

EXPERT
REVIEWS

Current challenges and controversies in the management of chronic spontaneous urticaria

Expert Rev. Clin. Immunol. Early online, 1–10 (2015)

Riccardo Asero*¹,
Elena Pinter²,
Alessandro Maria Marra²,
Alberto Tedeschi³,
Massimo Cugno⁴ and
Angelo Valerio Marzano⁵

¹Ambulatorio di Allergologia, Clinica San Carlo, Paderno Dugnano (MI), Italy

²UOC Immunologia Clinica A, Policlinico Umberto I, Roma, Italy

³Unità Operativa di Allergologia e Immunologia Clinica, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milano, Italy

⁴Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Medicina Interna, Università degli Studi di Milano, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milano, Italy

⁵Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Unità Operativa di Dermatologia, Università degli Studi di Milano, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milano, Italy

*Author for correspondence:
 r.asero@libero.it

Chronic spontaneous urticaria (CSU) is characterized by the recurrence of itchy wheals for at least 6 weeks, affects up to 1% of the general population and may severely impair quality of life. H1-antihistamines are the cornerstones of treatment, but in about 10% of cases they fail to control the disease even at higher than licensed doses. In these patients, short courses of oral steroids may induce a remission in about 50% of cases. Omalizumab, a monoclonal anti-IgE, is effective in antihistamine-unresponsive patients although optimal treatment duration needs to be defined. Immunosuppressive treatment with cyclosporine is also effective in the majority of antihistamine-resistant chronic spontaneous urticaria (CSU) patients, but its use is limited by potential side effects. In refractory patients, other approaches include intravenous immunoglobulin, rituximab, dapsone and anticoagulants. The present review looks with particular interest at the prevalence of treatment failures with the main third-level treatments (corticosteroids, omalizumab and cyclosporine) and discusses them in light of the possible different pathogenic mechanisms underlying chronic spontaneous urticaria.

KEYWORDS: chronic spontaneous urticaria • cyclosporine • corticosteroids • omalizumab

The recently updated EAACI/GA (2) LEN/EDF/WAO guidelines for the definition, classification, diagnosis and management of urticaria have proposed a novel classification of urticaria into spontaneous (either acute or chronic) and inducible (including those types formerly defined as physical, cholinergic and contact urticaria) and suggested a new diagnostic algorithm that takes into consideration also hereditary and acquired autoinflammatory diseases, as well as urticarial vasculitis and bradykinin-mediated angioedema [1]. The present review article will focus on chronic spontaneous urticaria. Chronic spontaneous urticaria (CSU) is a skin disorder characterized by the recurrent eruption of itchy wheals for at least 6 weeks [2]. The disease prevails in women (female/male ratio: at least 2:1) and is rather frequent as about 1% of the general population may be affected at some point in life [2,3]. CSU may heavily impair patients' quality of life, particularly in severe cases [4]. The present article will review the major challenges posed

by this disease to the physician and critically reappraise the most important controversies regarding the management and the mechanism of action of the drugs that are currently used in severe cases.

Treatment options for severely affected patients

Most patients with slight/moderate chronic spontaneous urticaria respond satisfactorily to second-generation antihistamines at a licensed, or higher than licensed, dose [1]. However, a minority of patients is unresponsive to these drugs at whatever dosage. After the exclusion of possible underlying causes or aggravating factors of urticaria such as infections, chronically taken drugs or pseudoallergic reactions to specific foods [1], these patients clearly need alternative treatments to control their disease. The drugs that have been more frequently used in these patients and are supported by the highest level of evidence include systemic corticosteroids, cyclosporine and omalizumab.

The rationale for the use of immunomodulatory and anti-inflammatory drugs in patients with severe CSU stems from the demonstration of histamine-releasing autoantibodies [5,6] and an increase in both inflammation and coagulation biomarkers [7,8] of the disease.

Corticosteroids

Although the effectiveness of systemic corticosteroids in patients with CSU not responding to antihistamines is undisputed, double-blind, placebo-controlled studies supporting their use are still lacking. To date, only one large retrospective study analyzed the effects of a short course of oral prednisone at a dose of 0.3–0.5 mg/kg in patients resistant to H1-antihistamine treatment [9]. The drug was able to induce a remission of the disease and subsequent control with H1-antihistamines at licensed doses in about 50% of cases, and a second course induced a persistent remission in about one-third of those who showed only a temporary response. The clinical effects appeared as early as the day after the first 25-mg dose of prednisone. Since long-term systemic steroid treatments may induce potentially severe side effects, including diabetes, hypertension, osteoporosis, gastrointestinal bleeding and others, their use is recommended only for short periods and at the minimal effective dose with the aim to control acute exacerbations of the disease [1,10,11]. In view of the short periods of treatment recommended, systemic corticosteroids are unlikely to influence significantly the quality of life of treated patients.

Cyclosporine

Case reports, case series [12–14] and controlled trials [15–18] have shown the effectiveness of cyclosporine in H1-antihistamine-resistant CSU at the dose of 3–5 mg/kg/day to be given for approximately 3–6 months. Blood pressure, kidney function and liver function should be regularly monitored during the treatment period. The treatment may lead to a long-lasting complete remission in about 50% of cases or to a decreased number of flare-ups and a restored response to antihistamine treatment in other patients [16]. For those who show a marked propensity to relapse after discontinuation, a low-dose, long-term maintenance therapy (1–2 mg/kg/day) for up to 2 years has been suggested [19]. Along with the worries for the possible occurrence of the major side effects mentioned above, some minor adverse reactions induced by cyclosporine, such as hypertrichosis, weakness, tremor and gingival hyperplasia, can worsen the quality of life of treated patients. Furthermore, its metabolism occurs predominantly in the liver and shows a variety of pharmacological interactions, most of which involve the liver cytochrome P-450. Agents that stimulate these enzymes, such as rifampicin, phenobarbital, carbamazepine, phenytoin, octreotide, ticlopidine, sulfonpyrazone and *Hypericum perforatum*-derived compounds may lower the plasma levels of the drug. In contrast, macrolides and imidazoles (ketoconazole, fluconazole, etc.), danazol, verapamil, metoclopramide, amiodarone, oral contraceptives and grapefruit juice may increase them.

