Biologics in Chronic Urticaria

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KEYWORDS

- Chronic urticaria • Biologics • Omalizumab • Therapy • Rituximab • TNF antagonist
- Intravenous immunoglobulin therapy

KEY POINTS

- Omalizumab is the only monoclonal antibody that is approved for chronic urticaria (CU).
- Randomized, placebo-controlled trials and extensive clinical experience show that omalizumab is both safe and efficacious for CU.
- A few reports demonstrated effectiveness of high-dose immunoglobulin therapy.
- Weak evidence supports rituximab and tumor necrosis factor antagonist efficacy in antihistamine-refractory CU.

Chronic urticaria (CU), also referred to as chronic spontaneous urticaria, is defined as wheals, angioedema, or both lasting longer than 6 weeks.[1] CU is associated with intense pruritus, disfiguring wheals, and higher odds of reporting depression, anxiety, and sleep difficulty.[2–4] Patients with CU experience a tremendous burden, with quality-of-life estimates on par with patients with coronary artery disease awaiting bypass.[5,6] Urticaria of any type is estimated to have a lifetime prevalence of 8.8%, whereas CU has an annual prevalence of 0.5% to 5.0% and a lifetime prevalence rate of 1.8%.[2,7–12] The first-line therapies for CU are second-generation H_1 antihistamines, often required at 2 to 4 times the doses approved by the Food and Drug Administration (FDA).[12] Unfortunately, many patients will fail antihistamines and will require alternative therapies to control their symptoms. For these patients, biologics have proven to be relatively safe and efficacious.

The FDA defines biologics as a wide range of products, such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins.[13] Although biologics have been used for years, the first licensed monoclonal antibody (mAb) was muromonob-CD3, an mAb directed at CD3, in 1986.[14] Since then, the use of targeted biological therapies has expanded. For the treatment of the urticarial diseases, mAb, recombinant antagonists, and donor immunoglobulin have played important roles (Fig. 1). The most important biologic used in CU is omalizumab.

ANTI–IMMUNOGLOBULIN E MONOCLONAL ANTIBODIES
Overview and Mechanism of Action of Omalizumab

Although the exact cause of CU is not entirely known, many patients have autoantibodies to the alpha chain of the high-affinity receptor FcεR1 or to immunoglobulin (Ig)E, with the former more specific for CU.[15] Omalizumab 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) and inhibits it from binding to the cell receptor.[16,17] Omalizumab binds to the free IgE, leading to a reduction of free IgE levels and, consequently, decreased expression of FcεRI receptors on mast cells, basophils, and dendritic cells.[18–22] This effect may reduce mast cell numbers, as mast cell proliferation and survival are theorized to depend on IgE-FcεRI–dependent pathways.[23] It is also
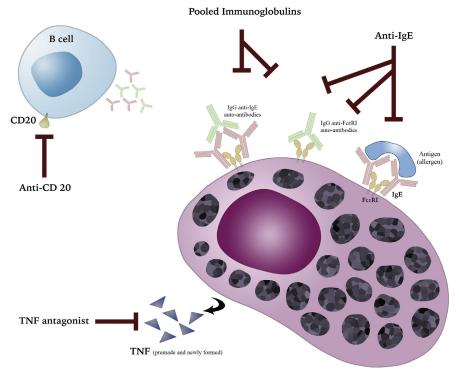

Fig. 1. The proposed mechanism of action of different biological agents in CU. Anti-IgE blocks the effect of IgE at the level of IgE-antigen cross-linking, IgE–anti-IgE IgG cross-linking, and anti-FcεRI IgG (downregulation). Anti-CD20 blocks CD20 B cells. TNF antagonist blocks both premade and newly synthesized TNF.

postulated that IgE-FcεRI interaction on mast cells lowers the threshold for degranulation to various stimuli, which would be attenuated with IgE depletion.[21] Recently, it has been proposed that omalizumab inhibits mast cell activation by dissociation of preattached IgE from its receptor.[24] This might explain the quick response (sometimes within 48 hours) seen in some patients after omalizumab initiation, which in this time frame would not be expected to decrease FcεRI expression. Omalizumab was originally approved for the treatment of moderate to severe persistent allergic asthma, but it quickly found a niche with CU.[12]

Omalizumab Proof-of-Concept and Phase 2 Studies

Early on, omalizumab was theorized to benefit patients with CU with autoantibodies.[25] Theory transitioned to practice with a few case reports showing the benefit of omalizumab.[26–32] Case reports were soon followed by small pilot studies. Kaplan and colleagues[33] performed one of the first of these studies in 2008. Twelve patients with autoimmune CU, identified by a basophil histamine release assay and/or autologous skin test, and a serum IgE of ≤700 IU/mL were randomized to 4 weeks of placebo followed by 16 weeks of omalizumab, with a dosing schedule based on the asthma package insert. All subjects had a significant reduction in hives and itch while on the omalizumab when compared with baseline and 7 of the 12 experienced complete remission.[33] A subsequent open-label prospective observational study assessed the efficacy of omalizumab on subjects with nonautoimmune CU refractory to antihistamines. The investigators included 9 subjects who were deemed nonautoimmune by negative basophil histamine release. All subjects experienced improvement in hive and itch with omalizumab with 2 experiencing complete remission.[34] A larger double-blind, placebo-controlled trial, performed by Maurer and colleagues,[35] enrolled 49 subjects with antihistamine-refractory CU with a positive IgE against thyroperoxidase. Subjects were randomized to either 24 weeks of omalizumab or placebo and dosed based on the asthma package insert using both body weight and serum IgE. The investigators showed efficacy of omalizumab in CU by a reduction in weekly urticaria activity score (UAS7) from baseline of 17.8, of a possible 42, compared with a reduction of 7.1 with placebo. Additionally, 19 subjects (70.4%) developed complete remission of wheals with the omalizumab compared with one with placebo.[35]

Saini and colleagues[36] performed a double-blind, placebo-controlled, dose-ranging study, using 90 subjects with antihistamine-refractory CU. The subjects were randomized to either 4 weeks of 75 mg, 300 mg, or 600 mg omalizumab or placebo then were followed for an additional 12 weeks after stopping omalizumab. The 300-mg and 600-mg omalizumab groups showed improvement over placebo in both itch and hive, whereas no difference from placebo was seen with the 75-mg omalizumab arm. Additionally, 36.0% of subjects in the 300-mg omalizumab group and 28.6% of subjects in the 600-mg omalizumab group achieved complete remission, whereas 0% in the placebo group achieved complete remission.[36] These data supported the doses chosen for the pivotal phase 3 studies described as follows.

