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Treatment of chronic spontaneous urticaria with an inadequate response to

H1-antihistamine

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ABSTRACT

The second-generation H1-antihistamines (sgAH) are the first-line symptomatic treatment of patients with chronic spontaneous urticaria (CSU). Up to 50% of the patients will not respond to licensed doses of sgAH. According to the guidelines, the dose of sgAH may be increased up to 4 times the conventional dose. However, even at higher doses, there is a subgroup of patients, are refractory to the antihistamine treatment.

The purpose of this article is to review the different treatment options of antihistamine-refractory CSU patients.

This revision examines the available literature for therapies used in chronic urticaria, including omalizumab, ciclosporin A, oral glucocorticoids, leukotriene receptor antagonists, H2 antihistamines, doxepin, dapsone, hydroxychloroquine, phototherapy, methotrexate, mycophenolate mofetil, azathioprine, autohemotherapy, intravenous immunoglobulins and rituximab, between others. After the exhaustive review of the medical literature only few high-quality studies have been identified, mostly for omalizumab. Omalizumab is an anti-immunoglobulin E monoclonal antibody, approved for the treatment of CSU, that has radically changed the management of the patients without good response to sgAH, allowing to reach complete responses in a high percentage of patients.

Although actually the therapeutic management of CSU is more effective and safe than before 2014, there is place even for new and more effective treatments. A good number of partial responders and slow responders to omalizumab and a little percentages still of non responders to available therapies stimulate the development of new drugs that also will be discussed.

INTRODUCTION

Chronic spontaneous urticaria (CU) is an inflammatory cutaneous disease characterized by the appearance of itchy wheals, angioedema or both persisting more than 6 weeks.¹ The

1 estimated prevalence of CU is 0.5-1% of the general population, and its annual incidence is
2
3 1.4%.² Middle aged women are more affected and angioedema is present approximately in
4
5 50% of cases. The last EAACI/GA²LEN/EDF/WAO guidelines¹ classify chronic urticaria in
6
7 spontaneous or inducible attending the relevance of the eliciting factors. In chronic
8
9 spontaneous urticaria (CSU), previously also called chronic idiopathic urticaria, it is not
10
11 possible to identify any eliciting factor so the appearance of symptoms is spontaneous. In
12
13 chronic inducible urticaria (CIndU) a specific, well identified, eliciting factor is involved (i.e.
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15 cold, pressure, exercise, UV light, heat, vibration, water). Both subtypes of chronic urticaria
16
17 can confluence in the same patient, conferring some special features in terms of activity,
18
19 duration of the disease and response to the treatment.³ **(Figure 1)**

22 The main effector cell in CSU is the cutaneous mast cell. Mast cell can be activated by a
23
24 large number of factors such as physical stimuli, drugs (e.g. non-steroidal anti-inflammatory
25
26 drugs [NSAIDs] or opioids), infections or autoimmune diseases. Once the mast cell is
27
28 activated, degranulation occurs. The release of vasoactive and proinflammatory mediators
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30 such as histamine or platelet activating factor (PAF) from mast cells in the skin seems to be a
31
32 key factor in urticaria pathogenesis.
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34

35 The autoimmune hypothesis of CSU, Chronic Autoimmune Urticaria (CAU) involve type I
36
37 type IIb autoimmunity. Type I autoimmunity or “autoallergy” shows IgE to different
38
39 potential auto antigens as e.g. TPO, ANAs or IL-24 capable to activate mast cell. About a
40
41 third of CSU patients have autoantibodies type IgG against the high affinity IgE receptor
42
43 (FcεRI) or the IgE itself type IIb CAU. The activity of these IgG autoantibodies can be
44
45 functionally detected by in vitro (Basophil Histamine Release Assay (BHRA) or Basophil
46
47 Activation Test (BAT)) or in vivo tests (autologous serum/plasma skin test, ASST or APST).
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49 The ASST is positive in about 50% of CSU patients, providing indirect evidence of
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51 functional factors in the serum of these patients.^{4, 5} Additionally, other autoimmune diseases
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such as Hashimoto thyroiditis or vitiligo can be associated in patients with CAUIIb. Kolkhir et al. proposed the concept of type I and type II autoimmunity. Type I autoimmunity, also called autoallergy, occurs when IgE autoantibodies anti self, for example IgE anti thyroid peroxidase, leads to degranulation of the cutaneous mast cell. On the other hand, type IIb autoimmunity would fit into the classical definition of chronic autoimmune urticaria with the presence of IgG autoantibodies against the FcεRI or the IgE itself.⁶ Despite the fact that important advances have been made in the knowledge of the pathogenesis of chronic urticaria in recent years, this is not yet fully understood.