Omalizumab

Omalizumab, a recombinant humanized monoclonal IgG antibody that binds free IgE has been shown to be effective in different subsets of H1-antihistamine-unresponsive urticaria by a number of case reports, case series and, lately, multicenter double-blind, placebo-controlled studies. Overall, in three Phase III clinical studies, 975 patients with moderate–severe CSU and persistent symptoms despite background treatment with antihistamines were enrolled [20–22]. When compared with placebo, add-on therapy with subcutaneous omalizumab 300 mg every 4 weeks for 12 or 24 weeks significantly reduced the severity of itching and the number and size of hives and the proportion of angioedema-free days. Omalizumab is well tolerated, although symptoms show a trend to gradually recur over a period of about 10 weeks after discontinuation [22]. Omalizumab-induced side effects are very rare and this, along with its proven efficacy, may have an adjunctive positive effect on the patient's quality of life.

Other immunosuppressive drugs

A number of immunosuppressive drugs have been used to treat severe, H1-antihistamine-resistant CSU as shown by uncontrolled studies [23]. Tacrolimus was effective in an observational study [24]. Methotrexate was effective and rather safe at a weekly mean dosage of 15 mg in patients unresponsive to conventional therapy [25,26]. Intravenous and oral cyclophosphamide [27,28] and azathioprine [29] have also been used in some cases with good results. Recently, mycophenolate mofetil and mizoribine, two purine biosynthesis inhibitors, have emerged as possible therapeutic options for recalcitrant CSU [29–32].

Other biologicals

The possible use of intravenous immunoglobulin (IVIG) in severe CSU is supported by some case reports and one open-label trial [33–36]. In the latter, nine out of 10 patients responded at a dose of 0.4 g/kg/day for five consecutive days and in three cases prolonged remission after a 3-year follow-up was observed. However, another study did not confirm these favorable results [37]. Although rather safe, IVIG is expensive and cannot be presently considered as a viable alternative treatment.

Rituximab, a chimeric monoclonal antibody against the protein CD20 primarily present on the surface of B cells, reduces the production of antibodies, including autoantibodies. It was effective in two patients with H1-antihistamine-resistant urticaria [38,39], but was unsuccessful in a third one [40].

Anticoagulants & drugs interfering with the coagulation

Recent studies found that CSU is characterized by an activation of the coagulation cascade via the extrinsic pathway whose intensity parallels disease severity [41–44]. Whether coagulation factors play a role in the pathogenesis of the disease or act simply as an amplification system is still unclear. Nonetheless, these findings provide *ex post* a rationale for some old observations of the effectiveness of both oral anticoagulants and heparin in some patients

with refractory CSU [45,46]. Heparin is an anticoagulant that potentiates the effect of antithrombin-III, a plasma protein that binds irreversibly to some serine protease enzymes (factors XIa, IXa, Xa, VIIa and thrombin) and blocks their activity. A more recent study trying both heparin and tranexamic acid did confirm these results [47], showing a more marked efficacy in patients with elevated plasma levels of D-dimer, a marker of coagulation activation and fibrinolysis. The idea of a potential effectiveness of a therapeutic approach based on the interference with the coagulation cascade comes also from recent Japanese studies [48], showing the effectiveness of nafamostat mesilate and camostat mesilate, two serine protease inhibitors that inhibit different proteases, including tryptase, kallikrein, complement, factor XII and plasmin, and show an anticoagulant effect similar to that of heparin [49]. In any case, at present, although conceptually interesting, anticoagulation cannot yet be considered as a routine option for the treatment of severe refractory CSU even in presence of elevated D-dimer plasma levels.

Other drugs

Mirtazapine, a tetracyclic antidepressant that increases both noradrenergic and serotonergic neurotransmission, has been successfully attempted in H1-antihistamine-resistant CSU [50,51]. Case reports [52] and, recently, a double-blind placebo-controlled study [53] support the effectiveness of dapson, an anti-inflammatory drug, in patients with recalcitrant CSU.

The potential efficacy of hydroxychloroquine in patients with refractory CSU has been reported both in open-label and randomized placebo-controlled studies [54,55]; although in the latter patients', the quality of life significantly increased, this was not associated with a reduction of urticaria score and medication requirement.

Altogether, although these drugs may have a potential usefulness in patients with recalcitrant CSU, experience is rather limited and the availability of more easily obtainable and effective alternatives that have been tested on thousands of patients makes them not recommended for a routine use.

Treatment of special populations

The recent European Academy of Allergy and Clinical Immunology guidelines [1] recommend treating children and pregnant women using the same algorithm suggested for other patients, that is using second-generation H1-antihistamines at licensed or higher than licensed doses. All further steps should be based on individual considerations looking at the risk-to-benefit ratio and according to recommendations published by regulatory authorities. Cyclosporine is not teratogenic but in animal models has been found to be embryo-toxic and in humans has been associated with preterm delivery and low birth weight. Systemic steroids and omalizumab should be less problematic in this sense.

Table 1. Clinical outcome in patients with severe chronic spontaneous urticaria treated with corticosteroids (prednisone).

Authors (year)	No.	Daily dose	Clinical response (%)			Time to efficacy (wks)	Ref.
			Complete	Partial	None		
Asero & Tedeschi (2010)	86	25 mg/day	47%	40%	13%	24 h	[9]
Loria et al. (2001)	10	20 mg/day	60%	40%	0%	Few days	[77]

Elderly patients may pose the challenge of a reduced renal function. As a consequence, the dosage of certain drugs, particularly cyclosporine, should be adjusted accordingly to avoid toxicity.

Controversial aspects: why do these drugs fail in a proportion of patients?

One of the most intriguing observations for physicians dealing with severe CSU is the large variability of the efficacy of third-level therapies (either corticosteroids, cyclosporine and/or omalizumab), which is reflected by the fact that patients who do not respond to one drug may respond satisfactorily to another one, and vice versa, in an unpredictable way.