Omalizumab Phase 3 Trials

The first large-scale phase 3 trial results published were from the ASTERIA II trial. This double-blinded study randomized 323 subjects with CU refractory to standard dosing of H1 antihistamines. Subjects were randomized to receive 3 subcutaneous injections of 75 mg, 150 mg, or 300 mg omalizumab or placebo, at 4-week intervals, followed by a 16-week observation period. The primary endpoint was change from baseline to week 12 in the weekly itch-severity score (of a possible 21). Weekly itch scores

improved for subjects receiving 150 mg omalizumab and 300 mg omalizumab by (-8.1 ± 6.4, $P = .001$) and (-9.8 ± 6.0, $P<.001$), respectively, but not in those assigned to either placebo or 75 mg omalizumab. In addition to the weekly itch score, the UAS7 improved significantly for both the 150 mg and 300 mg omalizumab groups when compared with baseline, whereas the placebo and 75-mg omalizumab groups did not change significantly. During the follow-up observation period, the mean UAS7 for all groups increased to reach the placebo group and none returned to baseline. Complete response was seen in 44% of 300-mg omalizumab group, 22% of the 150-mg group, 16% of the 75-mg omalizumab group, and 5% of the placebo group.[37]

GLACIAL was the next large phase III double-blinded placebo-controlled trial results published. This study, unlike prior studies, required subjects with CU to fail H_1 antihistamines plus an H_2-blocker and/or leukotriene antagonist. A total of 336 subjects were randomized in a 3:1 fashion to 24 weeks of either 6 monthly injections of 300 mg omalizumab or 6 monthly injections of placebo, respectively. Throughout the study, subjects were required to maintain stable doses of the prerandomization combination of H_1-antihistamines plus H_2 antihistamines and/or leukotriene antagonists. The primary outcome for the study was safety of omalizumab when compared with placebo. The adverse events for omalizumab and placebo groups during the study were similar (65.1% and 63.9%, respectively). Headaches and upper respiratory infections were the most common adverse events noted in the omalizumab group. Serious adverse events were reported in 6.9% of subjects during the study period, 7.1% in the omalizumab group and 6.0% in the placebo group, but none were deemed related to omalizumab. To assess efficacy, investigators evaluated the weekly itch-severity score and proportion of subjects with complete response by week 12 compared with baseline. The overall improvement in weekly itch score at week 12 compared with baseline, from 0 to 21 with higher indicating more severe symptoms, was –8.6 for the omalizumab arm and –4.0 for the placebo arm. As with prior studies, once the active medication was discontinued, the weekly itch score increased to equal the placebo scores, neither of which returned to baseline. In terms of complete responders, at week 12, 33.7% of subjects in the omalizumab group were free of urticaria symptoms, whereas only 4.8% of subjects in the placebo group were free of urticaria.[38] These benefits were sustained to week 24.

ASTERIA I was also a large-scale phase 3 clinical trial. This trial was a 40-week double-blind, placebo-controlled trial that was designed similarly to ASTERIA II, but the treatment phase of the trial was twice the length. A total of 319 subjects were randomized to 24 weeks of subcutaneous omalizumab at 75 mg, 150 mg, or 300 mg or placebo every 4 weeks. The primary endpoint for the study was weekly itch-severity score at 12 weeks compared with baseline. Interestingly, subjects in all groups noticed improvements in weekly itch score as early as week 1, most significantly in the omalizumab 300-mg group. All active groups of the trial showed improvement over baseline with a reduction in weekly itchy score of 6.46 with omalizumab 75 mg, 6.66 with omalizumab 150 mg, and 9.40 with omalizumab 300 mg. Placebo showed a reduction by 3.63 over baseline at week 12. The reduction in weekly itch score was generally maintained while on the active treatment, and on cessation of medication, the weekly itch scores rose to that of the placebo. Nearly 36% of subjects in the 300-mg omalizumab group experienced complete remission of symptoms versus approximately 9% in the placebo group.[39]

The X-ACT trial was double-blind, placebo-controlled trial evaluating the efficacy of omalizumab on antihistamine-refractory CU with angioedema. A total of 91 subjects were randomized to either 28 weeks of 300 mg omalizumab or placebo given as subcutaneous injections every 4 weeks. The primary outcome for this trial was the

treatment symptom score at 28 weeks when compared with baseline by using the Chronic Urticaria Quality of Life (CU-Q$_2$oL). Subjects assigned to the 300-mg omalizumab group had a threefold improvement in angioedema burden in days per week versus placebo, 0.3 and 1.1, respectively.[40]

These large clinical trials have shown that omalizumab is a safe and efficacious therapy for CU, often improving subjects' symptoms before week 4 with benefit persisting while on treatment.[41,42] In addition, the data suggest omalizumab is effective for CU despite background therapy.[39] Finally, omalizumab retreatment of patients with a recurrence of CU has been shown to be safe and effective (**Table 1**).[43]

Omalizumab and Urticaria Guidelines

The result of these large clinical trials is that the US and European guidelines for management of CU have added omalizumab as a recommended therapy following a stepwise approach. The American Academy of Allergy, Asthma, and Immunology and American College of Allergy, Asthma, and Immunology have recommended that omalizumab be added to therapy as a fourth step after failure of antihistamines at both standard and high doses, failure of the addition of an H$_2$-antihistamine and leukotriene antagonist, and failure of a high-potency antihistamine like doxepin or hydroxyzine (**Table 2**).[12] The European guidelines are slightly different, with the addition of omalizumab as the third step after the failure of nonsedating antihistamine at standard and high doses.[44]

Effectiveness of Omalizumab in Other Forms of Urticaria

Beyond CU, omalizumab has been used in urticarial vasculitis[30] and a variety of physical forms of urticaria. These include cholinergic urticaria,[29,45] cold-induced urticaria,[26,46,47] delayed pressure urticaria,[46,48,49] heat urticaria,[46,50,51] aquagenic urticaria,[52] dermatographism,[46] and solar urticaria.[31,46,53] Recently, omalizumab was investigated for the treatment of solar urticaria in a phase II trial evaluating the efficacy of 300 mg omalizumab given as 3 subcutaneous injections at 4-week intervals on 10 subjects. To qualify, subjects were required to have the appearance of wheals within 15 minutes following sun exposure and resolving in less than 2 hours in the shade. The primary outcome was the proportion of subjects who required a 10-fold increase in intensity of ultraviolet dose above baseline to trigger minimal urticarial dose at week 12 when compared with baseline. By the end of the 12 weeks, 2 of the 10 patients reached the primary endpoint. Although the trial did not reach statistical significance, it shows that omalizumab may have a role in the physical urticarias and more studies are needed.[54]

Omalizumab in Pregnancy

Although omalizumab is a safe and efficacious medication for most patients with CU, the safety in pregnancy is not completely elucidated. To assess this unique patient population, a registry was established for patients with asthma. By November 2012, 191 pregnant patients had been exposed to omalizumab during the first trimester. The outcomes of 169 of the pregnancies were known and the overall proportions of congenital anomalies, prematurity, and low birth weight were consistent with the general asthma population, without an apparent increased prevalence of major anomalies.[55] It is unlikely that this safety profile would differ in patients with CU.