BURDEN OF CHRONIC SPONTANEOUS URTICARIA

CU has a significant negative impact on patients' quality of life as well as on society and the healthcare system.⁷⁻⁹ According to Mendelson et al, the patients that suffers CSU presented higher prevalence of sleep difficulties, anxiety and depression. Furthermore, patients with poor controlled disease showed high rates of absenteeism and presenteeism when compared with healthy controls and these rates were very similar to those of patients with severe psoriasis.^{10, 11}

ASSESSMENT OF CHRONIC SPONTANEOUS URTICARIA ACTIVITY AND CONTROL

The use in the daily activities of the validated Patient Report Outcomes (PRO) is recommended by the urticaria expertise. The therapeutic goal is to obtain as fast as possible the complete relief and control of signs and symptoms. These tools are essential to involve the patient in their own knowledge of the disease. Disease activity outcomes in patients with CSU are usually measured by the Urticaria Activity Score (UAS) 7 score (UAS7: sum of the 7 previous days-UAS score).¹² UAS takes into account the number of wheals and the severity of pruritus and ranges from 0 to 42, being 0 complete control of the disease. This score is

very easy to perform and informative. Stull et al proposed a CSU activity categories according to the UAS7 results: 0 complete control, 1-6 well controlled disease, 7-15 mild, 16-27 moderate and 28-42 severe disease.¹³ There are other useful scores such as the Urticaria Control Test (UCT) to evaluate control of the disease¹⁴. The Angioedema Activity Score (AAS) is the validated tool when angioedema is concomitantly present.¹⁵ Since CSU is a disease with a significant psychological and social burden, the quality of life (QoL) evaluation is also very important in these patients. One of the most used questionnaires are the general Dermatology Life Quality Index (DLQI) but other specific questionnaires have been validated for assessing specifically de QoL in CSU patients (The Chronic Urticaria QoL Questionnaire (CU- Qo2L) and he Angioedema QoL Questionnaire (AE-QoL)).¹⁶⁻¹⁸

EVIDENCE BASED TREATMENT OF CHRONIC SPONTANEOUS URTICARIA

According to the EAACI/GA²LEN/EDF/WAO guidelines¹, the first-line therapy in CSU is the second-generation H1-antihistamines (sgAH) due to its high-quality evidence and their very good safety profile. Antihistamine drugs, specifically H1-antihistamines, are widely used to treat urticaria in any form (acute, chronic, inducible) since 1950s. H1-antihistamines relieve itching and reduce the number, size and duration of urticarial lesions acting as inverse agonist of the H1 receptors located in the endothelial cells (reducing vascular permeability and edema) and in the sensory nerves (reducing pruritus and erythema).

Modern, non-sedating, sgAH are the recommended therapy for the treatment of CSU. However, with the current standard of care (licensed doses of sgAH), only less than 50% of CSU patients will achieve a control of the disease.¹⁹ According to different studies, the rates of response to standard doses of sgAH varies between 20 and 50%.^{3, 19-23} This percentage seems higher when dealing with patients with CIndU, achieving up to 80-90% of antihistamine response.²⁴

There is evidence that that increasing the dosage up to fourfold, might control symptoms in these patients without main safety concerns. A recent systematic review and meta-analysis showed that 38.6% of patients with CSU responded to licensed doses of sgAH. From the non-responder patients, 63.2% achieved good control of the disease when up dosing, but a significant improvement was observed only in the pruritus variable of the urticaria activity score (UAS) scale.^{22, 23}

For these reason, the second step in the algorithm treatment of CSU is increase the dose of sgAH up to 4 fold the standard dose. **(Figure 2)** However, despite increasing the dose of antihistamines, there still remain a considerable percentage of patients that will not completely respond. Some clinical and laboratory parameters have been proposed to be linked with the response to antihistamines in patients with CSU. Sanchez-Borges M et al described that a low baseline Urticaria Activity score, the lack of other comorbidities such as allergic disorders, thyroid diseases or high blood pressure, the short duration of the wheals, the absence of serum autoreactivity (ASST and BAT negative) and low serum levels of D-dimer, allows us to predict a good response to antihistamines.²⁵

HOW TO TREAT PATIENTS WITH INADEQUATE CONTROL TO ANTIHISTAMINES?

In patients not responding to high doses of sgAH, the current EAACI/GA²LEN/EDF/WAO urticaria guidelines recommend omalizumab as the next step in the treatment of CSU.

(Figure 2)

OMALIZUMAB

Omalizumab (Xolair®) is a recombinant humanized monoclonal anti-Immunoglobulin E (IgE) antibody approved since 2014 for CSU in adults and adolescents 12 years of age and

older with inadequate response to sgAH. Omalizumab inhibits the binding of circulating IgE to its high affinity receptor (FcεR1) on both basophils and mast cells. This sequestration of serum-free IgE leads to a down-regulation of IgE receptors. However, the other mechanisms by which omalizumab acts so fast, is yet not well understood.

Omalizumab has demonstrated an excellent efficacy and safety in three randomized, double-blind, placebo-controlled phase III trials: ASTERIA I, ASTERIA II and GLACIAL.