Corticosteroids

In most cases, oral corticosteroids are effective if given at a proper dose, but the problem with them is the risk of side effects associated with a long-term use. This is the main reason why alternative drugs such as cyclosporine and omalizumab (but also many others such as dapson, mycophenolate mofetil, cyclophosphamide, methotrexate, etc.) have been sought and tried in severely affected patients. Nonetheless, also steroids may fail in a minority of cases, and most of these patients seem to respond properly to cyclosporine. In the only large study of the use of corticosteroids in CSU published so far, 13% (11/86) of H1-antihistamine-resistant patients did not respond to oral prednisone at a daily dose of 25 mg (TABLE 1) [9]. However, 82% (9/11) of them responded to cyclosporine, and one patient resistant to both corticosteroids and cyclosporine responded to oral cyclophosphamide. Another interesting point regarding the effect of oral corticosteroids is that is clinically evident as early as 24 h after the first administration in most cases, a time span that is far too short to be associated uniquely with the internalization of the drug in the effector cells and with its nuclear effects on gene transcription. A possible explanation of this phenomenon might be the nongenomic effects of corticosteroids. In effect, the timing of several responses to corticosteroids do not fit the classical genomic action. Nongenomic effects often involve the generation of intracellular second messengers after binding of steroids to cell membrane receptors. Various signal-transduction cascades, such as ion fluxes (often calcium), cyclic AMP modulation and protein kinase pathways, have been shown to be involved. Membrane binding sites for different glucocorticoids have been described in many tissues and cells. *In vitro*, at cellular levels,

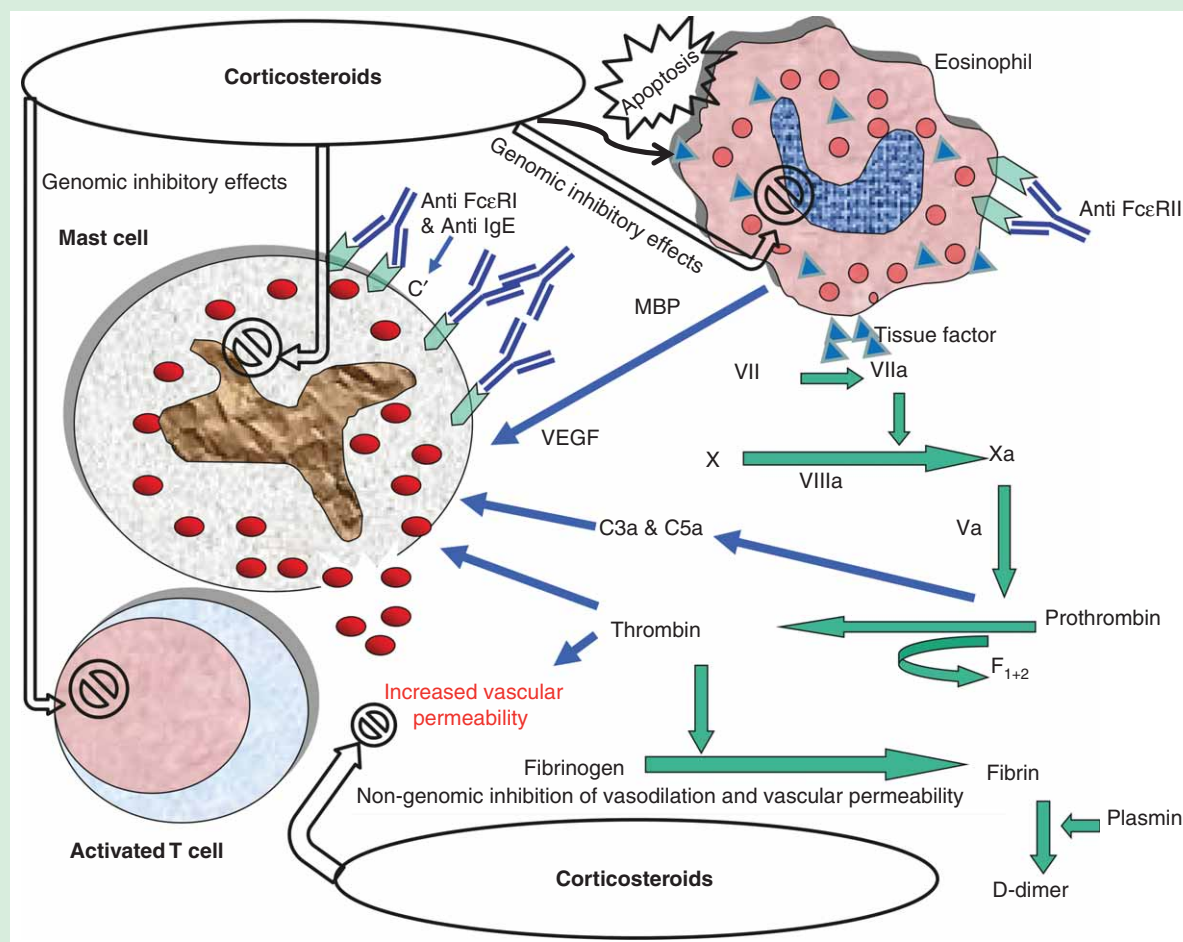


Figure 1. Mechanisms of action of corticosteroids on the main effector cells in the pathophysiology of chronic spontaneous urticaria. Corticosteroids exert a genomic inhibitory effect on the activation of mast cells, eosinophils and T lymphocytes, whereas they exert a nongenomic inhibition on vasodilation and vascular permeability.

C': Complement; FcεRI and FcεRII: High- and low-affinity IgE receptors; F1+2: Prothrombin fragment 1 + 2, MBP: Major basic protein; VEGF: Vascular endothelial growth factor.

dexamethasone has been reported to have very rapid effects (as short as <10 min) [56]. The nongenomic membrane receptor-mediated mechanisms of glucocorticoid action are assumed to participate in cellular processes that lead to apoptosis [56–58]. In CSU, in particular, glucocorticoids could lead to eosinophil apoptosis by both genomic and nongenomic mechanisms, and this might explain why some effects of corticosteroids can be seen as early as few hours after their administration. Another effect based on nongenomic mechanisms is the inhibition of vasodilatation and vascular permeability, two typical features of urticaria/angioedema. These effects might also be involved in the rapid response to systemic corticosteroids in CSU patients [9]. The effects of corticosteroids on the main pathogenetic pathways operating in CSU are illustrated in FIGURE 1.

Omalizumab

The rate of success/failure with omalizumab, as can be inferred from published studies involving a significant number of patients, is shown in TABLE 2 [59–66]. Some aspects clearly

appear. First, along with a majority of patients who show a prompt (1 week) response to the drug, there is a proportion ranging between 7 and 48% who do not seem to benefit from the treatment. Most of these omalizumab-unresponsive patients were corticosteroid-responsive before (as omalizumab was reportedly given just to avoid the side effects associated with the long-term use of systemic corticosteroids). Another interesting point is that some patients may become omalizumab-resistant over time (TABLE 2); [63,64], which suggests that the pathogenesis of the disease might rely on the activation of several distinct pathways, all eventually leading to histamine release from mast cells and basophils, whose relative prevalence may change in the different phases of the disease. Third, the clinical effects of omalizumab are appreciable as early as some days after the first administration. It has been suggested that most of the clinical effect of omalizumab relies on the down-regulation of the high-affinity IgE receptor on mast cells and basophils, which eventually leads to a reduced activation of these cells and a drop in degranulation and

Table 2. Clinical outcome in patients with severe urticaria treated with omalizumab.