Advances in Anti–immunoglobulin E Monoclonal Antibodies

New biologics targeting IgE are currently in development and will likely play an important role alongside omalizumab in the treatment of CU.[56] A second-generation anti-IgE

Table 1
Summary of the major trials involving omalizumab

Trial Name/First Author	Number of Subjects	Study Design	Key Inclusion	Key Exclusion	Change in Weekly Itch Score

XCUISITE/Maurer et al[35]	49	RDBPC trial
		3-wk screening period + 24-wk active phase
		Two arms:
		• Placebo
		• Omalizumab
		• Dosing per asthma guidelines
			Uncontrolled CU ≥6 wk despite standard dosed H_1-antihistamines
			• Weight 20–150 kg
			• Serum IgE from 30–700 IU/mL
			• Serum IgE–anti-TPO antibody level of ≥5.0 IU/mL at most 3 mo before randomization
			• UAS7 ≥10
				• Acute urticaria
				• Elevated serum IgE for reasons other than allergy or urticaria
				• Medications 4 wk before enrollment
				  ○ Systemic corticosteroids
				  ○ Methotrexate
				  ○ Cyclosporine
				  ○ Other immunosuppressants
					Mean (SD)
					ΔWIS baseline to week 12
					• Placebo
					  ○ −3.57 (4.95)
					• 150 mg omalizumab
					  ○ −5.9 (4.43)
					• 300 mg omalizumab
					  ○ −11.19 (6.46)
					• 600 mg omalizumab
					  ○ −11.19 (6.46)

MYSTIQUE/Saini et al[36]	90	RDBPC trial
		1-wk screening period + 1-wk run-in + 4-wk active phase + 12-wk follow-up
		Four arms:
		• Placebo
		• 75 mg omalizumab
		• 300 mg omalizumab
		• 600 mg omalizumab
			Uncontrolled CU ≥6 wk despite standard dosed H_1-antihistamines
			• UAS7 ≥12
				• A cause for the CU
				• Routine administration of the following medications 3 mo before enrollment:
				  ○ Dapsone
				  ○ Hydroxychloroquine
				  ○ Sulfasalazine
				  ○ Methotrexate
				  ○ Cyclophosphamide
				  ○ Intravenous immunoglobulin
				  ○ Plasmapheresis
				  ○ Other monoclonal antibodies
				• Routine administration of the following medication 6 wk before enrollment:
				  ○ Doxepin
				• Routine administration of the following medication 4 wk before enrollment:
				  ○ Cyclosporine
				• Use of systemic steroids was not allowed during the trial
					Mean (SD)
					ΔWIS baseline to wk 12
					• Placebo
					  ○ −3.5 (4.23)
					• 75 mg omalizumab
					  ○ −4.5 (5.84)
					• 300 mg omalizumab
					  ○ −9.2 (5.98)
					• 600 mg omalizumab
					  ○ −6.5 (5.63)

| ASTERIA II/Maurer et al[37] | 323 | RDBPC trial 2-wk screening period + 12-wk active phase + 16-wk follow-up period Four arms:
• Placebo
• 75 mg omalizumab
• 150 mg omalizumab
• 300 mg omalizumab | Uncontrolled CU for 6 mo despite use of standard dosed H$_1$-antihistamines
• UAS7 ≥16
• WIS ≥8 | • A cause for the CU
• The use of any of the following within 7 d before the screening visit.
  ○ H$_2$ - antihistamine
  ○ Leukotriene antagonist
• Routine administration of the following medications 30 d before enrollment:
  ○ Systemic glucocorticoids
  ○ Hydroxychloroquine
  ○ Methotrexate
  ○ Cyclosporine
  ○ Cyclophosphamide
  ○ Intravenous immuno globulin | Mean (SD) ΔWIS baseline to wk 12
• Placebo
  ○ −5.1 (5.6)
• 75 mg omalizumab
  ○ −5.9 (6.5)
• 150 mg omalizumab
  ○ −8.1 (6.4)
• 300 mg omalizumab
  ○ −9.8 (6.0) |
| GLACIAL/Kaplan et al[38] | 336 | RDBPC trial 2-wk screening period + 24-wk active phase + 16-wk follow-up period Two arms:
• Placebo
• 300 mg omalizumab | CU despite up to 4 times approved dose of H$_1$-antihistamines AND H$_2$- antihistamines or Leukotriene antagonist, or all 3 in combination
• UAS7 ≥16
• WIS ≥8 | • A cause for the CU
• Routine administration of the following medications 30 d before enrollment:
  ○ Systemic glucocorticoids
  ○ Hydroxychloroquine
  ○ Methotrexate
  ○ Cyclosporine
  ○ Cyclophosphamide
  ○ Intravenous immunoglobulin | Mean (95% confidence interval [CI]) ΔWIS baseline to wk 12
• Placebo
  ○ −4.0 (95% CI −5.3 to −2.7)
• 300 mg omalizumab
  ○ −8.6 (95% CI −9.3 to −7.8) |

Table 1 (continued)					
Trial Name/ First Author	**Number of Subjects**	**Study Design**	**Key Inclusion**	**Key Exclusion**	**Change in Weekly Itch Score**