In total, these clinical trials included 733 patients on omalizumab 75, 150, or 300 mg at 4-week intervals showing respectively a 19%, 24% and 15% of complete response (UAS7=0) at week 4. Moreover, between 58.8 and 52.4% of patients achieved a good control of the disease, defined as UAS7<6 at week 12.²⁶⁻²⁹ (see **table 1**) Based on these results, omalizumab was approved and is now considered a third-line agent in the treatment of patients that not respond to high doses of sgAH.¹ The approved dose of omalizumab is 300 mg subcutaneously every 4 weeks. Subsequently, other clinical trials have been conducted in Asian population (Japanese and Korean patients), since they represented a very low percentage in the clinical trials previously mentioned, showing similar results.³⁰ Angioedema is present in up to 50% of CSU patients, mostly associated with typical wheals. These patients with angioedema have a severely affected quality of life. Staubach et al studied the effect of omalizumab in the quality of life of patients with angioedema that were refractory to antihistamine treatment, even at high doses. Omalizumab showed to be very effective in the study patients that suffered from wheals and at least four episodes of angioedema during the last 6 months and this clinical improvement correlated directly with an improvement of the quality of life measured by (CU-Q2oL). The subgroup of patients that only suffers from histaminergic angioedema was not the scope in these study.³¹

After its approval, many real-world clinical studies have ratified, and even show better efficacy rates than in the clinical trials.^{32, 33}

A systematic review recently published, point that real-world evidence confirms the high effectiveness of omalizumab in the treatment of CSU patients, independently of their comorbidities, reducing the disease activity scores and improving the control of the disease and the quality of life, without main safety concerns.³⁴

How long should the treatment be maintained?

The duration of the treatment is not standardized yet.

It is well-known that the duration of CSU is variable and difficult to predict so the current recommendations suggest that we have to treat the disease until it goes. For some patients CSU may persist up to 5 years, or even more but most of them will be free of symptoms after the first year of treatment.³⁵ Some factors such as the activity of the disease, the presence of angioedema, autoreactivity and concomitant CIndU, is associated with longer duration of CSU.¹⁹

We observed that patients with concomitant CSU and inducible urticaria (CIndU) and those with relapsing and late-onset CSU (beyond 45 years old), show a longer duration of the disease. These clinical features factors of bad prognosis in relation to a longer duration of the disease should be taken into account in our therapeutic desitions as if we are considering stopping the treatment.⁵

We also must bear in mind that not all patients will respond equally fast.

The median time to achieve well-controlled urticaria (defined as $UAS7 \leq 6$) in the clinical trials was 3 to 6 weeks, and the median time to achieve complete control ($UAS7=0$) was 8 to 13 weeks.³⁶ It is well recognized early and late responders to omalizumab. Asero et al, define early responders when the time to omalizumab response is up to 4 weeks and late responders in those patients that takes up to 24 weeks to respond.³⁷ According to this data, it has been proposed that the evaluation of omalizumab response should be performed every 3 months.

Given that omalizumab is a treatment with a high economic impact, in those patients who are free of symptoms after several months of treatment, omalizumab can be stopped. However, since omalizumab is not a disease-modifying drug, some of these patients will relapse. It has been observed that the retreatment of these patients does not diminish the efficacy of the drug and even the speed of action of the same is greater.³⁸

Can we know which patient will respond later to the treatment?

Positive serum autoreactivity demonstrated by positive Basophil Histamine Release Assay (BHRA) and Autologous Serum Skin Test (ASST) are a significant predictors of slow response to omalizumab ($p < 0.01$). So, patients with type II autoimmunity, we can expect a later response.^{6, 39}

What can we do if there is no response to omalizumab 300mg/4 weeks after three months of treatment?

In this case, the decision to increase the dose could be considered. This approach is still not recommended by the guidelines but there is some evidence from real life showing that can be useful in some patients. In an observational study conducted by the Catalan and Balearic Island Chronic Urticaria Network (XUrcB) including 286 patients treated with omalizumab, the percentage of non-responder patients to omalizumab 300mg/4 weeks after 3 to 6 months of treatment was 35% ($n=99$). The dose of omalizumab was increased in 79 patients (450mg first, then increasing to 600 mg if inadequate control). Seventy-five per cent of them achieved control of the disease ($UAS7 \leq 6$) with doses of 450mg (55%) or up to 600mg/4 weeks (20%). Predictors of good response with up dosing were previous immunosuppressive therapy (Ciclosporin), obesity (Body Mass Index (BMI) > 30) and age > 57 years old.⁴⁰ According to these results, an algorithm for the treatment of CSU with omalizumab has been proposed by

the same group.⁴¹ Another study conducted by 2 urticaria centers (Istanbul and Barcelona) showed similar results. According to these authors, the factors that might determine which patients will require higher doses of omalizumab are, again, a higher BMI and a lower pre-omalizumab Urticaria Control Test (UCT).⁴² However, despite increasing the dose of omalizumab, there is still a subgroup of patients who will not respond.

Can we predict which patients will and will not respond to omalizumab?

The identification of reliable biomarkers of therapeutic response to different drugs is very important in clinical practice. To be able to predict response to biologic treatments such as omalizumab is even more important due to the high cost of these treatments. Some biomarkers have been proposed during the last few years. The most important are Immunoglobulin E (IgE) and the high-affinity IgE receptor (FcεRI). Other possible biomarkers are D-dimer, Basophil Activation Test (CD63/CD203c), Basophil Histamine Release Assay (BHRA) and Autologous Serum Skin Test (ASST).⁴³