Authors (year)	No.	Medication	Clinical response (%)			Time to efficacy (wks)	Ref.
			Complete	Partial	Poor (<50%)		
Kaplan <i>et al.</i> (2008)	12	OMA 300	58%	9%	33%	NA	[59]
Maurer <i>et al.</i> (2011)	26	OMA 300	64%	27%	9%	1 week	[60]
Saini <i>et al.</i> (2011)	45	OMA 300	33%	38%	29%	1 week	[20]
Labrador <i>et al.</i> (2013)	110	OMA 300	82%	11%	7%	NA	[61]
Maurer <i>et al.</i> (2013)	67	OMA 300	44%	22%	34%	1 week	[21]
Altman and Naimi (2013)	30	OMA 300	60%	13%	27%	NA	[62]
Kaplan <i>et al.</i> (2013)	252	OMA 300	34%	18%	48%	2 weeks	[22]
Song <i>et al.</i> (2013)	16	OMA 150	NA	NA	13% [†]	NA	[63]
Sussman <i>et al.</i> (2014)	68	OMA 150	69%	18%	13% [‡]	NA	[64]
Metz <i>et al.</i> (2014)	51	OMA 150	75%	0%	25%	1 week	[65]
Saini <i>et al.</i> (2014)	81	OMA 300	36%	16%	48%	1 week	[66]

[†]3/14 responders became refractory to Omalizumab subsequently.

[‡]Further 9% responders became refractory to Omalizumab subsequently.

NA: Data not available.

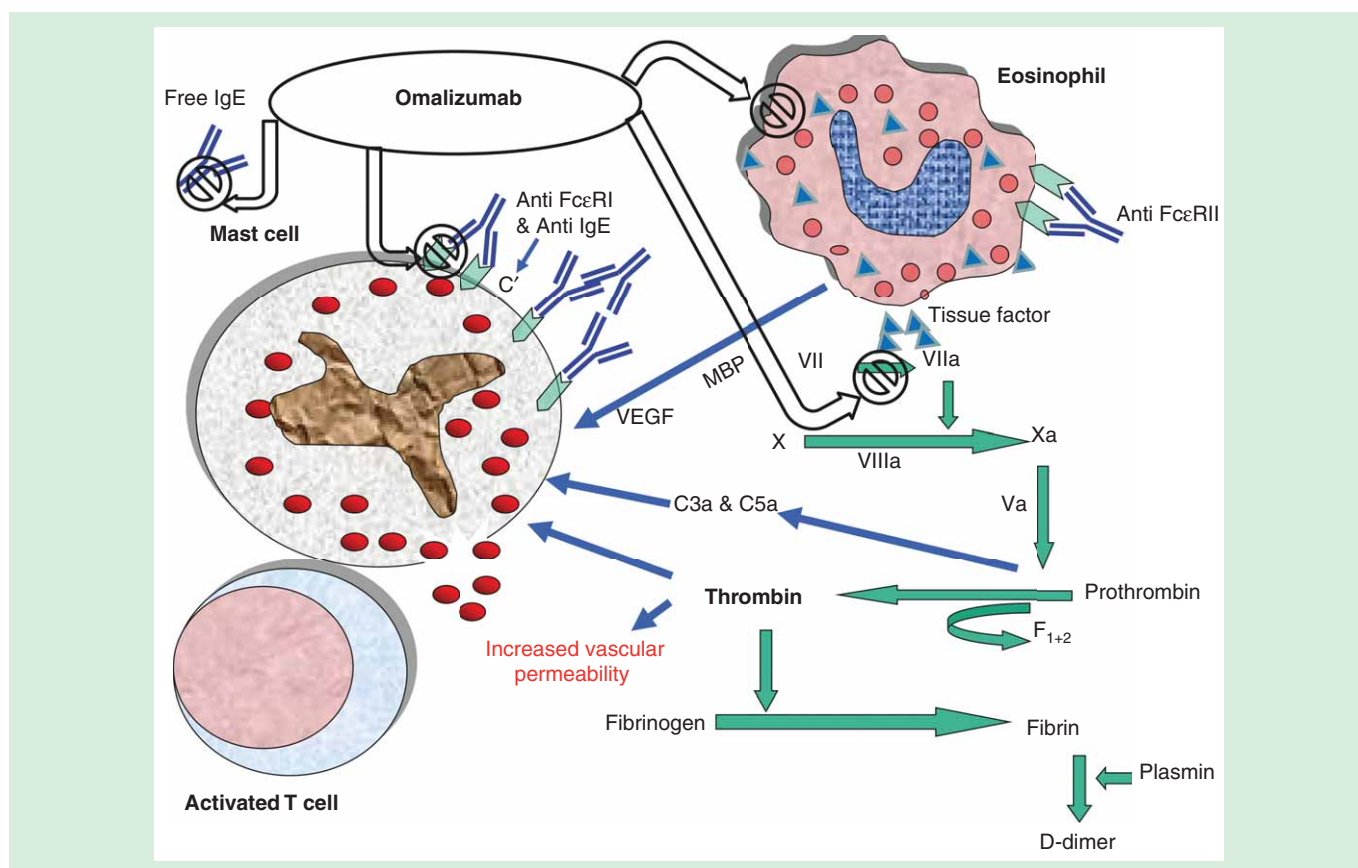


Figure 2. Sites of intervention of omalizumab in chronic spontaneous urticaria pathophysiology. Omalizumab binds free IgE, depleting its serum pool. Moreover, it down-regulates the expression of high-affinity IgE receptors on mast cells, induces eosinophil apoptosis and decreases coagulation activation.

C': Complement; FcεRI and FcεRII: High- and low-affinity IgE receptors; F1+2: Prothrombin fragment 1 + 2, MBP: Major basic protein; VEGF: Vascular endothelial growth factor.

Table 3. Clinical outcome in patients with severe chronic spontaneous urticaria treated with cyclosporine.