ASTERIA I/Saini et al[39]	319	RDBPC trial
		2-wk screening + 24-wk treatment + 16-wk follow-up
		Four arms:
		• Placebo
		• 75 mg omalizumab
		• 150 mg omalizumab
		• 300 mg omalizumab
			Uncontrolled CU for 8 mo despite use of H_1-antihistamines
			• UAS7 ≥16
			• WIS ≥8
				• A cause for the CU
				• The use of any of the following within 7 d before the screening visit:
				  ○ H_2-antihistamine
				  ○ Leukotriene antagonist
				• Routine administration of the following medications 30 d before enrollment:
				  ○ Systemic glucocorticoids
				  ○ Hydroxychloroquine
				  ○ Methotrexate
				  ○ Cyclosporine
				  ○ Cyclophosphamide
				  ○ Intravenous immunoglobulin
					Mean (SD)
					ΔWIS baseline to wk 12
					• Placebo
					  ○ −3.63 (5.22)
					• 75 mg omalizumab
					  ○ −6.46 (6.14)
					• 150 mg omalizumab
					  ○ −6.66 (6.28)
					• 300 mg of omalizumab
					  ○ −9.40 (5.73)

| X-ACT/Staubach et al[40] | 91 | RDBPC trial
2-wk screening +
 24-wk treatment +
 8-wk follow-up
Two arms:
● Placebo
● 300 mg omalizumab | Uncontrolled CU for 6 mo
 with 4 occurrences of
 angioedema despite
 use of 2–4 times
 standard dosed
 H$_1$-antihistamines
● UAS7 ≥14
● CU-Q$_2$oL ≥30 | ● Hereditary angioedema
● Acquired angioedema
● The use of any of the following
 within 7 d before the screening
 visit:
 ○ H$_2$-antihistamine
 ○ Leukotriene antagonist
● Routine administration of the
 following medications 30 d
 before enrollment:
 ○ Systemic glucocorticoids
 ○ Hydroxychloroquine
 ○ Methotrexate
 ○ Cyclosporine
 ○ Cyclophosphamide
 ○ Intravenous immunoglobulin | Mean (SD)
ΔWIS baseline to wk 12
● Placebo
 ○ −2.2 (8.99)
● 300 mg omalizumab
 ○ −8.3 (7.58) |

Abbreviations: CU, chronic urticaria; CU-Q$_2$oL, this questionnaire measures various aspects of quality of life (scale: 0–100; high scores indicate low quality of life) that are specific to chronic urticaria; RDBPC, randomized, double-blind, placebo-controlled; UAS7, weekly urticaria score and is a scoring system based on a daily diary that uses numeric severity ratings from 0 to 3 (0, none; 3, intense) for the number of wheals over 24 hours and the intensity of pruritus, therefore the total daily score (sum of the wheal and pruritus scores) could assume any value between 0 and 6 and is summed over a week with a maximum of 42 and minimum of 0; WIS, weekly itch score: a weekly itch scale based on a 7-day sum of a daily itch diary with symptoms on a scale ranging from 0 to 3, a weekly score of 0 to 21, with higher scores indicating more severe itching; ΔUAS7, the change in UAS7; ΔWIS, change in WIS score.

Table 2
Omalizumab indications, dosage, adverse effects, contraindications, and limitations as per the package insert approved by the US Food and Drug Administration

Agent	Indications	Dosage for CU	Side Effects	Contraindications	Limitations
Omalizumab (Xolair)	• Moderate to severe persistent asthma in patients 6 y of age and older with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids. • Chronic idiopathic urticaria in adults and adolescents 12 y of age and older who remain symptomatic despite H1 antihistamine treatment.	150 mg or 300 mg every 4 wk (dosing independent of IgE level and body weight).	The most common adverse reactions (≥2% Xolair-treated patients with urticaria and more frequent than in placebo) included the following: nausea, nasopharyngitis, sinusitis, upper respiratory tract infection, viral upper respiratory tract infection, arthralgia, headache, and cough and injection site reaction. Black box warning for anaphylaxis.	Absolute: Severe hypersensitivity (previous immediate-type hypersensitivity or anaphylaxis) Relative: Malignancy, severe cardiovascular disease, active parasitic infection.	• Cost. • Insurance approval. • Reconstitution and preparation. • Lack of approval for other urticarial forms.

Abbreviation: CU, chronic urticaria.

mAb, QGE031 (ligelizumab), is now being studied for both asthma and CU. This humanized monoclonal $IgG1_K$ anti-IgE has a 40-fold to 50-fold higher affinity to the $C\varepsilon3$ domain of IgE compared with omalizumab.[57] An initial trial evaluating its efficacy versus placebo and omalizumab for 20 weeks in patients with CU is ongoing (clinicaltrial.gov NCT02477332). Another study is evaluating the long-term safety of QGE031 for 52 weeks in CU (clinicaltrial.gov NCT02649218).

Quilizumab is another novel humanized IgG1 mAb recently studied in asthma and CU. Unlike anti-IgE antibodies, quilizumab targets the M1-prime segment of membrane-expressed IgE on IgE-switched and memory B cells, leading to their depletion. Recently, the results of the first filed trial of quilizumab in asthma were published.[58] Total IgE was reduced by approximately 40%. However, there were no significant improvements in asthma outcomes versus placebo. The results of a recently completed trial assessing the efficacy and safety of quilizumab in CU resistant to antihistamine therapy for 20 weeks have yet to be published (clinicaltrial.gov NCT01987947).

ANTI-CD20 MONOCLONAL ANTIBODY

Rituximab is a chimeric mAb that is a cytolytic antibody that targets CD20 on B cells. CD20 is known to be expressed at high levels on B cells, including immature, mature, and memory cells. By targeting the B cells that produce IgE and functional IgG autoantibodies against $Fc\varepsilon RI$, rituximab is postulated to be an effective way to treat refractory CU. Currently, rituximab is indicated for the treatment of multiple hematology malignancies and patients with certain autoimmune diseases.[59] Given the medication's efficacy with autoimmune diseases and its potential mechanism of action, the drug has been tried on multiple occasions for patients with severe refractory CU.