Immunoglobulin E

Non-responders to omalizumab seems to have low total IgE levels. Cugno et al, found that patients with good response to omalizumab showed baseline levels of IgE and D-Dimer higher than non-responder patients.⁴⁴ These patients with elevated baseline serum levels of IgE and D-Dimer also show an early response to the treatment.^{45, 46} Another study conducted by Straesser et al, found similar results. According to these authors, low serum IgE (≤ 15.2 IU/mL) would correlate with lower omalizumab response.⁴⁷ Ertas et al, also showed that low baseline IgE (< 43 UI/ mL) was associated with a poor response to omalizumab. Moreover, these authors found that the change of IgE from baseline to week 4 of omalizumab treatment was even better as a predictor of response. Following this observation, they propose a rule to

predict response to omalizumab: the 2x4 rule, especially helpful in patients with baseline low IgE levels. This rule says that when baseline IgE levels fail to double within the first 4 weeks of treatment, non-response needs to be expected.⁴⁸

High-affinity IgE receptor (FcεRI)

A very low, even lower than the baseline levels in healthy controls, baseline expression of basophil FcεRI in peripheral blood help to predict no response to omalizumab treatment in CSU patients. Baseline FcεRI expression also helps to predict fast and slow responders to omalizumab.⁴⁶ Once omalizumab is active a reduction in the expression of FcεRI is observed after the first administration that is maintained stable along the treatment.⁴⁹ This reduction of FcεRI levels on peripheral blood basophils was also observed by Metz et al. These authors also found that omalizumab normalized levels of FcεRI⁺ and IgE⁺ skin cells in lesional and non-lesional skin (dermis) of patients with CSU.⁵⁰

In patients that not respond even at high doses of omalizumab during at least 6 months, it is important to reevaluate the diagnosis and rule out other cutaneous diseases that can resemble urticaria such as autoinflammatory syndromes, neutrophilic dermatoses or urticarial vasculitis, between others. (See **table 2**) If there are no doubts in the diagnosis of CSU, the patients may be switched to ciclosporin. (**Figure 2**)

CICLOSPORIN A

Ciclosporin A (CsA) is a calcineurin inhibitor that exerts immunomodulatory effects mainly by preventing the activation of T-lymphocytes, antibody formation and release of mast-cell

mediators which are implicated in the pathogenesis of chronic urticaria and other inflammatory skin disorders.⁵¹

Despite not being a licensed drug for the treatment of chronic urticaria, it has been widely used for many years to control the disease in patients with severe chronic urticaria with poor response to H1-antihistamines, mostly before omalizumab approval. In patients with serum autoreactivity (positive Autologous Serum Skin Test, ASST) or autoimmune chronic urticaria (ACU), CsA seems to be more effective and still a good treatment option.⁵²

The efficacy of CsA in the treatment of chronic urticaria has been studied in two double-blind, placebo controlled clinical trials.^{53, 54} (See table 1) Grattan et al, studied the efficacy of ciclosporin (4mg/Kg/day) during 4 weeks in 29 patients with severe chronic 'idiopathic' urticaria with poor response to antihistamine and positive ASST. They observed a significant reduction in UAS7 (12.7-point reduction; 95% CI:6.6-18.8) compared with placebo (2-3-point reduction; 95% CI: 3.3 to 7.9), $p=0.005$. In another clinical trial, CsA was administered in decreasing doses (from 5mg to 3mg/Kg/day) during 8 or 16 weeks. Patients treated with CsA showed significantly better improvement than those receiving placebo in the evaluation scale (five-point scale) at the end of the treatment period (16 week) (62.5% of treated patients vs 23.3% of the placebo group, $p=0.03$).⁵⁴

The optimal dose and duration of the treatment has not yet been defined. In a prospective, controlled study, Inaloz HS et al. treated 27 patients with moderate to severe chronic 'idiopathic' urticaria unresponsive to antihistamines, with 2.5mg/Kg/day of CsA for 4 weeks. Forty per cent of patients presented positive ASST and 70.37%, achieved complete remission without significant side effects ($p<0.005$).⁵⁵ Another prospective, controlled, open-label study including 30 patients with autoimmune chronic urticaria (ASST+) treated with low-doses of CsA (between 1.5-2.5mg/Kg/day) for 5 months showed a response of 88%. So it seems that low-doses of CsA (up to 2.5mg/Kg/day) can be effective in patients with CU, mostly when

ASST is positive, with minimum side-effects.⁵⁶ Galindo Bonilla et al suggested treating patients with 3mg/Kg/d for 6 weeks followed by 2mg/Kg/d for 3 weeks and 1mg/Kg/d for 1 week.

The results of a recent meta-analysis conducted by Kulthanan et al, show that doses between 2 and 4mg/Kg/d of CsA for 12 weeks, improved clinical severity in 70% of CSU patients. These authors propose to start at 3mg/Kg/d.^{57, 58}

However, the use of CsA is not recommended beyond the 2 years of treatment due to its cumulative nephrotoxicity. It is mandatory to perform periodic blood pressure measures and blood tests including kidney function to monitor these well-known but potentially serious side effects.

Despite its known effectiveness, the latest CSU guidelines position ciclosporin as a fourth-line treatment after omalizumab, because its off-label nature and its worst safety profile.¹ (see **treatment algorithm, figure 2**)

Some biomarkers of ciclosporin effectiveness in chronic spontaneous urticaria have been described. Patients with CSU with positive serum autoreactivity (positive ASST/BAT/BHRA) respond better to ciclosporin treatment than those with negative results.

A better response to CsA should also be expected in patients with higher activity at the beginning of the disease measured by the UAS7, short duration of the disease, positive autoreactivity (positive ASST/BAT/BHRA) and low levels of D-Dimer.²⁵

HOW TO USE ORAL CORTICOSTEROIDS?