Authors (year)	No.	Daily dose	Clinical response (%)			Time to efficacy (wks)	Ref.
			Complete	Partial	None		
Toubi <i>et al.</i> (1997)	23	3 mg/kg	57%	26%	17%	1 week	[13]
Grattan <i>et al.</i> (2000)	29	4 mg/kg	66%		33%	NA	[15]
Loria <i>et al.</i> (2001)	10	5 mg/kg	70%	20%	10%	5 days	[77]
Di Gioacchino <i>et al.</i> (2003)	40	5 mg/kg	45%	50%	5% [†]	NA	[16]
Vena <i>et al.</i> (2006)	43	5 mg/kg day 0 to day 13 4 mg/kg day 14 to day 27 3 mg/kg day 28 on	63%	NA	9%	NA	[18]
Kessel & Toubi (2010)	100	3 mg/kg	62%	20%	18%	NA	[19]

[†]Non responders responsive to 25 mg/day prednisolone.
NA: Not available.

release of inflammatory mediators [67]. However, such effects require 3–4 weeks to occur, at least on mast cells, which is a far longer time than the few days needed to see the decrease in urticaria severity score. In fact, omalizumab exerts a number of other effects [68], not least on the coagulation pathway

where it leads to a marked reduction of D-dimer plasma levels [69] in a way similar to heparin [68]. Notably, some studies have shown the clinical efficacy of anticoagulant therapy in patients with CSU [45–48,70]. Another relevant point is that omalizumab reduces basophil histamine release after as short

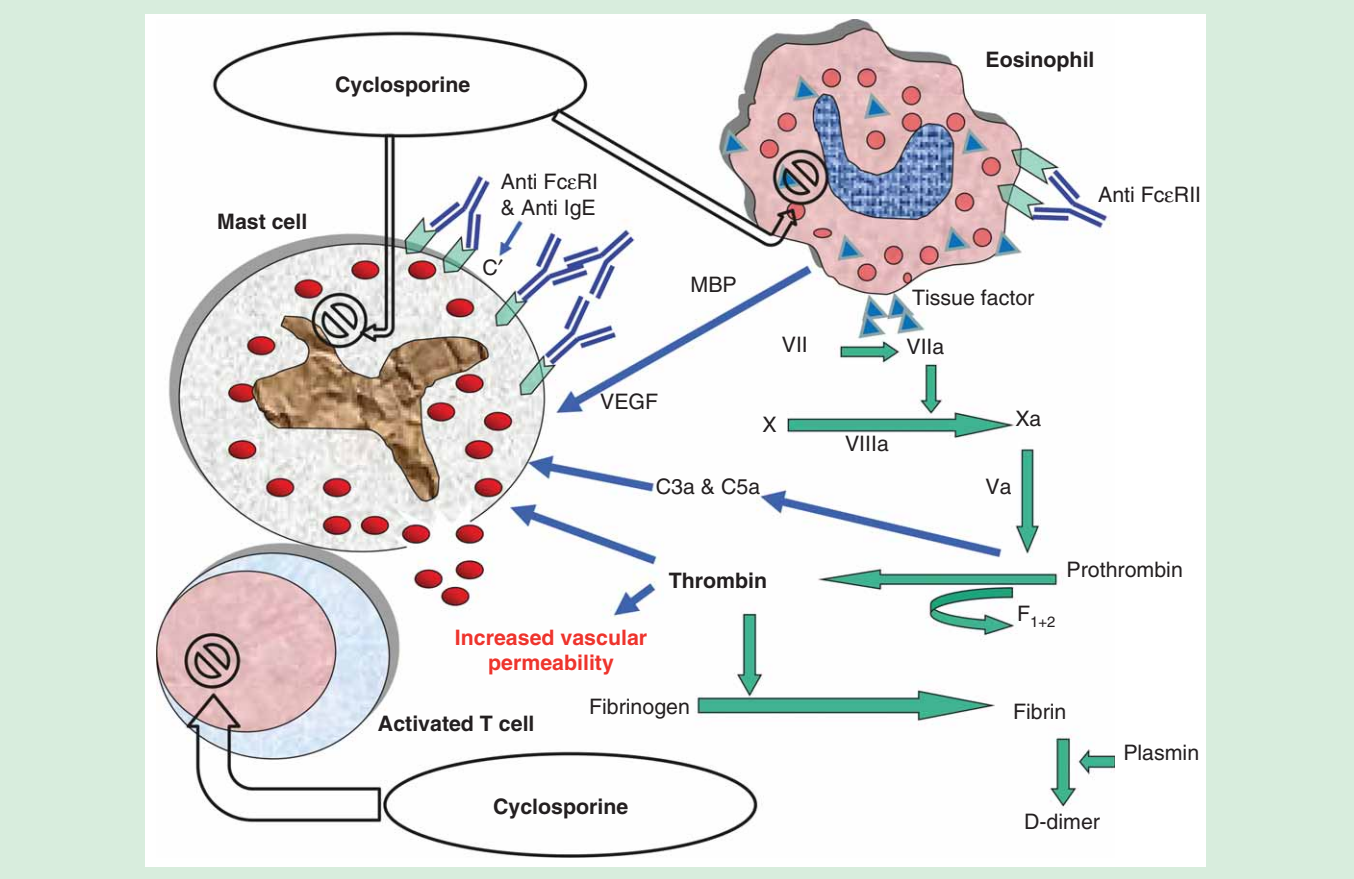


Figure 3. Inhibitory effects of cyclosporine on the activation of mast cells, eosinophils and T lymphocytes in chronic spontaneous urticaria.

C': Complement; FcεRI and FcεRII: High- and low-affinity IgE receptors; F1+2: Prothrombin fragment 1 + 2, MBP: Major basic protein; VEGF: Vascular endothelial growth factor.

Table 4. Cellular effects and time to efficacy of cyclosporine, omalizumab and corticosteroids.

Drug	Mechanism of action	Cells involved	Timing	Ref.
Cyclosporine	Inhibition of calcineurin Inhibition of T-cell activation Inhibition of transcription Inhibition of histamine release from basophils and skin mast cells	T-cells, mast cells and basophils and skin mast cells	5–7 days	[13,19,61]
Omalizumab	Binding of free IgE Down-regulation of IgE receptors on mast cells and basophils Inhibitory effects on eosinophils Decrease of IgE synthesis	Mast cells and basophils Eosinophils B-cells	1 week	[20–22,62]
Corticosteroids	Genomic effects: Switch off of many inflammatory genes encoding for inflammatory proteins Non genomic effects: Inhibition of vasodilatation and vascular permeability by binding membrane receptors and activating inhibitory signaling cascade	T lymphocyte, B lymphocyte, Eosinophils, Endothelial cells Inflammatory cells infiltrate	>24 h <24 h	[9,50–52]

as 2 weeks of the first administration, in parallel with its clinical effect, both in asthma and in urticaria, at a time point when mast cells are still active [71,72]. Furthermore, the drug seems to exert an inhibitory effect on eosinophils [71], a cell line that has been associated with the hyperexpression of tissue factor and the activation of the coagulation cascade [73,74]. Interestingly, the clinical effect of omalizumab ceases about 1 month after the last administration, suggesting that the drug does not induce a long-lasting change in cellular mechanisms of inflammation, but rather seems to act like pressing an 'off' button that stops working as soon as it is released. In effect, recent studies suggest that the rapid response to omalizumab is probably the result of the elimination of an activating signal rather than the generation of a negative inhibitory signal [75]. It has been also found that omalizumab decreases IgE synthesis by B cells, inducing a state of anergy [76] although the relevance of such effect in CSU patients is unclear. FIGURE 2 shows the possible sites of intervention of omalizumab in CSU pathophysiology.

