Urticaria Therapy and Management. Looking Forward

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Emek Kocatürk, Zuotao Zhao, and Ana M. Giménez-Arnau

Core Messages

The future of chronic urticaria depends on three major steps in the understanding of the disease. First, how shall we best manage the disease? Urticaria Reference and Excellence centers are the answer to this question; these are the centers established by GA^{2}LEN where the excellence in care and management of chronic urticaria is based on particular criteria and assured to follow the most recent guidelines. Second, does precision medicine apply to the treatment of chronic urticaria, are there biomarkers to show disease activity and response to treatment? The answer to this question is not established currently but CRP, D-Dimer or Total IgE/IgERI were suggested as biomarkers of disease activity response to treatments. Third, what are the future drugs for the treatment of chronic urticaria? We have a wide range of future drugs that are currently being tested for the treatment of chronic urticaria such as ligelizumab, siglec-8, bruton kinase inhibitors, anti-IL-5, Syk-inhibitors, and dupilumab. Future will show how effective these drugs will be and if there will be specific endotypes of chronic urticaria that will benefit from silencing a particular pathway in the pathogenesis of the disease.

E. Kocatürk
Department of Dermatology, Koç University School of Medicine, Istanbul, Turkey

Z. Zhao
Department of Dermatology, First Hospital, Peking University, Beijing, China

A. M. Giménez-Arnau (✉)
Department of Dermatology, Hospital del Mar, IMIM, Universitat Autònoma, Barcelona, Spain
e-mail: 22505aga@comb.cat

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15.1 Looking Forward, Clinical Knowledge of Chronic Urticaria (CU)

Chronic Urticaria (CU) is a heterogeneous condition that causes significant morbidity [1, 2]. CU is characterized by the sudden appearance of wheals, angioedema, or both that persist for 6 weeks or longer [2]. Spontaneous CU (CSU) shows unpredictable symptoms, while inducible CU (CIndU) is provoked by, e.g., cold, heat, pressure, friction, or protein contact among others. Both types can be concomitantly present in the same patient. The average duration of CSU episodes is from 1 to 5 years [3, 4]. CSU is estimated to affect from 0.5 to 1% of the general population, with an annual incidence rate of 1.4% and it seems to increase [5, 6]. The exact CU prevalence and patient characteristics are still unknown in many countries. Because CSU imposes a significant economic burden and also has a substantial negative impact on patients' quality of life (QoL) there is an evident interest to identify such patients that are not medically controlled. An effective treatment as soon as the CSU or CIndU episodes start is crucial [7–9].

The EAACI/GA^{3}LEN/EDF/WAO Urticaria Guidelines, acknowledged and accepted by the European Union of Medical Specialists (UEMS) with the participation of 48 delegates of 42 national and international societies is the most global guideline in urticaria, specially focused in chronic urticaria [2]. It is a clear and evidence based guideline nevertheless the degree of monitoring the urticaria guidelines by primary care physicians and specialists is generally still poor [10]. It is important to develop anticipated efforts in continuing medical education that can improve the critical judgment of the guidelines and their implementation in daily medical assistance.

Successful approach to CU patients would preferentially be developed in local, national, or international networks of experts. In this sense "Centers of reference and excellence in urticaria" (UCAREs) can help to improve the management of hard to treat conditions such as urticaria. The main aims of GA^{2}LEN UCAREs are to provide excellence in urticaria management, to increase the knowledge of urticaria by research and education, and to promote the awareness of urticaria by advocacy activities. This program was created in 2016 and promotes the "never give up attitude" treating CU [11]. In the immediate future coming from a communal work some present unmet needs will have a global answer as, e.g., the dilemma of differential diagnosis, indicators of urticaria prognosis, or the management of urticaria in pregnancy/lactation or geriatrics.

Very little is known about the genetic profile of the urticaria patients who suffer CSU or CIndU. Some recent approach to the transcriptome of patients suffering a severely active CSU refractory to antihistamine treatment through the bioinformatic analysis of the whole Human Genome with Oligo Microarrays and Quantitative Real-Time Polymerase Chain Reaction (qPCR) showed an overall immunological skin involvement showing a peculiar gene profile involving lesional and non-lesional skin. The wheal overexpressed genes are involved in a variety of biological functions as epidermal differentiation, intracellular signal function, transcriptional

factors, cell cycle differentiation, inflammation, or coagulation. Differentially expressed genes uniformly increase or decrease along the skin worsening until the wheal appearance [12]. Omalizumab's effect on gene expression in skin biopsies from CSU patients was shown over upregulated transcript in lesional skin (vs non-lesional and/or healthy volunteers skin) suggested increased mast cell/leukocyte infiltration (FCER1G, C3AR1, CD93, S100A8, and S100A9), increased oxidative stress, vascularization (CYR61), and skin repair events (KRT6A, KRT16) [13]. Nevertheless genotype expression and its further correlation with CSU phenotypes are still unknown.