Despite its wide use to treat acute exacerbations of the disease, the scientific evidence of oral corticosteroids (OCS) in the treatment of CSU is scarce. However, it is well-known that oral

corticosteroids are very effective in controlling acute flare ups of CSU, providing quick relief of the symptoms particularly when angioedema is present. Relapse of CSU is not rare after stopping the treatment, so it is important to taper down slowly. Chronic use of OCS should be avoided due to its side effects, including mood disturbances, hypertension, hyperglycemia, increased appetite and weight gain, osteoporosis and cataracts.

Topical corticosteroids should not be used in CSU. The EAACI/GA²LEN/EDF/WAO guidelines¹ recommend the use of OCS in short courses of 7-10 days at doses between 20 and 50mg/day.

OTHER TREATMENTS BEYOND THE GUIDELINES

A large number of medications, belonging to different classes and with different mechanisms of action, have been used for the treatment of chronic urticaria. The evidence for using them is low and are no longer included in the guidelines.¹ Nonetheless, some of them have been widely used by dermatologists, especially in the pre-omalizumab era.

LEUKOTRIENE RECEPTOR ANTAGONISTS

Leukotriene receptor antagonists are anti-inflammatory (LTRA) drugs that have been used to treat refractory chronic urticaria in combination with H1 and H2 antihistamines. The rationale of treatment with anti-leukotrienes arises after observation that injected leukotriene D4 induces a wheal and serum of patients with CSU can release leukotrienes between other mediators.⁵⁹ The most widely used LTRA is Montelukast. There are a few, mostly small and heterogeneous, randomized controlled trials for leukotriene receptor antagonists in the treatment of chronic urticaria but the results of these clinical trials show inconsistent results.⁵⁹⁻⁶¹ Montelukast seems to be effective in chronic urticaria induced or exacerbated by acetylsalicylic acid (ASA) or other nonsteroidal anti-inflammatory drugs (NSAIDs) and food

additive hypersensitivity but not in chronic spontaneous urticaria. There are some experience treating CIndU in acquired cold urticaria, delayed-pressure urticaria and dermographism. In the previous guidelines, montelukast appeared as add-on therapy to fourfold sgAH as third line treatment of CSU along with Ciclosporin and omalizumab.⁶² Although in the most updated guidelines LTRA have been taken out of the treatment algorithm due its low level of evidence the experts cannot made a recommendation against its use.¹

H2 ANTIHISTAMINES

The H2-antihistamines were used as add-on therapy to H1-antihistamines to treat chronic spontaneous urticaria with modest efficacy. Only few old studies of small size were performed. Although some studies reported a slight improvement of the symptoms of urticaria, a Cochrane analysis found that the evidence was very limited, weak and unreliable.⁶³

DOXEPIN

Doxepin is a tricyclic antidepressant with potent H1 and H2 antihistamine effects, being nearly 800 times more potent than diphenhydramine. Given their antipruritic effects, doxepin and other tricyclic antidepressants (such as amitriptyline) have been used for the treatment of pruritus and urticaria, especially if an additional sedative effect is required. Dosages used in dermatology (10 to 25mg/day at night) are usually much less than psychotropic dosage, which is up to 300 mg daily.⁶⁴ Moreover, patients with CSU frequently exhibit psychiatric comorbidity, mostly anxiety and depression.¹⁰ The antidepressant effect might be useful in these patients. Anticholinergic and sedative effects are dose limiting in these patients.

Doxepin was effective in small and old placebo-controlled studies.^{65, 66}

DAPSONE

Dapsone is an antibiotic related to the sulfonamides that also has anti-inflammatory actions by inhibiting the function of neutrophils (chemotaxis and myeloperoxidase activity) and the formation of leukotrienes and prostaglandins. Due to its anti-inflammatory effect dapsone is used in many neutrophil-rich dermatological disorders (e.g. urticarial vasculitis, bullous disorders, neutrophilic dermatoses, etc.). Some patients with CSU have neutrophilic infiltrates in their skin biopsies. These patients are usually more prone to have difficult-to-treat CSU. There is some evidence that dapsone may be useful in these patients and might be considered.⁶⁷ However, evidence for dapsone in CSU is weak.

A double-blind placebo-controlled crossover trial including 22 patients with antihistamine refractory CSU showed that dapsone 100mg daily improved visual analog score ($p=0.04$) and itch scores ($p=0.047$) at 3 and 6 weeks of treatment, compared with placebo.⁶⁸ In a non-blinded, prospective randomized clinical trial, 65 patients with refractory CSU were randomized to receive dapsone 50mg plus desloratadine 10mg/day ($n=38$) or desloratadine alone ($n=27$) during 12 weeks. Both groups were followed during 12 additional weeks after treatment was discontinued. There were no differences between groups in UAS change at week 12 but a reduction in UAS change was observed with dapsone at the end of the study (24 weeks). Five patients in the dapsone group showed complete remission of the disease.⁶⁹

For most dermatological conditions, the dose varies between 25 and 200mg daily. Glucose-6-phosphate dehydrogenase (G6PDH) deficiency must be ruled out before treatment. The initial dose should not exceed 50mg/day to ensure that there are no immediate or severe adverse effects such as hypersensitivity or agranulocytosis. Other side effects that need to be monitored by laboratory tests are dose-dependent hemolysis and hemolytic anemia, methemoglobinemia and hepatotoxicity.