One of the first reports of the use of rituximab in CU occurred in a patient with both urticaria and angioedema along with pressure-induced urticaria of the hands and feet. The patient had failed conventional and nonconventional therapy, including immunomodulators and intravenous immunoglobulin (IVIG) and became corticosteroid dependent. The patient received 4 weekly infusions of rituximab 375 mg/m^2. Unfortunately, the patient did not respond to the rituximab.[60] Since then, a few additional case reports have shown promising results. One case was of a 12-year-old boy with refractory CU with angioedema and immunodeficiency who was treated with 4 infusions of rituximab 375 mg/m^2. A week after the first infusion, the patient become asymptomatic, and the effect lasted for 12 months. Although symptoms did eventually recur, they were easily managed with antihistamines.[61] Another investigator examined the effects of rituximab in a patient with CU and an urticarial lesion biopsy showing IgG autoantibodies against $Fc\varepsilon RI$ on immunohistochemistry. Four weekly intravenous infusions of rituximab at 375 mg/m^2 were administered. Six weeks after the last infusion, the patient achieved complete remission with evidence of basophil activation suppression.[62] More recently, a patient with refractory steroid-dependent CU received 2 infusions of rituximab 1 g 2 weeks apart, and had temporary remission lasting for 10 months. Antihistamines were restarted, and the patient was advised to undergo another cycle of rituximab.[63]

Rituximab also has been tried in urticarial vasculitis. The first was in a patient with hypocomplementemic urticarial vasculitis (HUVS) who had failed mycophenolate mofetil and corticosteroids. Rituximab was given at 375 mg/m^2 in 4 weekly doses. Complete remission of the HUVS was attained following rituximab therapy.[64] Another case of steroid-dependent refractory urticarial vasculitis in a patient with ulcerative colitis was treated with rituximab. Two cycles of 1 g rituximab resulted in remission for

8 months before relapse.[65] Despite these few case reports of the possible therapeutic efficacy of rituximab in CU and urticarial vasculitis, more studies are needed to support its utility in those who fail standard of care.

INTRAVENOUS IMMUNOGLOBULIN

IVIG is a purified preparation of human polyclonal IgG prepared by pooling plasma obtained from thousands of healthy donors. IVIG is used as a replacement therapy for patients with primary and secondary immunodeficiency, as well as an immunomodulator in autoimmune and inflammatory disorders at higher doses.[66] IVIG appears to work as an immune suppressant by a variety of immune effector responses, including Fc receptor blockade, enhanced autoantibody clearance, immune regulation of B-cell and T-cell functions, amelioration of regulatory T cells, and upregulation the $Fc\gamma RIIB$ expression.[67] These immunomodulatory mechanisms are likely responsible for its effectiveness in autoimmune and inflammatory disorders, such as Kawasaki syndrome, myositis disorders, idiopathic thrombocytopenia, and myasthenia gravis.[68–71] As indicated earlier, autoantibodies to the α chain of high-affinity $Fc\varepsilon R1$ or IgE are present in approximately 30% to 40% of cases of CU, with some proposing that the vast majority of CU may have an autoimmune mechanism.[72,73] The detection of these autoantibodies can be determined by histamine-releasing activity, autologous serum skin test (ASST), Western blot, and enzyme-linked immunosorbent assay.[73,74] However, the role of these autoantibodies in CU pathogenesis has not been definitively elucidated.[72] Due to the potential role that autoimmunity plays in CU, IVIG has been evaluated by multiple therapeutic trials in CU.

Plasmapheresis was the gate that backed IVIG use as a potential therapeutic option in CU with autoantibodies based on ASST. In 1992, Grattan and colleagues[75] used plasmapheresis in subjects with CU deemed as autoimmune by ASST. Fifty percent of the patients responded at least somewhat and 25% had complete remission. This finding prompted other investigators to try IVIG in patients with CU with a positive ASST. In their trial, O'Donnell and colleagues[76] treated 10 patients with severe autoimmune CU with 0.4 g/kg per day IVIG for 5 days. They reported that 9 of 10 responded and 3 had complete remission at 3-year follow-up. Later reports examined the effectiveness of low-dose IVIG in patients with refractory CU. One report evaluated 2 doses of 0.2 g/kg given at 4 weeks apart with reporting an improvement in the urticarial score.[77] Another report evaluated the effect of monthly infusion of 0.15 g/kg IVIG on patients with CU. Subjects underwent infusions from 6 to 51 months; 90% of subjects who received IVIG had a response with 65% having complete remission.[78] More recently, a retrospective study to assess the efficacy and safety of high-dose IVIG (2 g/kg over 2 days every 4–6 weeks) on patients with refractory CU was conducted.[13] Of 6 patients, 5 had complete remission and 1 had a partial response after 1 to 11 cycles of IVIG and 11 to 24 months of follow-up. The mechanisms of IVIG therapeutic benefits in CU are not yet clear, with some reports questioning its efficacy as a true immunomodulatory therapy rather than as an anti-idiotype therapy.[79,80]

Perhaps resulting from the positive response seen in CU, IVIG has been tried in a variety of physical urticarias. Dawn and colleagues[81] examined the use of high-dose IVIG of 2 g/kg over 2 to 3 days on 8 patients with delayed pressure urticaria. Five of 8 patients responded to the infusions with 3 achieving complete remission. IVIG also has been evaluated for its utility in solar urticaria. IVIG is theorized to help by targeting the Fc receptors of specific IgE of a hypothetical provocative chromophore allergen activated by ultraviolet light in patients with solar urticaria.[82] A few case series have showed IVIG to be an efficacious therapeutic modality in solar urticaria.[83–85] In a

retrospective analysis of 7 patients with solar urticaria treated with IVIG (1.4–2.5 g/kg over 2–5 days), 5 of 7 patients had complete remission.[82] Recently, Aubin and colleagues[86] evaluated IVIG in a phase II open-label trial involving 9 patients with refractory solar urticaria. The patients were treated with 2 g/kg over 2 days and then evaluated at 4 and 12 weeks. Of the 9 patients, only 2 showed remission at 4 and 12 weeks.

Although IVIG has been used for many years for a variety of conditions, it has been associated with a few adverse effects. The main adverse effects of IVIG include flushing, myalgia, headache, fever, chills, nausea or vomiting, chest tightness, wheezing, changes in blood pressure, tachycardia, and aseptic meningitis.[13,86] Before initiation of this therapy, the risks and benefits must be assessed. Available data based on several case series and small uncontrolled studies imply that IVIG may work in specific groups of patients with CU with autoantibodies. However, the lack of strong evidence, need for intravenous access, prolonged infusions, costs, and adverse effects make this medication a less favorable option.

