Mitzel-Kaoukhov H, Staubach P, Muller-Brenne T. Effect of high-dose intravenous immunoglobulin treatment in therapy-resistant chronic spontaneous urticaria. Ann Allergy Asthma Immunol. 2010; 104:253-8.
173. Pereira C, Tavares B, Carrapatoso I, *et al*. Low-dose intravenous gammaglobulin in the treatment of severe autoimmune urticaria. Eur Ann Allergy Clin Immunol. 2007; 39:237-42.
174. O'Donnell, Barr, Kobza B, *et al*. Intravenous immunoglobulin in autoimmune chronic urticaria. British Journal of Dermatology. 1998; 138:101-6.
175. Asero R. Are IVIG for chronic unremitting urticaria effective? Allergy. 2000; 55:1099-101.
176. Jiang X, Lu M, Ying Y, *et al*. A Case Report of Double-Filtration Plasmapheresis for the Resolution of Refractory Chronic Urticaria. Therapeutic Apheresis and Dialysis. 2008; 12:505-8.
177. Grattan CE, Francis DM, Barlow RJ, *et al*. Plasmapheresis for severe, unremitting, chronic urticaria. The Lancet. 1992; 339:1078-80.

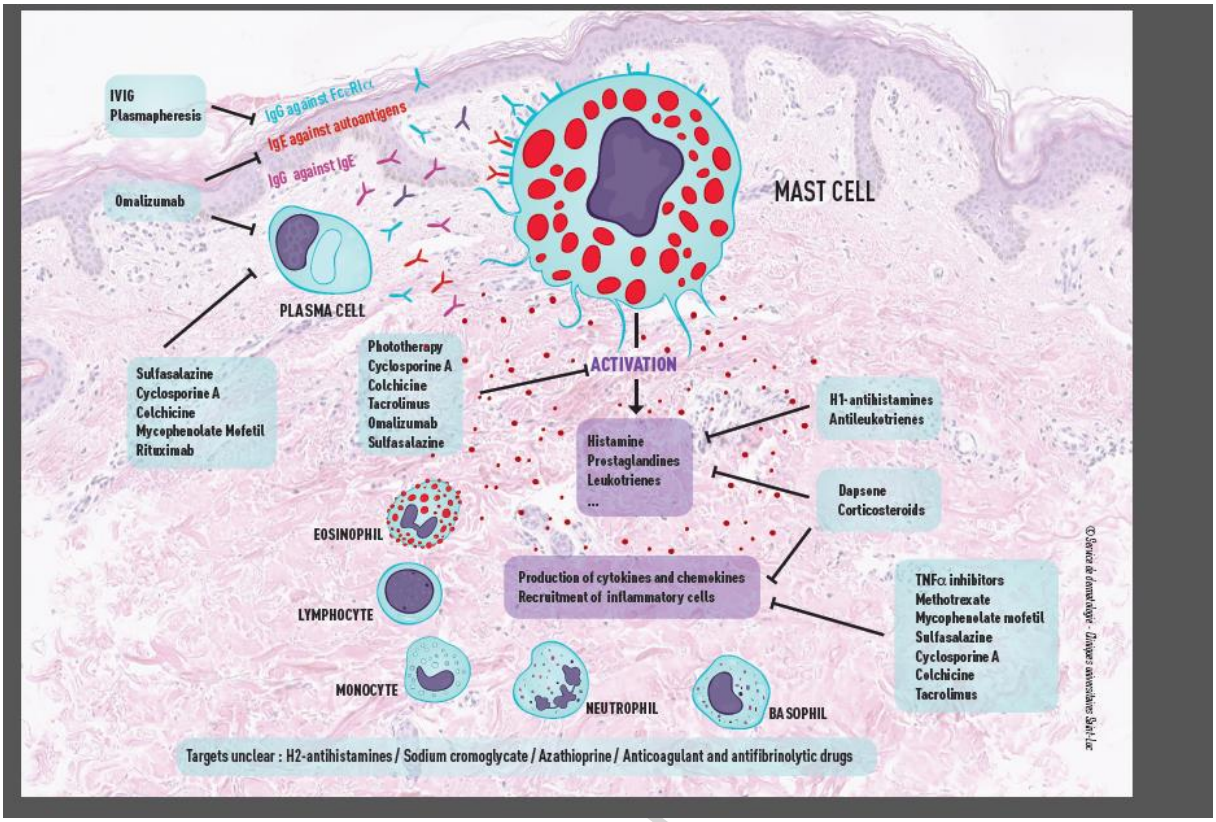

Figure 1: Probable immunological targets of treatments in chronic spontaneous urticaria.

Highlights

- The main event in pathway of chronic spontaneous urticaria is mast degranulation with release of histamine. However, IgE, autoantibodies, T-lymphocytes and B-lymphocytes are also implicated and could possibly be targeted by chronic spontaneous urticaria treatments.
- H_1-antihistamines, antileukotrienes, cyclosporine and omalizumab are treatments validated by randomized placebo controlled trials in chronic spontaneous urticaria.
- Others medications, mostly anti-inflammatory and immunosuppressive drugs, could be effective in chronic spontaneous urticaria treatment but with lower level of evidence.