



Review Article

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, basophils 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.

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1. Introduction

The main event in pathway of chronic spontaneous urticaria (CSU) is mast cell and basophil degranulation with release of histamine, leuko-

trienes, prostaglandins and different inflammatory mediators [1–5]. 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 [6].

Among mediators released by mast cells and basophils, histamine is the most important one. Histamine is a low-molecular-weight amine

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synthesized 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 [7]:

- 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 [8] responsible for pruritis [8].

Mast cell and basophils activation in CSU can be explained by several non-mutually exclusive hypotheses, which are debated [9,10]:

- Presence of autoantibodies directed against the α subunit of mast cells high-affinity IgE receptor (Fc ϵ R1 α). 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 [11–13];
- Presence of immunoglobulin E (IgE) against autoantigens. In conventional thinking, the involvement of IgE in mast cell activation requires the cross-linking of Fc ϵ R1 α -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 [14,15]. These IgE are considered highly cytokinergic ones. All IgEs exhibit different ability to induce the production and secretion of cytokines by mast cells. Highly cytokinergic IgEs can efficiently induce production of cytokines and have antiapoptotic effects on mast cells whereas poorly cytokinergic IgEs induce these effects inefficiently [16]. Interestingly, level of anti-thyroid peroxidase IgE [17] and anti-dsDNA IgE [18] 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. These antibodies exhibit histamine-releasing properties from basophils and mast cells [19,20] but their implication in CSU is not well established. Indeed, identification of these antibodies in CU patients is inconstant, and probably of low specificity, as they are present in atopic and even in healthy subjects [21,22].
- Binding of anaphylatoxins C3a and C5a to their receptor on basophils [23];
- Binding of thrombin and factor VIIa to PAR (proteinase activated receptor) on mast cells [24,25].

The possibility of one or more circulating histamine-releasing factors being involved in the pathogenesis of CSU was demonstrated, among others, by the autologous serum skin test (ASST) [26]. 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. H₁-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. Fig. 1 summarizes 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 H₁-antihistamines, antileukotrienes, cyclosporine and omalizumab, the conclusions of trials recommend them. Concerning H₂-antihistamines, there is only one randomized placebo controlled trial, which did not recommended them.

2.1.1. H₁-antihistamines

2.1.1.1. Mechanisms of action. H₁-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 [7] in asthma that H₁-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.

H₁-antihistamines also inhibit NF- κ B in human lymphocytes and monocytes [7,27].

First-generation H₁-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 [28,29].

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/GA²LEN/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 [30].

2.1.1.2. Efficacy of H₁-antihistamines in chronic spontaneous urticaria. Several randomized (placebo) controlled trials have proved their efficiency in CSU [31]. Cetirizine seems to be more effective than fexofenadine [32] and levocetirizine more effective than desloratadine