HYDROXYCHLOROQUINE

Hydroxychloroquine (HCQ) is an antimalarial drug widely used in the management of systemic lupus erythematosus (SLE), other forms of cutaneous lupus erythematosus and also in a variety of cutaneous disorders such as chronic urticaria due to its autoinflammatory properties. The evidence for antimalarial drugs in the treatment of CSU is limited.

In a single blinded, placebo controlled trial of 18 patients with refractory CSU, hydroxychloroquine 200mg twice daily, improved the global symptom severity score and the quality of life of patients at 12 weeks ($p < 0.01$ and $p < 0.05$ respectively) with a good safety profile.⁷⁰ In a very recent single blind, placebo controlled trial, hydroxychloroquine 400mg daily plus fourfold antihistamines ($n=24$) was compared with antihistamines alone ($n=24$, placebo group) for 12 weeks. Patients treated with HCQ showed greater and significant improvement in the severity score and the quality of life and five patients achieved complete remission of the disease at 12 weeks but non on placebo group ($p=0.01$) In a follow up trial, non-responder patients were offered open-label HCQ (in placebo group) vs LTRA (in the HCQ group) for 12 additional weeks. The severity score significantly decreased in HCQ group compared to the LTRA group, with no differences in QoL index.⁷¹

Hydroxychloroquine is a well-tolerated medication being gastrointestinal tract disturbances the most common side effects. Retinopathy is the most feared side effect, but the risk is low during the first 5 years of use. However, a periodic evaluation by an ophthalmologist is recommended in these patients.

PHOTOTHERAPY

Phototherapy reduces the number of cutaneous mast cells in the superficial dermis and has been used for the treatment-resistant chronic urticaria and symptomatic dermographism in combination with antihistamines for periods between 1 and 3 months.^{72, 73}

Data regarding phototherapy in CSU is limited. Of the different modalities, narrowband ultraviolet B (NB-UVB) seems to be the most effective as adjuvant therapy. Long-term efficacy (up to 3 months after of the end of treatment) has been observed in some cases.

A recent randomized, prospective, single-blinded study of 50 patients with steroid dependent chronic urticaria not responding to four-fold increased doses of sgAH were administered either PUVA (group A) or NB-UVB (group B) for 90 days, with a post treatment follow-up of 90 days. All patients took levocetirizine 10mg daily. NB-UVB phototherapy was found to be statistically better than PUVA at different time points. These authors proposed the combination of antihistamines with NB-UBV prior 3rd line treatments such as omalizumab.⁷⁴ Another study comparing narrowband ultraviolet B (NB-UVB) three times weekly combined with levocetirizine 10mg daily (n=45) vs levocetirizine alone (n=33) showed that UAS was lower in the NB-UVB group at session 20 [17.4 vs 20]. VAS was also significantly lower after 3 months of stopping the treatment in the NB-UVB group ($p<0.01$).⁷⁵

METHOTREXATE

Methotrexate (MTX) is a derivative of folic acid and classified as an antimetabolite cytotoxic agent. At low doses it has anti-inflammatory actions and can be useful in some cases as corticosteroid sparing agent.⁷⁶

MTX is used in many dermatological conditions such as psoriasis or atopic dermatitis at doses of 10-15mg per week. In CSU have been used in corticosteroid-dependent patients.

Evidence with methotrexate in CSU is limited to case reports, case series and one randomized, placebo-controlled, double blind clinical trial is available comparing methotrexate 15mg weekly plus levocetirizine 5mg daily (n=14) and levocetirizine alone (n=15, placebo group). These authors did not find any additional benefit of MTX over antihistamines.⁷⁷

Moreover, MTX is frequently associated with many side effects such as gastrointestinal tract problems, stomatitis, headache, fatigue, hepatotoxicity, pulmonary toxicity, carcinogenicity and myelosuppression. Periodic monitoring by blood test is mandatory in patients under treatment with MTX.

MYCOFENOLATE MOPHETIL

Mycophenolate mofetil (MMF) is a lymphocyte selective immunosuppressive agent used in dermatology, mostly in autoimmune diseases, because its potential steroid-sparing effects and its relative lack of toxicity.

Shahar et al treated 9 patients refractory to antihistamines and/or steroids with 1000mg of MMF twice daily for 12 weeks showing a significant improvement of the disease measured by UAS ($p < 0.001$) and allowing a complete discontinuation of prednisone at the end of the study without relapse during 6 months of follow-up.⁷⁸ In a retrospective study, 19 patients with CSU refractory to other therapies were treated with mycophenolate mofetil at doses between 1 and 6 g/day. Improvement was observed in 89% of patients and in 59% of them, complete control of the disease was achieved. The complete resolution of the urticaria was seen more frequently in patients with serum autoreactivity.⁷⁹