CSU shows a heterogeneous activity, evolution, associated comorbidities, and response to treatment. The identification of clinical prognostic factors that help to predict disease course and response to standardized treatments would be very useful. Factors that have been described as worst prognostic factors in terms of CSU duration and/or CSU activity: suffer multiple CSU episodes (19.2% suffered more than one lifetime CSU), late-onset (63.6% showed >45 years once the CSU started), concomitant CIndU (20.2%), and functional serum autoreactivity [14]. CSU+CIndU patients required more frequent therapy after 5 years and higher doses of second-generation H1-antihistamines [14]. According to Curto L et al, 84.6% of patients with a baseline Urticaria Activity Score 7 (UAS7) between 16 and 42 required ciclosporin or omalizumab to achieve symptom control in contrast to 15.4% of patients with baseline UAS7 between 0 and 15 ($p = 0.0013$) [14]. Although different types of CU shared a common clinical expression, phenotypically the patients may show differences regarding triggers, activity, prognosis, and therapeutic response. The knowledge of phenotypical differences observed in CU helps to design an individual management plan improving symptoms control and quality of life, decreasing the burden of the disease.

The success of the management of CSU lies on a strategic plan. The EAACI/GA2LEN/EDF/WAO Urticaria guideline is continuously updated [2]. By consensus, a successful therapy should target the rapid and complete resolution of signs (hives and angioedema) and symptoms (itch and pain). A basic principle of efficacy and safety is desirable; it is the therapeutic goal, as the clinical experience holds that treatment should continue for extended periods of time, with adaptations according to changes in symptoms. Nowadays, the unique recommended third line treatment consists of adding omalizumab and we can define accurately a protocol of its use in daily practice. We have learned from our practice and we have data on prediction of CSU fast-slow or no response, the need to up-dose, relapse, and retreatment, use in special populations, efficacy for angioedema and CIndUs, or safety of long-term treatment [15]. Recently, several reports have suggested that certain parameters could be considered as potential disease-related biomarkers. Moreover, with the advent of such biomarkers, newer biologic agents are coming forth to revolutionize management of CSU. Based on molecular and genetic pathogenic findings several new treatments can also be proposed for CU. Ongoing new therapeutic development includes more potent anti-IgE therapy and other drugs targeting different pathogenic pathways.

15.2 Emerging Biomarkers in CU, Looking Forward

According to the National Institute of Health (NIH) Biomarkers Definitions Working Group, a biomarker is a "characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention." Essential characteristics of a good biomarker are its sensitivity, specificity, and reproducibility for the identification and/or measurement of a particular disease state [16]. In addition, the ease with which the biomarker can be collected and measured at the point of care is crucial [17]. The identification and validation of reliable biomarkers in CSU would be useful in CU to define the patient's disease status leading to a more individualized and personalized treatment and follow-up not only in everyday clinical care, but also in clinical trials.

15.2.1 Biomarkers for Disease Activity

Several markers have been investigated for their possible link to CSU activity. Inflammatory mediators such as the C-reactive protein (CRP) and interleukin (IL)-6 are increased in patients with more active CSU and are significantly lower upon spontaneous remission [18–29]. Likewise, levels of mean platelet volume (MPV), which is considered a marker of platelet reactivity, also show a positive correlation with CSU activity [30–42]. CSU is an immune-mediated chronic inflammatory disease resulting from immunological activation events following the exposure to different triggers [43]. The detection of increased levels of D-dimer and prothrombin fragment 1+2 (F1+2) in patients with more active disease demonstrates the involvement of the coagulation cascade and fibrinolysis in CSU, positioning themselves as potential biomarkers of disease activity [18–29, 34–46].

On the other hand, various abnormalities related to basophils and their functions have also been described in patients with active disease. For example, a negative correlation between blood basophil count and CSU activity suggesting that circulating basophils may be recruited from blood into urticarial skin lesions during the activity of the disease [47–50]. Increased levels of basophil CD63 or CD203c expression induced by CSU serum may also predict the highest CSU activity reflected by impairment in quality of life, higher frequency of emergency department use, and higher itch severity [51–53]. Several studies also support the notion that a positive autologous serum skin test (ASST), which is a simple in-vivo clinical test suggesting an autoimmune pathogenesis, is linked to more active CSU [54–57].