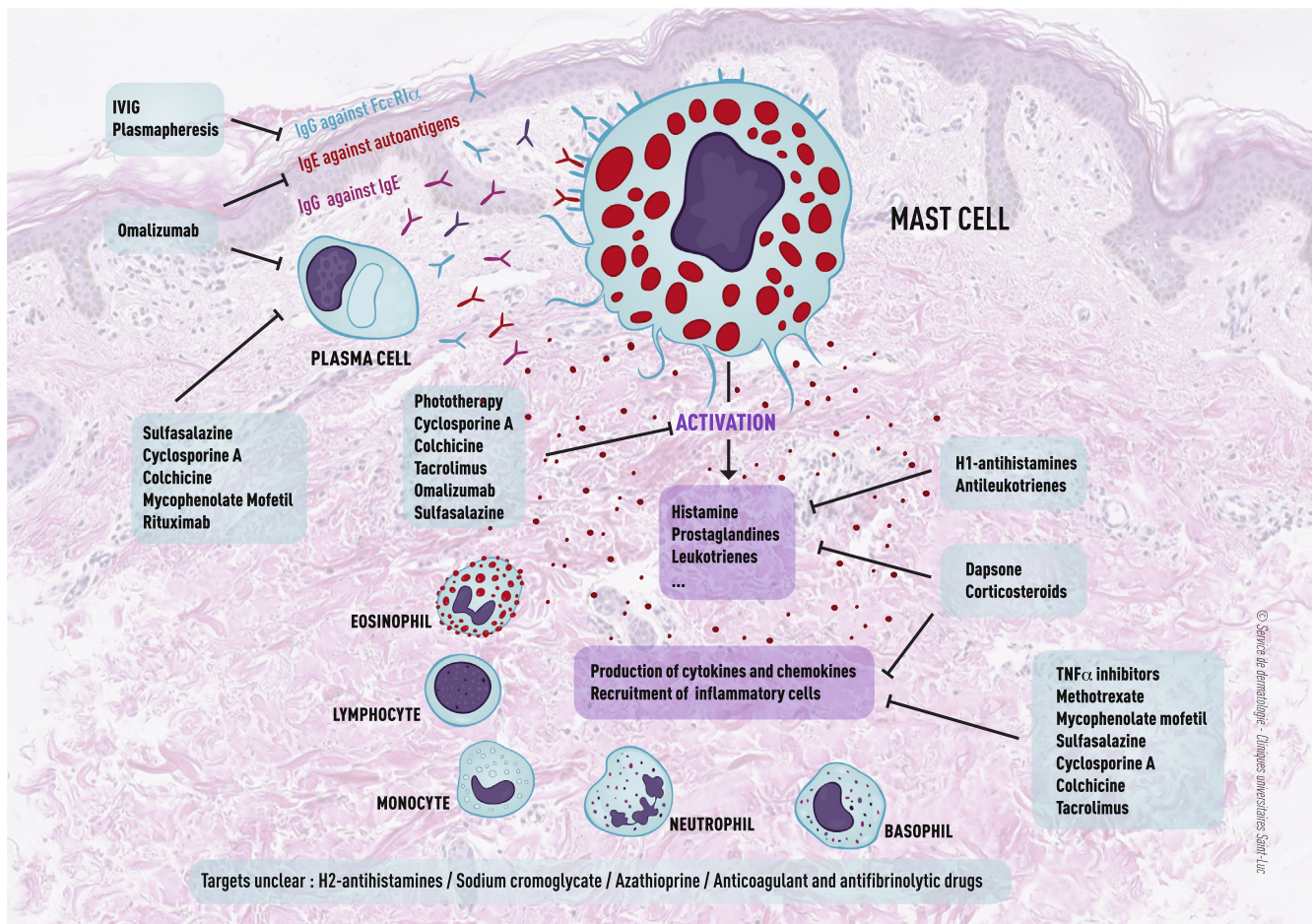


Fig. 1. Probable immunological targets of treatments in chronic spontaneous urticaria.

[33]. However, rupatadine seems to be more effective than cetirizine [34], while levocetirizine seems to be more effective than rupatadine in another study [35].

There are studies showing the benefit and safety of increasing up to 4 times conventional doses of bilastine (20 mg), desloratadine (5 mg), levocetirizine (5 mg), fexofenadine (180 mg) in difficult-to-treat CU [36–41]. Concerning rupatadine (10 mg), one study showed safety of increasing up to 4 times the conventional doses [42] but the real benefit could only be proved in CU when increasing up to 2 times conventional doses [43]. Concerning ebastine, one study showed superiority of 20 mg compared to 10 mg in CSU [44]. Moreover, ebastine at dose up to five times the recommended therapeutic dose did not cause any clinically relevant change in QTc interval [45].

2.1.2. Antileukotrienes

2.1.2.1. Mechanisms of action. Leukotrienes are mediators synthesized 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 [46], allergic rhinitis [47] and CU [48].

Leukotrienes are also known to produce local effects on cutaneous blood vessels [49]. Soter et al. [50] demonstrated that injection of a leukotriene D₄ 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 D₄ agonist [51].

2.1.2.2. Efficacy of antileukotrienes in chronic spontaneous urticaria. A few randomized double or simple-blind controlled trials were published.

Concerning antileukotrienes separately, Nettis et al. [52] 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 [53].