AZATHIOPRINE

Azathioprine (AZA) is an immunosuppressive medication used as steroid-sparing drug in many dermatological conditions. Few evidence is available for the use of AZA in CSU. A single-blind, placebo-controlled study including 60 patients with ASST-positive CSU were randomized to receive AZA 50mg/day + levocetirizine (5mg) vs levocetirizine alone at the

same dosage, during 8 weeks (with a 36-weeks follow up). In azathioprine-treated patients, significant reduction of the disease intensity, measured by the total severity score, was observed along with a reduction of the rescue medication.⁸⁰

AUTOLOGOUS WHOOLE BLOOD

Treatment with intramuscular autologous whole blood (autohemotherapy) has been studied for the treatment of patients with ASST-positive CSU refractory to conventional therapies. The rationale for the use of whole blood injections in CSU is that the autologous whole-blood could induce tolerance to circulating histamine-releasing factors in CSU patients, mostly with positive ASST. There are two small controlled studies showing controversial results.^{81, 82}

INTRAVENOUS IMMUNOGLOBULIN

Intravenous immunoglobulin (IGIV) have been used in refractory cases of CSU. The exact mechanism of action of IGIV in CSU is not well understood. IGIV may act blocking the H1 receptors instead of the IgG autoantibodies or neutralizing them, preventing the release of histamine and the development of wheals. Other effects such as modulation of complement function and inflammation have also been proposed.

There are few evidence of IGIV in solar urticaria, delayed pressure urticaria and CSU refractory patients with quite good results. A clinical improvement was observed in many patients, including complete remissions and long-term responses.

Most authors used the dose of 0.4mg/Kg/day for 5 days every 4-6 weeks but lower doses (0.15mg/Kg/day), have also been explored with good results. However, there are no controlled studies.

The most frequent side effect observed in patients treated with IGIV are infusion reactions (including fever, chills and headache). These reactions are usually predictable and easy to

manage. Other less frequent and more severe side effects include allergic reactions, aseptic meningitis, thromboembolic disease or renal failure. The use of IGIV in off-label indications is restricted due to its high economic cost and limited availability.^{83, 84}

RITUXIMAB

Rituximab is a chimeric IgG monoclonal antibody directed against the CD20 on B cells (specifically immature, mature and memory cells). According to its mechanism of action, rituximab may play a role in the treatment of chronic autoimmune urticaria by eradicating the autoantibodies produced by B cells. Some case report of patients with refractory CAU have been published, but no controlled trials have been performed.⁸⁴

OTHERS

Other treatments and therapeutic strategies have been used for many years, with low levels of evidence, in the management of patients with refractory CSU (pre-omalizumab era), see table 3.⁸⁵

FUTURE PERSPECTIVES, NEW TREATMENTS

The management of patients with antihistamine-refractory CSU has completely changed since the introduction of omalizumab. However, there is still a percentage of patients with CSU in whom omalizumab does not alleviate the symptoms of the disease. Therefore, urticaria does not end with omalizumab, and there is a need to develop new effective drugs for the management of these patients. In this sense, many new biological drugs are being developed for the treatment of patients with refractory CSU.

LIGELIZUMAB (QGE031)

Ligelizumab is a humanized IgG1 monoclonal antibody that binds to the Cε3 domain of IgE. In vitro studies have shown that Ligelizumab produces a greater and longer suppression of free IgE and IgE on the surface of basophils than omalizumab. A phase 2b dose-finding study including 382 patients have been completed in June 2017 (NCT02477332) and the phase III studies of efficacy and safety of Ligelizumab in adolescents and adults, are ongoing (NCT03580369, NCT03580356).⁸⁶

BRUTON TYROSINE KINASE INHIBITORS

Bruton Tyrosine Kinase (BTK) plays a crucial role in B cell maturation and mast cell activation through the high affinity IgE receptor (FcεRI). BTK inhibitors have been approved to treat B cell malignancies (e.g. relapsed mantle cell lymphoma, chronic lymphocytic leukemia and Waldenström's macroglobulinemia). In dermatology, they are being investigated in diseases related to B lymphocytes (mostly autoimmune diseases such as pemphigus vulgaris) and also in chronic urticaria. GDC-0853 is a BTK inhibitor administered orally that is being investigated in patients with refractory CSU (NCT03137069).⁸⁶

BENRALIZUMAB AND MEPOLIZUMAB

Benralizumab is an anti-IL-5 inhibitor that binds to the alfa chain of the IL-5 receptor in the eosinophils and basophils. These binding leads to a depletion of these inflammatory cells.

A phase 4 study in patients with CSU refractory to H1-antihistamines is ongoing (NCT03183024). Other anti-IL-5 drugs such as mepolizumab have also been investigated in CSU (NCT03494881).⁸⁶

SPLEEN TYROSINE KINASE INHIBITORS (GSK2646264)

Spleen tyrosine kinase (SyK) is a member of the tyrosine kinase family that mediates signal transduction of a variety of cell surface receptors including B cell, T cell and mast cell receptors. SyK inhibitors target intracellular signaling pathways in mast cells, thus, the inhibition of SyK may have an important role in the treatment of chronic spontaneous urticaria by blocking the release of histamine, leukotriene and other cytokines from the mast cells. A SyK inhibitor (GSK2646264) is now being evaluated topically in patients with cold urticaria and CSU (NCT02424799).⁸⁶

Other drugs such as dupilumab (anti-IL-4/IL-13), rituximab (anti-CD20), adalimumab (anti-TNF- α) or canakinumab (anti-IL-1), between others, are being evaluated in clinical trials to treat refractory chronic spontaneous urticaria with different results.⁸⁶

CONCLUSIONS

The treatment of chronic spontaneous urticaria refractory to antihistamines has changed radically in recent years, especially as a result of the approval of omalizumab.