In summary, CRP, IL-6, MPV, D-dimer, and F1+2 deserve further exploration for their value as biomarkers of disease activity based on the high level of evidence (i.e., several studies from different centers showing the same association), consistency (i.e., reproducibility), feasibility, and clinical relevance. Nevertheless, other suggested biomarkers, especially those related to inflammation and coagulation, are not specific enough for urticaria. Its interpretation in CSU should be prudent.

15.2.2 Biomarkers for Response to Treatment

The establishment of personalized treatment plans remains one of the biggest challenges in CSU. In this regard, and given the emergence of new therapies in CSU, there is a growing interest to look for objective markers that reliably predict the disease prognosis and the effectiveness of a specific therapeutic intervention.

In the case of antihistamine therapy, D-dimer is the most promising biomarker. In an Italian study, patients with insufficient response to antihistamines were more likely to present elevated D-dimer levels [58]. This observation was confirmed by Kolkhir et al., who suggest that the evaluation not only of D-dimer, but also fibrinogen, CRP and erythrocyte sedimentation rate (ESR) should be considered before starting treatment with non-sedating antihistamines, since high levels of these markers may predict an unsatisfactory therapeutic response [28]. Another investigation reported that antihistamine-resistant CSU might show increased complement C5a fraction, higher disease activity; longer duration of wheals, and higher positivity of ASST [59].

Baseline levels of D-dimer have been also linked to response to ciclosporin. D-dimer levels showed a highly significant negative correlation with response to treatment and were also considered a useful tool to monitor this clinical response [60]. Another biomarker for ciclosporin responsiveness could be the basophil histamine release assay (BHRA). Thus, two independent investigations, including a double-blind placebo-controlled study, showed that patients with a positive BHRA are more likely to show a satisfactory response to ciclosporin than those with a negative BHRA [61, 62].

Regarding the undergoing treatment with omalizumab, a significant association has been shown between levels of IL-31, a major dermal pruritogen, and response to anti-IgE therapy, with lower baseline levels observed in patients showing a satisfactory clinical response [63]. Levels of total serum IgE and the high-affinity IgE receptor (FcεRI) expression on basophils are also interesting biomarkers for omalizumab responsiveness. In two recent studies Deza and coworkers reported how slow and complete non-responders CSU patients to omalizumab showed significantly lower baseline levels of basophil FcεRI expression than fast responders, suggesting that the deficient FcεRI downregulation experienced during treatment could be an explanation for the non-responder status [64, 65]. Ertas and coworkers postulate that total IgE levels and their change may also predict omalizumab responsiveness during treatment, particularly by the week 4/baseline ratio of total IgE [66]. Lastly, Palacios et al observed that the lack of basophil CD203-c upregulating activity, which is thought to reflect the presence of autoantibodies to IgE and/or FcεRI receptor, might also correlate with the clinical response to anti-IgE therapy [67]. In addition to the response to treatment, some studies investigated potential biomarkers for different categories of omalizumab response. For example, a positive BHRA and ASST have been proposed as predictors of slow therapeutic response, [68] while increased IgE levels seem to be linked to faster relapse in patients with omalizumab-discontinued CSU [69].

15.2.3 Biomarkers for Disease Course

The biomarkers discussed by their usefulness to predict the course of the disease, i.e., the time to spontaneous remission, show still a low level of evidence due to the small number of available studies. The most promising biomarker for CSU course seems to be the presence of serum anti-thyroid antibodies (ATA). Disease duration is significantly longer if ATA are detected in CSU patients [70]. Levels of vitamin D and total IgE have been also linked to disease duration. Woo et al showed that serum vitamin D levels are more likely to be critically low in CSU patients and can also be inversely related to disease duration [71, 72]. Meanwhile, Kessel et al. showed a significant association between increased total serum IgE levels and urticaria duration lasting more than 2 years [73].

Due to limited published data and different methodologies and/or study designs used, there is sometimes conflicting evidence for a particular biomarker. For example, profound basopenia has been linked to increased serum autoreactivity, greater impairment in quality of life, and poorly controlled disease in adult patients with CSU [47]. However, the same markers have been associated with a better prognosis in pediatric CSU. Children with CSU showed high scores on the basophil activation test using CD63 marker expression and absence of blood basophils being more likely to exhibit an earlier spontaneous resolution of urticaria [74]. This favorable prognosis associated with higher CD63 expression could be related to autoantibody production induced by transient viral and bacterial infections, which are quite common in children and represent well-known triggers of urticaria. Differences in etiologic and/or pathogenic factors (e.g., differences in the mechanism of autoimmunity) in both groups of patients could explain such results [75–77].