Concerning antileukotrienes in combination with H₁-antihistamines, a randomized, single-blind, placebo-controlled study showed benefit superiority of combining montelukast with H₁-antihistamines compared to placebo with H₁-antihistamines to treat CSU [54]. 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 [55].

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 H₁-antihistamines treatment [56].

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 [57]. 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 [53,58].

Antileukotrienes are recommended in second line by AAAAI/ACAAI Joint Task Force in 2014, and in third line by EAACI/GA²LEN/EDF/WAO Guidelines 2013 for CSU treatment.

2.1.3. Cyclosporine A

2.1.3.1. 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 [59–62] and basophils [63] in vitro as well as and in vivo [11,12]. This action on mast cells explains early response of CsA for CSU patients [64]. 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 [65].

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) [66–70], the most significant one being IL-2, which acts as the major T cells activator in numerous immunological processes in interaction with mast cells [71]. Indeed, decrease of serum IL-2 receptor, TNF- α and IL-5 was observed in CSU subjects treated with CsA [71].

CsA also reduces antibody production, i.e. IgG anti-Fc ϵ RI α , IgG anti-IgE, IgE against autoantigens [64].

Finally, CsA decreases inflammatory cells recruitment by inhibition of different cell adhesion molecules in humans [61,63], and by reduction of IgE dependent TNF- α secretion by mast cells in mice [72].

2.1.3.2. 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% [64,73,74], 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/GA²LEN/EDF/WAO Guidelines 2013 and by AAAAI/ACAAI Joint Task Force 2014 as fourth line therapy.

2.1.4. Omalizumab

2.1.4.1. 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 Fc ϵ RI receptor on the surface of target cells, including mast cells, basophils and dendritic cells. Recently, Serrano-Candelas and al. [75] 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 autologous IgE in CSU.

In asthma, it has been suggested that the accumulation of omAb-IgE immune complexes might help to sequester incoming allergen molecules [76]. In CSU, accumulation of omAb-IgE immune complexes [77] 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 Fc ϵ RI receptor expression on mast cells, basophils, and

antigen-presenting cells. The reduction in Fc ϵ RI levels possibly results of degradation of unbound Fc ϵ RI when they are not stabilized by binding to IgE [78–82]. Metz et al. [83] found that baseline levels of Fc ϵ RI- and IgE-positive cells were higher in CSU patients than in controls, and that after 12 weeks of OmAb treatment their levels in lesional and non-lesional skin of CSU patients decreased, and is comparable to that of control patients.

Additionally, OmAb downregulates CD23 (also called Fc ϵ RII) on B cells [84]. 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 [85].

Moreover, OmAb has anti-inflammatory activity demonstrated by induction of eosinophil apoptosis and downregulation of the inflammatory cytokines IL-2, IL-4, IL-8 and IL-13 [86,87].

The overall effect of omAb is that the IgE–Fc ϵ RI–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 [60].

2.1.4.2. 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 (75 mg, 150 mg, 300 mg). OmAb was clearly more effective than placebo at the dose of 300 mg [88,89].

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 Weekly Urticarial Activity Score (UAS7) ≤ 6 [90]. 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/GA²LEN/EDF/WAO Guidelines 2013 and in fourth line therapy by AAAAI/ACAAI Joint Task Force 2014. OmAb is now approved for severe and H₁-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 ≥ 3 monthly doses to respond [88]. 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 [89,91].

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.

2.2.1.1.1. 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 [92–94]. Nonetheless, these mechanisms take time and CS such as prednisolone are usually effective in CSU only after 24 h. Moreover, CS don't exert any effect on cutaneous mast cell degranulation [95] or on complement activation [96]. Hence, it has been suggested that the rapid clinical effect of CS observed in CSU is due to the direct inhibition of inflammatory cells [96]. An inhibitory effect on the release of mediators from eosinophils (notably, a cell type recently found to be activated in CSU [97,98] has also been reported [99]. Similarly, an effect on histamine release from basophils has been identified [100]. Moreover, vasodilation and vascular

permeability inhibition [101] might also be involved in the rapid response to CS in CSU patients.

2.2.1.1.2. Efficacy of corticosteroids in chronic spontaneous urticaria. Topical CS was not able to prevent acute experimental urticaria (caused by histamine or codeine) [102].