TUMOR NECROSIS FACTOR-α ANTAGONISTS

Three biological tumor necrosis factor-α (TNF-α) antagonists, etanercept (TNF receptor fusion protein against TNF-α), infliximab (mAb against TNF-α), and adalimumab (mAb against TNF-α), have been tried as therapeutic options in different types of urticarial disorders. The rationale for using TNF-α antagonists is that there are data to suggest that CU is associated with an upregulation of TNF-α expression and increased TNF-α production in CU epidermis compared with control, thereby playing a significant role in the pathogenesis of CU.[87,88] One particular patient with a history of refractory delayed pressure urticaria and psoriasis underwent treatment with etanercept 25 mg twice per week for 8 weeks. Symptoms remitted in this patient and antihistamines were no longer needed after 5 days of starting etanercept. Later, etanercept was increased to 50 mg and then switched to infliximab because of uncontrolled psoriasis. The therapeutic effect of TNF-α antagonists on the urticaria persisted throughout the treatment period.[89] Etanercept was also reported to be effective in a patient with cold urticaria and psoriasis.[90] There was a subsequent case series of 6 patients with either CU or urticarial vasculitis who were treated successfully with TNF-α antagonists. Interestingly, all patients experienced a dramatic improvement that lasted for several years in some cases.[91] In another observational study, a total of 20 patients with urticarial disorders (CU with and without autoantibodies, physical urticaria, and neutrophilic urticaria) received either etanercept or adalimumab for periods ranging from 2 to 39 months. Sixty percent had complete to near complete remission, whereas 15% had partial response and the rest were unresponsive.[92]

Although these results are promising, the data are limited to case reports and small uncontrolled studies. Additionally, in many cases, physical urticarias and urticarial vasculitis was the primary problem. Therefore, it is difficult to recommend these agents until better, well-controlled trials are done with close comparison to safer alternatives, including other biologics such as omalizumab.

INTERLEUKIN-1 ANTAGONISTS

CU is a heterogeneous disease with distinct inflammatory processes key in some forms, but not others. IL-1 inhibitors (eg, canakinumab, anakinra) have been studied in distinct subsets of urticarial disease (urticarial vasculitis) with some effectiveness, and this has led to their evaluation in CU.[93] Canakinumab is a human anti–IL-1β mAb that is currently under investigation for CU (clinicaltrial.gov NCT01635127).

SUMMARY

Years of clinical experience and multiple studies suggest that certain biological agents may have an important role in the treatment of antihistamine-refractory CU. Of these biological agents evaluated, omalizumab is the first approved by the FDA for the treatment of CU. The medication is both safe and efficacious for patients with antihistamine-refractory CU. Due to the success of omalizumab, other anti-IgE agents are currently under investigation for use in antihistamine-refractory CU. Although less well studied, other biologics like rituximab, IVIG and TNF-α antagonists may be considered as an alternative option to resistant cases. The success of these biological agents are a benefit to the patients and may help with the understanding of the pathogenesis of CU and further classification of CU endotypes.

REFERENCES

1. Powell RJ, Leech SC, Till S, et al. BSACI guideline for the management of chronic urticaria and angioedema. Clin Exp Allergy 2015;45(3):547–65.
2. Balp MM, Vietri J, Tian H, et al. The impact of chronic urticaria from the patient's perspective: a survey in five European countries. Patient 2015;8(6):551–8.
3. Vietri J, Turner SJ, Tian H, et al. Effect of chronic urticaria on US patients: analysis of the National Health and Wellness Survey. Ann Allergy Asthma Immunol 2015;115(4):306–11.
4. Staubach P, Dechene M, Metz M, et al. High prevalence of mental disorders and emotional distress in patients with chronic spontaneous urticaria. Acta Derm Venereol 2011;91(5):557–61.
5. O'Donnell BF. Urticaria: impact on quality of life and economic cost. Immunol Allergy Clin North Am 2014;34(1):89–104.
6. O'Donnell BF, Lawlor F, Simpson J, et al. The impact of chronic urticaria on the quality of life. Br J Dermatol 1997;136(2):197–201.
7. Broder MS, Raimundo K, Antonova E, et al. Resource use and costs in an insured population of patients with chronic idiopathic/spontaneous urticaria. Am J Clin Dermatol 2015;16(4):313–21.
8. Zuberbier T, Balke M, Worm M, et al. Epidemiology of urticaria: a representative cross-sectional population survey. Clin Exp Dermatol 2010;35(8):869–73.
9. Sanchez-Borges M, Asero R, Ansotegui IJ, et al. Diagnosis and treatment of urticaria and angioedema: a worldwide perspective. World Allergy Organ J 2012;5(11):125–47.
10. Gaig P, Olona M, Munoz Lejarazu D, et al. Epidemiology of urticaria in Spain. J Investig Allergol Clin Immunol 2004;14(3):214–20.
11. Lapi F, Cassano N, Pegoraro V, et al. Epidemiology of chronic spontaneous urticaria: results from a nationwide, population-based study in Italy. Br J Dermatol 2016;174(5):996–1004.
12. 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(5):1270–7.
13. Mitzel-Kaoukhov H, Staubach P, Muller-Brenne T. Effect of high-dose intravenous immunoglobulin treatment in therapy-resistant chronic spontaneous urticaria. Ann Allergy Asthma Immunol 2010;104(3):253–8.
14. Liu JK. The history of monoclonal antibody development—progress, remaining challenges and future innovations. Ann Med Surg (Lond) 2014;3(4):113–6.
15. Kaplan AP. Therapy of chronic urticaria: a simple, modern approach. Ann Allergy Asthma Immunol 2014;112(5):419–25.