Cyclosporine

Cyclosporine is a cyclic oligopeptide macrolide that binds an intracellular protein (cyclophilin). The complex then binds to the cytoplasmic protein calcineurin, leading to an inhibition of its activity, and hence inhibiting T-cell activation. Cyclosporine blocks the induction of genes for a variety of

cytokines and cytokine receptors, resulting in immunomodulating activity. It exerts its effects on cytokines involved in the activation, proliferation and survival of cells important in the immune response, including lymphocytes, mast cells and eosinophils [16,19,77]. The response to cyclosporine treatment in CSU patients is generally as short as 5–7 days. The outcome in patients with severe urticaria treated with cyclosporine in studies published so far [13,15,16,18,19,77] is shown in TABLE 3. The possible mechanisms of action of cyclosporine are depicted in FIGURE 3. As with corticosteroids and omalizumab, a variable proportion of patients did not respond to the drug and responded to corticosteroids.

Discussion

Looking at the data presented above (TABLE 4), it seems conceivable that several distinct inflammation pathways may be activated in CSU; all of them eventually lead to histamine release from mast cells and basophils, but each of them may prevail on the others in a specific subset of patients. The effect of corticosteroids, cyclosporine and omalizumab at a cellular level are summarized in TABLE 5 and illustrated in FIGURES 1–3. Large studies of H1-antihistamine-resistant patients, plotting the clinical responses to the different drugs against histochemical finding, histamine-release assays, autoimmunity investigations and coagulation studies, are needed with the aim to get a more precise picture of the situation, and perhaps to identify specific

Table 5. Effect of third-level treatments on different cell types.

Drug	Mast cells	Basophils	Eosinophils	T lymphocytes	B lymphocytes	Endothelial cells
Cyclosporine	+	++	+/-	+++	+/-	No data
Omalizumab	+++	+++	+	No data	+	No data
Corticosteroids	NO	NO	+++	+++	++	++
	DIRECT	DIRECT				
	EFFECT	EFFECT				

phenotypes of the disease showing a better or worse responsivity to the different therapeutic approaches. In conclusion, CSU can be considered as a mast cell- and basophil-dependent inflammatory disorder of the skin, in which an acute phase response occurs [78]. Such features, along with the autoimmune phenomena provide the rationale for anti-inflammatory and immunosuppressive therapies.

Expert commentary

Most patients with chronic spontaneous urticaria respond to one or more of the drugs presently recommended to treat this disease. Nonetheless, in some cases, the treatments fail, and we need to learn more about the pathogenesis of this disease to classify patients into 'phenotypes' that can be associated with a better response to the single available drugs.

Five-year view

Presently, there is little knowledge regarding what induces histamine release from mast cells and basophils in patients with chronic urticaria. A better understanding of the multiple pathogenic mechanisms involved in this disease will probably lead to novel, more patient-tailored treatment strategies for those unresponsive to H1-antihistamines and, possibly, even causal treatments.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Key issues

- Chronic spontaneous urticaria is a frequent disorder that may heavily worsen the quality of life.
- Chronic spontaneous urticaria may be severe and unresponsive to H1-antihistamine treatment.
- In severely affected patients, several drugs have been used but only systemic steroids, cyclosporine and omalizumab are presently recommended by the guidelines.
- Systemic steroids are extremely effective but cannot be used in the long term due to side effects.
- Cyclosporine is effective and can be used for long-term treatments, but is associated with some side effects and many pharmacological interactions.
- Omalizumab is effective and well tolerated but quite expensive.
- Some patients fail to respond to one or more of these three drugs.
- A better knowledge of the pathogenic mechanisms underlying the disease will lead to understand better the reasons for these failures and to a more patient-tailored therapy.

References

Papers of special note have been highlighted as:

• of interest

•• of considerable interest

1. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA(2) LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy* 2014;69: 868-87
2. Greaves MW, Tan KT. Chronic urticaria: recent advances. *Clin Rev Allergy Immunol* 2007;33:134-43
3. Gaig P, Olona M, Munoz Lejarazu D, et al. Epidemiology of urticaria in Spain. *J Investig Allergol Clin Immunol* 2004;14: 214-20
4. Baiardini I, Giardini A, Pasquali M, et al. Quality of life and patients' satisfaction in chronic urticaria and respiratory allergy. *Allergy* 2003;58:621-3
5. Grattan CE, Francis DM, Hide M, Greaves MW. Detection of circulating histamine releasing autoantibodies with functional properties of anti-IgE in chronic urticaria. *Clin Exp Allergy* 1991;21:695-704
6. Hide M, Francis DM, Grattan CEH, et al. Autoantibodies against the high affinity IgE receptor as a cause of histamine release in chronic urticaria. *N Engl J Med* 1993;328: 1599-604
7. Tedeschi A, Asero R, Lorini M, et al. Plasma levels of matrix metalloproteinase-9 in chronic urticaria patients correlate with disease severity and C-reactive protein but not with circulating histamine-releasing factors. *Clin Exp Allergy* 2010;40:875-81
8. Cugno M, Marzano AV, Asero R, Tedeschi A. Activation of blood coagulation in chronic urticaria: pathophysiological and clinical implications. *Intern Emerg Med* 2010;5:97-101
9. 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
10. Sánchez-Borges M, Asero R, Ansotegui IJ, et al. Diagnosis and treatment of urticaria and angioedema: a worldwide perspective. *World Allergy Organ J* 2012;5:125-47
- **A well-written and user-friendly review of urticaria/angioedema pathogenesis, diagnosis and treatment.**
11. Bernstein JA, Lang DM, Khan DA, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. *J Allergy Clin Immunol* 2014;133:1270-7
- **The "American view".**
12. Fradin MS, Ellis CN, Goldfarb MT, Voorhees JJ. Oral cyclosporine for severe chronic idiopathic urticaria and angioedema. *J Am Acad Dermatol* 1991;25:1065-7
13. Toubi E, Blant A, Kessel A, Golan TD. Low-dose cyclosporin A in the treatment of