Conversely, Asero et al. [103] have treated 86 H₁-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 H₁-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 [104].

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 H₁-antihistamines [105].

AAAAI/ACAAI Joint Task Force 2014 and EAACI/GA²LEN/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

2.2.1.2.1. Mechanisms of action. Dapsone (4-4'-diaminodiphenylsulfone) is a sulfonamide antibiotic which has been shown to inhibit neutrophils chemotaxis [106] and reactive oxygen species production. This explains its efficacy in neutrophilic diseases, such as pyoderma gangrenosum or urticarial vasculitis [107]. Dapsone also inhibits 5-lipoxygenase in human polymorphonuclear cells and in rat mast cells [108,109], 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 [107].

2.2.1.2.2. 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 [110].

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 [111].

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 [112].

2.2.1.3. Sulfasalazine

2.2.1.3.1. 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 [9]. 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 [113–115]. Sulfasalazine also increases prostaglandin (PG) E₂ which may have anti-inflammatory properties, such as inhibition of release of inflammatory mediators from mast cells [116,117]. Sulfasalazine also inhibits the synthesis of leukotrienes [118].

2.2.1.3.2. 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 [119].

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 [120].

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

2.2.1.4. Colchicine

2.2.1.4.1. 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 [9,121–124].

2.2.1.4.2. 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 [123,125,126]. No randomized controlled trial has been carried out, indicating low-grade evidence to support its use.

2.2.2. Immunosuppressive treatments

2.2.2.1. Tacrolimus

2.2.2.1.1. 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 [127–129].

2.2.2.1.2. 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 [127]. 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, side effects caused frequent discontinuation of treatment [130].

2.2.2.2. Azathioprine

2.2.2.2.1. Mechanisms of action. Azathioprine inhibits purine nucleotide synthesis and causes, among others, T cell apoptosis.

2.2.2.2.2. Efficacy of azathioprine in chronic spontaneous urticaria. 2 patients with severe refractory CU were treated with azathioprine [131]. 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 H₁-antihistamines) [132].

2.2.2.3. Cyclophosphamide

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

2.2.2.3.2. Efficacy of cyclophosphamide in chronic spontaneous urticaria. There are only 2 case reports published showing effectiveness in severe recalcitrant CSU [133,134].

2.2.2.4. Mycophenolate mofetil

2.2.2.4.1. 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 [135].

2.2.2.4.2. Efficacy of mycophenolate mofetil in chronic spontaneous urticaria. Only a small open-label uncontrolled trial with 9 CSU patients (taking CS and H₁-antihistamines) has shown enough efficacy of mycophenolate mofetil so that all patients were able to withhold CS [135,136].

2.2.2.5. Methotrexate

2.2.2.5.1. 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 [137]. By adenosine increase, MTX inhibits neutrophils recruitment [137–139]. In rheumatoid arthritis, MTX reduces leukotriene B₄ neutrophils synthesis [140], modifies cytokines profile (IL-1, IL-6 reduction and IL-2 increase) [141] and alters activity of proteolytic enzymes [142].

2.2.2.5.2. 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, H₁-antihistamines). These background medications could be reduced while still improving symptoms. However, the diagnosis of CSU was not quite clear for one patient [143]. Another group of 4 CSU patients recalcitrant to H₁-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 H₁-antihistamines alone [144]. Finally 10 CS-dependent CSU patients unresponsive to H₁-antihistamines were treated with methotrexate (5 to 25 mg weekly) in addition to CS treatment. 5 patients had considerable benefits and steroid could be stopped or reduced [145]. However, the use of MTX is also limited by its side effects.

2.2.2.6. Rituximab

2.2.2.6.1. 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 [146,147].

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

2.2.2.6.2. 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 H₁-antihistamines for one year [148]. Two other cases of good efficacy in CSU were reported. One patient took combination of rituximab and CS [149]. The other one could stop CS and remained free of symptoms for 10 months [150].

Conversely, a single case report showed no improvement of CSU with rituximab [149].

2.2.2.7. TNF-alpha inhibitors

2.2.2.7.1. Mechanisms of action. Three biologic TNF- α inhibitors (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.