16. Normansell R, Walker S, Milan SJ, et al. Omalizumab for asthma in adults and children. Cochrane Database Syst Rev 2014;(1):CD003559.
17. Easthope S, Jarvis B. Omalizumab. Drugs 2001;61(2):253–60 [discussion: 61].
18. Niimi N, Francis DM, Kermani F, et al. Dermal mast cell activation by autoantibodies against the high affinity IgE receptor in chronic urticaria. J Invest Dermatol 1996;106(5):1001–6.
19. Holgate ST, Djukanovic R, Casale T, et al. Anti-immunoglobulin E treatment with omalizumab in allergic diseases: an update on anti-inflammatory activity and clinical efficacy. Clin Exp Allergy 2005;35(4):408–16.
20. Saavedra MC, Sur S. Down regulation of the high-affinity IgE receptor associated with successful treatment of chronic idiopathic urticaria with omalizumab. Clin Mol Allergy 2011;9(1):2.
21. 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(2):337–42.
22. Beck LA, Marcotte GV, MacGlashan D, et al. Omalizumab-induced reductions in mast cell Fc epsilon RI expression and function. J Allergy Clin Immunol 2004; 114(3):527–30.
23. Kawakami T, Galli SJ. Regulation of mast-cell and basophil function and survival by IgE. Nat Rev Immunol 2002;2(10):773–86.
24. Serrano-Candelas E, Martinez-Aranguren R, Valero A, et al. Comparable actions of omalizumab on mast cells and basophils. Clin Exp Allergy 2016;46(1):92–102.
25. Mankad VS, Burks AW. Omalizumab: other indications and unanswered questions. Clin Rev Allergy Immunol 2005;29(1):17–30.
26. Boyce JA. Successful treatment of cold-induced urticaria/anaphylaxis with anti-IgE. J Allergy Clin Immunol 2006;117(6):1415–8.
27. Spector SL, Tan RA. Effect of omalizumab on patients with chronic urticaria. Ann Allergy Asthma Immunol 2007;99(2):190–3.
28. Sands MF, Blume JW, Schwartz SA. Successful treatment of 3 patients with recurrent idiopathic angioedema with omalizumab. J Allergy Clin Immunol 2007; 120(4):979–81.
29. Metz M, Bergmann P, Zuberbier T, et al. Successful treatment of cholinergic urticaria with anti-immunoglobulin E therapy. Allergy 2008;63(2):247–9.
30. Dreyfus DH. Observations on the mechanism of omalizumab as a steroid-sparing agent in autoimmune or chronic idiopathic urticaria and angioedema. Ann Allergy Asthma Immunol 2008;100(6):624–5.
31. Guzelbey O, Ardelean E, Magerl M, et al. Successful treatment of solar urticaria with anti-immunoglobulin E therapy. Allergy 2008;63(11):1563–5.
32. Callejas-Rubio JL, Sanchez-Cano D, Lara MA, et al. Omalizumab as a therapeutic alternative for chronic urticaria. Ann Allergy Asthma Immunol 2008;101(5):556.
33. Kaplan AP, Joseph K, Maykut RJ, et al. Treatment of chronic autoimmune urticaria with omalizumab. J Allergy Clin Immunol 2008;122(3):569–73.
34. Ferrer M, Gamboa P, Sanz ML, et al. Omalizumab is effective in nonautoimmune urticaria. J Allergy Clin Immunol 2011;127(5):1300–2.
35. 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(1):202–9.e5.
36. 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(3): 567–73.e1.

37. Maurer M, Rosen K, Hsieh HJ, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. N Engl J Med 2013;368(10):924–35.

38. Kaplan A, Ledford D, Ashby M, et al. Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. J Allergy Clin Immunol 2013;132(1):101–9.

39. 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 H antihistamines: a randomized, placebo-controlled study. J Invest Dermatol 2015;135(3):925.

40. Staubach P, Metz M, Chapman-Rothe N, et al. Effect of omalizumab on angioedema in H -antihistamine resistant chronic spontaneous urticaria patients: results from X-ACT, a randomised controlled trial. Allergy 2016;71(8):1135–44.

41. Kaplan A, Ferrer M, Bernstein JA, et al. Timing and duration of omalizumab response in patients with chronic idiopathic/spontaneous urticaria. J Allergy Clin Immunol 2016;137(2):474–81.

42. Casale TB, Bernstein JA, Maurer M, et al. Similar efficacy with omalizumab in chronic idiopathic/spontaneous urticaria despite different background therapy. J Allergy Clin Immunol Pract 2015;3(5):743–50.e1.

43. Metz M, Ohanyan T, Church MK, et al. Retreatment with omalizumab results in rapid remission in chronic spontaneous and inducible urticaria. JAMA Dermatol 2014;150(3):288–90.

44. 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(7):868–87.

45. Otto HF, Calabria CW. A case of severe refractory chronic urticaria: a novel method for evaluation and treatment. Allergy Asthma Proc 2009;30(3):333–7.

46. Metz M, Altrichter S, Ardelean E, et al. Anti-immunoglobulin E treatment of patients with recalcitrant physical urticaria. Int Arch Allergy Immunol 2011;154(2):177–80.

47. Brodska P, Schmid-Grendelmeier P. Treatment of severe cold contact urticaria with omalizumab: case reports. Case Rep Dermatol 2012;4(3):275–80.

48. Bindslev-Jensen C, Skov PS. Efficacy of omalizumab in delayed pressure urticaria: a case report. Allergy 2010;65(1):138–9.

49. Rodriguez-Rodriguez M, Antolin-Amerigo D, Barbarroja-Escudero J, et al. Successful treatment of severe delayed pressure angio-oedema with omalizumab. Allergol Immunopathol (Madr) 2014;42(1):78–80.

50. Bullerkotte U, Wieczorek D, Kapp A, et al. Effective treatment of refractory severe heat urticaria with omalizumab. Allergy 2010;65(7):931–2.

51. Carballada F, Nunez R, Martin-Lazaro J, et al. Omalizumab treatment in 2 cases of refractory heat urticaria. J Investig Allergol Clin Immunol 2013;23(7):519–21.

52. Rorie A, Gierer S. A case of aquagenic urticaria successfully treated with omalizumab. J Allergy Clin Immunol Pract 2016;4(3):547–8.

53. Waibel KH, Reese DA, Hamilton RG, et al. Partial improvement of solar urticaria after omalizumab. J Allergy Clin Immunol 2010;125(2):490–1.

54. Aubin F, Avenel-Audran M, Jeanmougin M, et al. Omalizumab in patients with severe and refractory solar urticaria: a phase II multicentric study. J Am Acad Dermatol 2016;74(3):574–5.

55. Namazy J, Cabana MD, Scheuerle AE, et al. The Xolair Pregnancy Registry (EXPECT): the safety of omalizumab use during pregnancy. J Allergy Clin Immunol 2015;135(2):407–12.

56. Liour SS, Tom A, Chan YH, et al. Treating IgE-mediated diseases via targeting IgE-expressing B cells using an anti-CepsilonmX antibody. Pediatr Allergy Immunol 2016;27(5):446–51.

57. Arm JP, Bottoli I, Skerjanec A, et al. Pharmacokinetics, pharmacodynamics and safety of QGE031 (ligelizumab), a novel high-affinity anti-IgE antibody, in atopic subjects. Clin Exp Allergy 2014;44(11):1371–85.

58. Harris JM, Maciuca R, Bradley MS, et al. A randomized trial of the efficacy and safety of quilizumab in adults with inadequately controlled allergic asthma. Respir Res 2016;17:29.