In addition to laboratory values, some clinical markers have been also linked to CSU duration. Concomitant angioedema or inducible urticaria may show longer disease duration, longer time to remission, and/or lower resolution rates [78–81]. Also, disease activity, evaluated through clinical scores, could also be related to CSU duration [57, 73, 82]. Some rare clinical features, such as arterial hypertension or hypersensitivity reactions to non-steroidal anti-inflammatory drugs, may result in a distinct CSU phenotype showing longer disease duration [83, 84].

To conclude, modern techniques allowed the identification of potential useful CSU biomarkers, such as RNA sequencing, microarrays, and proteomic or metabolomic analysis [12]. For example, by proteomics analysis, serum clusterin, a protein involved in multiple functions including modulation of the complement system, regressing angiogenesis, and cleaning bioactive cell debris, has been found to be increased in patients with a positive ASST and in those showing a satisfactory clinical response to antihistamine therapy [85]. Similarly, polymorphisms determined by Sequenom Mass Array technology on the FCER1A gene, which encodes the α-chain of the FcεRI receptor, have been linked to the therapeutic efficacy of non-sedating antihistamines and also to the risk for CSU in Chinese patients [86]. Recently, certain microRNAs were found to be significantly increased in patients

with positive CU index (a functional anti-FcεRI test that supports the autoimmune basis of the disease) [87]. These microRNAs, which may be considered potential biomarkers for chronic autoimmune urticaria, target some genes that are associated with several biologic functions such as cellular movement, tissue development, regulation of leukocyte migration or inflammatory response. Although larger population sizes and multicenter studies are needed to confirm such preliminary observations, the implementation of these techniques might help in the near future to not only identify potential disease biomarkers of the disease, but also to increase our knowledge regarding the pathogenesis of CSU.

15.3 Treatments for Chronic Urticaria, Looking Forward

Treatment of chronic urticaria (CU) moved forward in the recent few years after the introduction of omalizumab into standard treatment. Treatment with omalizumab provides effective and safe symptom control in 52–90% of the patients and urticaria activity scores decrease significantly in clinical trials and real life studies [3, 88–94]. Still there is a proportion of CU patients that require more effective treatments. There are a number of clinical trials now running on for the treatment of CU (Table 15.1). Potential other molecules will also be mentioned which could be targets of treatment in the future (Fig. 15.1).

Table 15.1 Drugs under investigation for CU

Study drug	Type of the drug	Clinicaltrials.gov identifier	Phase
Ligelizumab (QGE-031)	Anti-IgE	NCT02477332	P2b
		NCT02649218	P2
		NCT03437278	P2b
		NCT03580356	P3
		NCT03580369	P3
UB-221	Anti-IgE	NCT03632291	P1
GSK2646264	Syk inhibitor	NCT02424799	P1
AK002	Siglec-8	NCT03436797	P2
Abatacept	Soluble protein[a]	NCT00886795	P1/P2
Canakinumab	Anti-IL-1	NCT01635127	P2
Rilonacept	Anti-IL-1	NCT02171416	P2
Fenebrutinib	Bruton kinase inhibitor	NCT03137069	P2
		NCT03693625	P2
Benralizumab	Anti-IL-5Rα	NCT03183024	P4
Mepolizumab	Anti-IL-5	NCT03494881	P1
Dupilumab	Anti-IL-4Rα		P2

[a]Abatacept is a fusion protein binds to CD80 and CD86 receptors on APC and blocks the interaction of CD80/CD86 receptors to CD28 and inhibiting T cell proliferation and B cell immunological response