TNF α 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 [151,152].

2.2.2.7.2. 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 [153]. Concerning etanercept, the condition of 6 CSU patients was improved by the treatment [153,154]. A group of 14 CSU patients were treated with adalimumab, which was effective in 11 patients but ineffective in 3 patients [154].

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

2.2.3.1.1. Mechanisms of action. H₂-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 H₂-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, H₂-antihistamines don't have any antipruritic properties [155].

Nevertheless, H₂-antihistamines reduce blood vessels vasodilation and vascular permeability induced by HR2 on myocytes and endothelial cells [156].

2.2.3.1.2. Efficacy of H₂-antihistamines in chronic spontaneous urticaria. Several clinical studies have demonstrated additional benefits by combining H₁-antihistamine with H₂-antihistamine (especially with cimetidine), compared to H₁ antihistamines monotherapy [157–160] 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 [161]. Currently, ranitidine is more frequently used than cimetidine.

In 2012 The Cochrane review [162] adopted no clear position about the use of H₂-antihistamines for urticaria. H₂-antihistamines were still recommended in EAACI/GA²LEN/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 [163].

2.2.3.2. Sodium cromoglicate

2.2.3.2.1. 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 ragweed, as demonstrated in one study [164]. Moreover, skin mast cells seem to be less or unresponsive to sodium cromoglicate compared to mast cells of tonsils or lungs [165].

Sodium cromoglicate seems to reduce pruritus by its action on non-myelinated C-type fibers [166].

More recently, sodium cromoglicate is identified as potent G-protein-coupled receptor 35 (GPR35) agonists. GPR35 is expressed in human mast cells, basophils and eosinophils [167].

2.2.3.2.2. Efficacy of sodium cromoglicate in chronic spontaneous urticaria. The only study published is a double-blind cross-over trial which showed no superiority of sodium cromoglicate versus placebo [168].

2.2.3.3. Anticoagulant and antifibrinolytic drugs

2.2.3.3.1. 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 [24, 25, 169].

Activation of the extrinsic pathway of coagulation seems to be important in CSU physiopathology. Cugno and al. [97] 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) [170]. Wang et al. [171] 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 antithrombin III itself blocking thrombin and others factors [172, 173].

2.2.3.3.2. 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 [174].

A study with 5 CSU patients treated with warfarin (associated with CS) showed total/partial response for 2/2 patients [175]. A case report of a CSU patient showed improvement both with warfarin and with acenocoumarol [176].

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 [172]. A single case report described a CU patient cured by heparin treatment [172, 173].

One limited double-blind study with tranexamic acid alone in CU showed no superiority compared to placebo [177].

2.2.3.4. Phototherapy

2.2.3.4.1. 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. [178] 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.

Phototherapy can also exert suppressive effects on T cells, as in psoriatic patients [179, 180].

Another important aspect of UV immunomodulation concerns the induction of apoptosis in skin infiltrating cells. Guhl et al. [181] also demonstrated that human mast cells undergo apoptosis in response to irradiation with UVB or UVA1.

2.2.3.4.2. 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 [182]. 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) [183]. A randomized controlled trial comparing UVA and psoralen with narrowband-UVB in 24 CSU patients showed comparable improvement in both groups [184]. However, no randomized placebo controlled trial has been carried out.

2.2.3.5. Intravenous immunoglobulins

2.2.3.5.1. 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 [185]. Moreover, IVIG contains anti-idiotypic antibodies (e.g. anti-DNA, anti-intrinsic factor, anti-thyroglobulin, and anti-desmoglein-3 antibodies) [186, 187], which act as immunomodulators against autoantibodies [188] and explain their efficacy in various autoimmune disorders [189].

2.2.3.5.2. 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 [190]. 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 [191]. 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) [192].

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 [193].

2.2.3.6. Plasmapheresis

2.2.3.6.1. 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 [194].

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.

2.2.3.6.2. 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 [194]. In another study, among 8 CSU patients treated with plasmapheresis (alone or together with antihistamines) efficacy was observed in 5 patients [195].

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 H₁-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, sulfasalazine, 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.

Conflict of interest

None.

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