Omalizumab has been shown to be a very effective and safe drug that achieves complete resolution of symptoms in a high percentage of patients with CSU refractory to antihistamines. It has also been shown to be effective in the treatment of histaminergic angioedema and in improving the quality of life of these patients.

However, there is still a percentage of patients with CSU who do not respond to omalizumab.

There exist some biomarkers that can predict response to omalizumab, such as the baseline expression of total IgE or basophil Fc ϵ RI in peripheral blood that need to be implemented and validate by the urticaria community.

Today for omalizumab-refractory patients, ciclosporin A is a good treatment option and the fourth step in the CSU treatment algorithm. In any case, ciclosporin is a drug that cannot be

1 used in the long term, so new therapeutic options are needed for these patients refractory to
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3 antihistamines and omalizumab. The list of alternative treatments in the CSU is long and the
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5 evidence variable, but generally poor, as mentioned before. In recent years, multiple clinical
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7 trials are being conducted with promising new treatments, most of them biological drugs,
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9 that can give dermatologists new tools to handle these complicated patients, resistant to
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11 conventional drugs.
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First author, year, reference	Study Drug	Study Design	Duration	n	Intervention
Saini, 2011 (MYSTIQUE) ²⁶	Omalizumab	Double-blind, Placebo-Controlled	4-week treatment/12-week follow-up	90	Omalizumab 75mg (n=23) vs 300mg (n=25) vs 600mg (n=21) vs Placebo (n=21). All received antihistamines.
Maurer, 2011 (XCUISITE) ²⁷	Omalizumab	Double-blind, Placebo-Controlled	24-week treatment	49	Omalizumab 300mg (n=27) vs Placebo (n=22). All received antihistamines.
Maurer, 2013 (ASTERIA I) ²⁸	Omalizumab	Double-blind, Placebo-Controlled	12-week treatment/16-week follow-up	323	Omalizumab 75mg (n=82) vs 150mg (n=83) vs 300mg (n=79) vs Placebo (n=79). All received antihistamines.
Kaplan, 2013 (GLACIAL) ²⁹	Omalizumab	Double-blind, Placebo-Controlled	24-week treatment/16-week follow-up	336	Omalizumab 300mg (n=252) vs Placebo (n=84) as add-on therapy to the daily treatment (H1-antihistamine treatment plus H2-antihistamines, LTRAs, or both).
M Hide 2017 (POLARIS) ³⁰	Omalizumab	Double-blind, Placebo-Controlled	12-week-treatment/12-week follow-up	218	Omalizumab 150mg (n=71) vs 300mg (n=73) vs Placebo (n=74). All received antihistamines.
Staubach, 2016 (X-ACT) ³¹	Omalizumab	Double-blind, Placebo-Controlled	28-week treatment/8-week follow-up	91	Omalizumab 300mg (n= 44) vs placebo (n= 47). All received high doses of antihistamines
Grattan, 2000 ⁵³	Ciclosporin A	Double-blind, Placebo-Controlled	4-weeks treatment/20-week follow-up	30	Ciclosporin A 4mg Kg-1 daily (n=20) vs Placebo (n=10). All received antihistamines.
Vena, 2006 ⁵⁴	Ciclosporin A	Double-blind, Placebo-Controlled	16-week treatment/24-week follow-up	99	Ciclosporin A for 16 weeks (days 0-13, 5mg/Kg; days 14-27, 4mg/Kg; day 28+, 3mg/Kg) (n=31). Ciclosporin A for 8 weeks (dose as above) then Placebo for 8 weeks (n=33). Placebo for 16 weeks (n=35). All received antihistamines.

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Table 2. Differential diagnosis of Chronic Spontaneous Urticaria

Differential Diagnosis	
Autoinflammatory syndromes	
Familial cold urticaria	
Muckle-Wells syndrome	
Schnitzler's syndrome	
Urticaria pigmentosa (mastocytosis)	
Urticarial vasculitis	
Bullous pemphigoid	
Lupus erythematosus	
Well's syndrome	
Eosinophilic annular erythema	
Insect bites	
Neutrophilic dermatoses (e.g. Sweet syndrome)	
Erythema multiforme	
Pruritic Urticarial Papules and Plaques of Pregnancy	
Hypereosinophilic syndrome	
Scabies	
Interstitial granulomatous dermatitis	
Contact Urticaria Syndrome	
Gleich's syndrome	
Autoimmune Progesterone Dermatitis	
Nonhistaminergic angioedema (e.g. Hereditary Angioedema, HAE)	

Table 3. Alternative therapies in CSU⁸⁵

Other alternative therapies	
Stanozol	Sulfasalazine
Theophylline	Histaglobulin
Dipyridamole	Probiotics
Levamisole	Mizoribine
Miltefosine	Cyclophosphamide
Vitamin D3	Mirtazapine
Warfarin	Nafamostat/camostat mesylate
Inhibitors of TNF alfa	Heparin
Tacrolimus	Heparin and tranexamic acid

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