- severe chronic idiopathic urticaria. *Allergy* 1997;52:312-16
14. 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. *J Dermatol* 2008;35:276-82
 15. Grattan CE, O'Donnell BF, Francis DM, et al. Randomized double-blind study of cyclosporin in chronic 'idiopathic' urticaria. *Br J Dermatol* 2000;143:365-72
 16. Di Gioacchino M, Di Stefano F, Cavallucci E, et al. Treatment of chronic idiopathic urticaria and positive autologous serum skin test with cyclosporine: clinical and immunological evaluation. *Allergy Asthma Proc* 2003;24:285-90
 17. Baskan EB, Tunali S, Turker T, Saricaoglu H. Comparison of short- and long-term cyclosporine A therapy in chronic idiopathic urticaria. *J Dermatolog Treat* 2004;15:164-8
 18. Vena GA, Cassano N, Colombo D, Neo-I-30 Study Group. Cyclosporine in chronic idiopathic urticaria: a double-blind, randomized, placebo-controlled trial. *J Am Acad Dermatol* 2006;55:705-9
 19. Kessel A, Toubi E. Cyclosporine-A in severe chronic urticaria: the option for long-term therapy. *Allergy* 2010;65:1478-82
 20. Saini S, Rosen KE, Hsieh HJ, et al. A randomized, placebo-controlled, dose-ranging study of single-dose omalizumab in patients with H1-antihistamine-refractory chronic idiopathic urticaria. *J Allergy Clin Immunol* 2011;128:567-73
 - **One Phase III study of omalizumab in chronic spontaneous urticaria.**
 21. Maurer M, Rosén K, Hsieh HJ, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med* 2013;368:924-35
 - **One Phase III study of omalizumab in chronic spontaneous urticaria.**
 22. Kaplan A, Ledford D, Ashby M, et al. Omalizumab in chronic idiopathic/spontaneous urticaria patients symptomatic despite standard combination therapy. *J Allergy Clin Immunol* 2013;132:101-9
 - **One Phase III study of omalizumab in chronic spontaneous urticaria.**
 23. Tedeschi A, Airaghi L, Lorini M, Asero R. Chronic urticaria: a role for newer immunomodulatory drugs? *Am J Clin Dermatol* 2003;4:297-305
 24. 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
 25. Perez A, Woods A, Grattan CE. Methotrexate: a useful steroid-sparing agent in recalcitrant chronic urticaria. *Br J Dermatol* 2010;162:191-4
 26. Sagi L, Solomon M, Baum S, et al. Evidence for methotrexate as a useful treatment for steroid-dependent chronic urticaria. *Acta Derm Venereol* 2011;91:303-6
 27. Bernstein JA, Garrazone SM, Lower EG. Successful treatment of autoimmune chronic idiopathic urticaria with intravenous cyclophosphamide. *Ann Allergy Asthma Immunol* 2002;89:212-14
 28. Asero R. Oral cyclophosphamide in a case of cyclosporine and steroid-resistant chronic urticaria showing autoreactivity on autologous serum skin testing. *Clin Exp Dermatol* 2005;30:582-3
 29. Tedeschi A. Paradoxical exacerbation of chronic urticaria by H1-antihistamines and montelukast. *Eur Ann Allergy Clin Immunol* 2009;41:187-9
 30. Shahar E, Bergman R, Guttman-Yassky E, Pollack S. Treatment of severe chronic idiopathic urticaria with oral mycophenolate mofetil in patients not responding to antihistamines and/or corticosteroids. *Int J Dermatol* 2006;45:1224-7
 31. Zimmerman AB, Berger EM, Elmariam SB, Soter NA. The use of mycophenolate mofetil for the treatment of autoimmune and chronic idiopathic urticaria: Experience in 19 patients. *J Am Acad Dermatol* 2012;66:767-70
 32. Hashimoto T, Kawakami T, Ishii N, et al. Mizoribine treatment for antihistamine-resistant chronic autoimmune urticaria. *Dermatol Ther* 2012;25:379-81
 33. O'Donnell BF, Barr RM, Kobza Black A, et al. Intravenous immunoglobulin in autoimmune chronic urticaria. *Br J Dermatol* 1998;138:101-6
 34. 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
 35. Klote MM, Nelson MR, Engler RJ. Autoimmune urticaria response to high-dose intravenous immunoglobulin. *Ann Allergy Asthma Immunol* 2005;94:307-8
 36. Wetter DA, Davis MD, Yiannias JA, et al. Effectiveness of intravenous immunoglobulin therapy for skin disease other than toxic epidermal necrolysis: a retrospective review of Mayo Clinic experience. *Mayo Clin Proc* 2005;80:41-7
 37. Asero R. Are IVIG for chronic unremitting urticaria effective? *Allergy* 2000;55:1099-100
 38. Arkwright PD. Anti-CD20 or anti-IgE therapy for severe chronic autoimmune urticaria. *J Allergy Clin Immunol* 2009;123:510-11
 39. Chakravarty SD, Yee AF, Paget SA. Rituximab successfully treats refractory chronic autoimmune urticaria caused by IgE receptor autoantibodies. *J Allergy Clin Immunol* 2011;128:1354-5
 40. Mallipeddi R, Grattan CE. Lack of response of severe steroid-dependent chronic urticaria to rituximab. *Clin Exp Dermatol* 2007;32:333-4
 41. Asero R, Tedeschi A, Coppola R, et al. Activation of the tissue factor pathway of blood coagulation in patients with chronic urticaria. *J Allergy Clin Immunol* 2007;119:705-10
 42. 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
 - **A study showing the correlation between chronic urticaria and activation of the coagulation cascade.**
 43. Takeda T, Sakurai Y, Takahagi S, et al. Increase of coagulation potential in chronic spontaneous urticaria. *Allergy* 2011;66:428-33
 44. Cugno M, Marzano AV, Tedeschi A, et al. Expression of tissue factor by eosinophils in patients with chronic urticaria. *Int Arch Allergy Immunol* 2009;148:170-4
 45. Parslew R, Pryce D, Ashworth J, Friedmann PS. Warfarin treatment of chronic idiopathic urticaria and angio-oedema. *Clin Exp Allergy* 2000;30:1161-5
 46. Chua SL, Gibbs S. Chronic urticaria responding to subcutaneous heparin sodium. *Br J Dermatol* 2005;153:216-17
 47. 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
 - **A study showing the potential effect of anticoagulant treatment in patients with severe disease.**