59. Townsend MJ, Monroe JG, Chan AC. B-cell targeted therapies in human autoimmune diseases: an updated perspective. Immunol Rev 2010;237(1):264–83.

60. Mallipeddi R, Grattan CE. Lack of response of severe steroid-dependent chronic urticaria to rituximab. Clin Exp Dermatol 2007;32(3):333–4.

61. Arkwright PD. Anti-CD20 or anti-IgE therapy for severe chronic autoimmune urticaria. J Allergy Clin Immunol 2009;123(2):510–1 [author reply: 511].

62. Chakravarty SD, Yee AF, Paget SA. Rituximab successfully treats refractory chronic autoimmune urticaria caused by IgE receptor autoantibodies. J Allergy Clin Immunol 2011;128(6):1354–5.

63. Steinweg SA, Gaspari AA. Rituximab for the treatment of recalcitrant chronic autoimmune urticaria. J Drugs Dermatol 2015;14(12):1387.

64. Saigal K, Valencia IC, Cohen J, et al. Hypocomplementemic urticarial vasculitis with angioedema, a rare presentation of systemic lupus erythematosus: rapid response to rituximab. J Am Acad Dermatol 2003;49(5 Suppl):S283–5.

65. Swaminath A, Magro CM, Dwyer E. Refractory urticarial vasculitis as a complication of ulcerative colitis successfully treated with rituximab. J Clin Rheumatol 2011;17(5):281–3.

66. Negi VS, Elluru S, Siberil S, et al. Intravenous immunoglobulin: an update on the clinical use and mechanisms of action. J Clin Immunol 2007;27(3):233–45.

67. Ballow M. The IgG molecule as a biological immune response modifier: mechanisms of action of intravenous immune serum globulin in autoimmune and inflammatory disorders. J Allergy Clin Immunol 2011;127(2):315–23 [quiz: 24–5].

68. Leung DY, Schlievert PM, Meissner HC. The immunopathogenesis and management of Kawasaki syndrome. Arthritis Rheum 1998;41(9):1538–47.

69. Dalakas MC. Polymyositis, dermatomyositis and inclusion-body myositis. N Engl J Med 1991;325(21):1487–98.

70. Neunert C, Lim W, Crowther M, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood 2011; 117(16):4190–207.

71. Donofrio PD, Berger A, Brannagan TH 3rd, et al. Consensus statement: the use of intravenous immunoglobulin in the treatment of neuromuscular conditions report of the AANEM ad hoc committee. Muscle Nerve 2009;40(5):890–900.

72. Saini SS. Chronic spontaneous urticaria: etiology and pathogenesis. Immunol Allergy Clin North Am 2014;34(1):33–52.

73. Kaplan AP, Greaves M. Pathogenesis of chronic urticaria. Clin Exp Allergy 2009; 39(6):777–87.

74. Hide M, Francis DM, Grattan CE, et al. Autoantibodies against the high-affinity IgE receptor as a cause of histamine release in chronic urticaria. N Engl J Med 1993;328(22):1599–604.

75. Grattan CE, Francis DM, Slater NG, et al. Plasmapheresis for severe, unremitting, chronic urticaria. Lancet 1992;339(8801):1078–80.

76. O'Donnell BF, Barr RM, Black AK, et al. Intravenous immunoglobulin in autoimmune chronic urticaria. Br J Dermatol 1998;138(1):101–6.

77. Kroiss M, Vogt T, Landthaler M, et al. The effectiveness of low-dose intravenous immunoglobulin in chronic urticaria. Acta Derm Venereol 2000;80(3):225.

78. 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(7):237–42.

79. Asero R. Are IVIG for chronic unremitting urticaria effective? Allergy 2000;55(11):1099–101.

80. Hrabak T, Calabria CW. Multiple treatment cycles of high-dose intravenous immunoglobulin for chronic spontaneous urticaria. Ann Allergy Asthma Immunol 2010;105(3):245 [author reply: 245–6].

81. Dawn G, Urcelay M, Ah-Weng A, et al. Effect of high-dose intravenous immunoglobulin in delayed pressure urticaria. Br J Dermatol 2003;149(4):836–40.

82. Adamski H, Bedane C, Bonnevalle A, et al. Solar urticaria treated with intravenous immunoglobulins. J Am Acad Dermatol 2011;65(2):336–40.

83. Correia I, Silva J, Filipe P, et al. Solar urticaria treated successfully with intravenous high-dose immunoglobulin: a case report. Photodermatol Photoimmunol Photomed 2008;24(6):330–1.

84. Hughes R, Cusack C, Murphy GM, et al. Solar urticaria successfully treated with intravenous immunoglobulin. Clin Exp Dermatol 2009;34(8):e660–2.

85. Maksimovic L, Fremont G, Jeanmougin M, et al. Solar urticaria successfully treated with intravenous immunoglobulins. Dermatology 2009;218(3):252–4.

86. Aubin F, Porcher R, Jeanmougin M, et al. Severe and refractory solar urticaria treated with intravenous immunoglobulins: a phase II multicenter study. J Am Acad Dermatol 2014;71(5):948–53.e1.

87. Hermes B, Prochazka AK, Haas N, et al. Upregulation of TNF-alpha and IL-3 expression in lesional and uninvolved skin in different types of urticaria. J Allergy Clin Immunol 1999;103(2 Pt 1):307–14.

88. Piconi S, Trabattoni D, Iemoli E, et al. Immune profiles of patients with chronic idiopathic urticaria. Int Arch Allergy Immunol 2002;128(1):59–66.

89. Magerl M, Philipp S, Manasterski M, et al. Successful treatment of delayed pressure urticaria with anti-TNF-alpha. J Allergy Clin Immunol 2007;119(3):752–4.

90. Gualdi G, Monari P, Rossi MT, et al. Successful treatment of systemic cold contact urticaria with etanercept in a patient with psoriasis. Br J Dermatol 2012;166(6):1373–4.

91. Wilson LH, Eliason MJ, Leiferman KM, et al. Treatment of refractory chronic urticaria with tumor necrosis factor-alfa inhibitors. J Am Acad Dermatol 2011;64(6):1221–2.

92. Sand FL, Thomsen SF. TNF-alpha inhibitors for chronic urticaria: experience in 20 patients. J Allergy (Cairo) 2013;2013:130905.

93. Krause K, Mahamed A, Weller K, et al. Efficacy and safety of canakinumab in urticarial vasculitis: an open-label study. J Allergy Clin Immunol 2013;132(3):751–4.e5.