48. Takahagi S, Shindo H, Watanabe M, et al. Refractory chronic urticaria treated effectively with the protease inhibitors, nafamostat mesilate and camostat mesilate. *Acta Derm Venereol* 2010;90:425-6
- **A study indirectly supporting the relevance of proteases in the pathogenesis of chronic urticaria.**
49. Yang JW, Han BG, Kim BR, et al. Superior outcome of nafamostat mesilate as an anticoagulant in patients undergoing maintenance hemodialysis with intracerebral hemorrhage. *Ren Fail* 2009;31:668
50. Thormann H, Bindslev-Jensen C. Mirtazapine for chronic urticaria. *Acta Derm Venereol* 2004;84:482-3
51. Bigatà X, Sais G, Soler F. Severe chronic urticaria: response to mirtazapine. *J Am Acad Dermatol* 2005;53:916-17
52. Boehm I, Bauer R, Bieber T. Urticaria treated with dapsone. *Allergy* 1999;54:765-6
53. Morgan M, Cooke A, Rogers L, et al. Double-blind placebo-controlled trial of dapsone in antihistamine refractory chronic idiopathic urticaria. *J Allergy Clin Immunol Pract* 2014;2:601-6
54. Baumgart KW, Mullins R. Use of hydroxychloroquine in refractory urticaria. *J Allergy Clin Immunol* 2000;105:795-6
55. Reeves GE, Boyle MJ, Bonfield J, et al. Impact of hydroxychloroquine therapy on chronic urticaria: chronic autoimmune urticaria study and evaluation. *Intern Med J* 2004;34:182-6
56. Losel RM, Falkenstein E, Feuring M, et al. Nongenomic steroid action: controversies, questions, and answers. *Physiol Rev* 2003;83:965-1016
57. Wehling M, Lösel R. Non-genomic steroid hormone effects: membrane or intracellular receptors? *J Steroid Biochem Mol Biol* 2006;102:180-3
58. Tillmann HC, Stuck BA, Feuring M, et al. Delayed genomic and acute nongenomic action of glucocorticosteroids in seasonal allergic rhinitis. *Eur J Clin Invest* 2004;34:67-73
59. Kaplan AP, Joseph K, Maykut RJ, et al. Treatment of chronic autoimmune urticaria with omalizumab. *J Allergy Clin Immunol* 2008;122:569-73
60. Maurer M, Altrichter S, Bieber T, et al. Efficacy and safety of omalizumab in patients with chronic urticaria who exhibit IgE against thyroperoxidase. *J Allergy Clin Immunol* 2011;128:202-9
61. Labrador-Horrillo M, Valero A, Velasco M, et al. Efficacy of omalizumab in chronic spontaneous urticaria refractory to conventional therapy: analysis of 110 patients in real-life practice. *Expert Opin Biol Ther* 2013;13:1225-8
62. Altman MC, Naimi DR. Comment on Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med* 2013;368:2528-30
63. Song CH, Stern S, Giruparajah M, et al. Long-term efficacy of fixed-dose omalizumab for patients with severe chronic spontaneous urticaria. *Ann Allergy Asthma Immunol* 2013;110:113-17
64. Sussman G, Hébert J, Barron C, et al. Real-life experiences with omalizumab for the treatment of chronic urticaria. *Ann Allergy Asthma Immunol* 2014;112:170-4
65. Metz M, Ohanyan T, Church MK, Maurer M. Omalizumab is an effective and rapidly acting therapy in difficult-to-treat chronic urticaria: a retrospective clinical analysis. *J Dermatol Sci* 2014;73:57-62
66. Saini SS, Bindslev-Jensen C, Maurer M, et al. Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic on H1 antihistamines: a randomized, placebo-controlled study. *J Invest Dermatol* 2015;135:67-75
67. Chang TW, Chen C, Lin CJ, et al. The potential pharmacologic mechanisms of omalizumab in patients with chronic spontaneous urticaria. *J Allergy Clin Immunol* 2015;135:337-42
68. Yalcin AD. An overview of the effects of anti-IgE therapies. *Med Sci Monit* 2014;20:1691-9
69. Yalcin AD, Celik B, Gumuslu S. D-dimer levels decreased in severe allergic asthma and chronic urticaria patients with the omalizumab treatment. *Expert Opin Biol Ther* 2014;14:283-6
70. Meyer-De, Schmid JJ, Neuman A. Treatment of chronic urticaria with heparin. *Bull Soc Fr Dermatol Syphiligr* 1952;59:286-7
71. Eckman JA, Sterba PM, Kelly D, et al. Effects of omalizumab on basophil and mast cell responses using an intranasal cat allergen challenge. *J Allergy Clin Immunol* 2010;125:889-95
72. Savage JH, Courneya JP, Sterba PM, et al. Kinetics of mast cell, basophil, and oral food challenge responses in omalizumab-treated adults with peanut allergy. *J Allergy Clin Immunol* 2012;130:1123-9
73. Asero R, Cugno M, Tedeschi A. Eosinophils in chronic urticaria: supporting or leading actors? *World Allergy Organ J* 2009;2:213-17
- **A review highlighting the potential relevance of eosinophils in the pathogenesis of the disease.**
74. Tedeschi A, Kolkhir P, Asero R, et al. Chronic urticaria and coagulation: pathophysiological and clinical aspects. *Allergy* 2014;69:683-91
75. Gericke J, Ohanyan T, Church MK, et al. Omalizumab may not inhibit mast cell and basophil activation in vitro. *J Eur Acad Dermatol Venereol* 2014. [Epub ahead of print]
76. Chan MA, Gigliotti NM, Dotson AL, Rosenwasser LJ. Omalizumab may decrease IgE synthesis by targeting membrane IgE+ human B cells. *Clin Transl Allergy* 2013;3:29
77. Loria MP, Dambra PP, D'Oronzio L, et al. Cyclosporin A in patients affected by chronic idiopathic urticaria: a therapeutic alternative. *Immunopharmacol Immunotoxicol* 2001;23:205-13
78. Kasperska-Zajac A. Acute-phase response in chronic urticaria. *J Eur Acad Dermatol Venereol* 2012;26:665-72