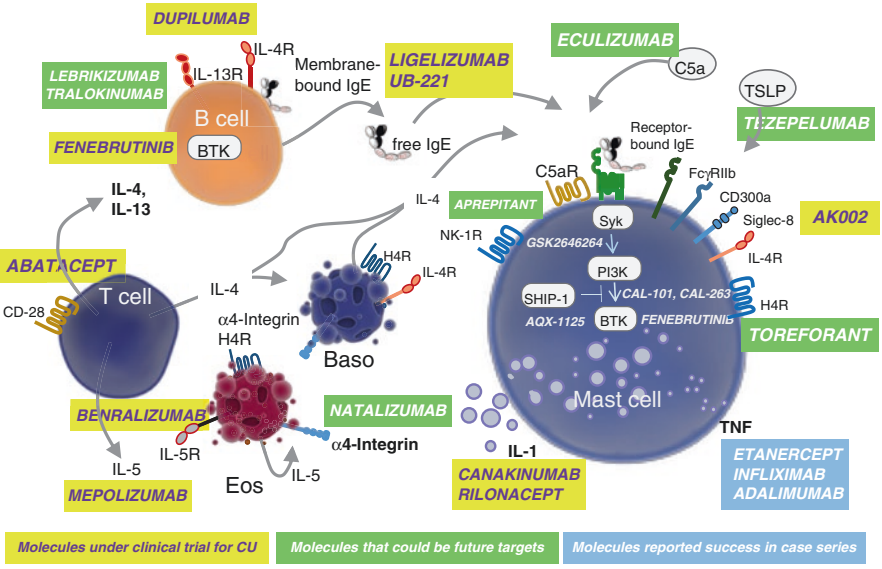

Fig. 15.1 Potential future targets of CU treatment. *Baso* basophil, *Eos* eosinophil, *H4R* histamine 4 receptor, *NK* neurokinin, *C5* complement 5, *IgE* immunoglobulin, *IL* interleukin, *LTR, PI3K* Phosphoinositide 3-kinase, *SHIP* Src-homology-containing inositol phosphatase 1, *Syk* spleen tyrosine kinase, *TSLP* thymic stromal lymphopoietin, *TNF* tumor necrosis factor, *BTK* Bruton kinase, *Siglec* sialic acid-binding, immunoglobulin-like lectins

15.3.1 Mast Cells/Basophils

15.3.1.1 Anti-IgEs

The most frequent cause of chronic spontaneous urticaria (CSU) is considered to be autoimmunity where two types of reactions are implicated. Type I autoimmunity is characterized by IgE to autoallergens and also termed as "autoallergy" while type-IIb autoimmunity is characterized by, e.g., IgG autoantibodies to IgE or its receptor (type 2b) and is different from cytotoxic/cytolytic hypersensitivity (type 2a) involving complement induced lysis [95, 96]. The fast responders to omalizumab are considered to have type I autoimmunity in which omalizumab rapidly binds free IgE autoantibodies and thus reduce mast cell activation, while slow responders are suggested to have type 2b autoimmunity in which the response depends on FcεRI receptor loss [95].

The growing interest on IgE as a therapeutical target promoted the production of new IgE-targeting strategies among which ligelizumab has the highest evidence and will be available soon.

Ligelizumab (QGE031)
Ligelizumab is a humanized IgG1 monoclonal antibody that binds with higher affinity to IgE than omalizumab. Like omalizumab, it inhibits the binding of free IgE to mast cells and basophils, thereby blocking the allergic reaction cascade. It shows 6 to 9-fold greater suppression of allergen-induced skin prick tests and provides greater and longer suppression of free IgE and IgE on the surface of circulating basophils [97]. The phase 2b study of ligelizumab included 382 patients with CSU (NCT02477332) and examined the efficacy and safety of ligelizumab compared to omalizumab. At the end of week 20, both ligelizumab 72 mg and 240 mg showed earlier and greater improvements in clinical responses compared to ligelizumab 24 mg, omalizumab 300 mg, and placebo [98]. Four studies are running to evaluate the efficacy and safety of ligelizumab in adolescent and adult patients with CSU (NCT03437278, NCT03580356, NCT03580369) as well as a safety extension study to evaluate the long-term safety of 240 mg subcutaneous (sc) ligelizumab given every 4 weeks for 52 weeks (NCT02649218). It seems that ligelizumab would be more effective than omalizumab in treating slow responders where type-IIb autoimmunity has been implicated.

UB-221
UB-221 is a third generation humanized anti-IgE monoclonal antibody which can neutralize IgE and can also regulate B cells through CD23, thereby blocking the production of IgE [99]. A phase I, open-label, dose-escalation study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of a single dose of UB-221 as an add-on therapy in patients with CSU is now running (NCT03632291).

15.3.1.2 Other Anti-IgE Strategies
Many strategies to target IgE are on the way of production, which focus on IgE neutralization in blood, IgE-effector cell elimination, or IgE+ B cell reduction [100]. IgE-Fc3-4 mutant (IgE-R419NFc3-4), MEDI4212, recombinant single chain variable fragment (ScFv) antibody, antiFcεRI Fab conjugated celastrol loaded polymeric micelles, bispecific IgECD3 antibody, XmAb7195 constitute examples for new anti-IgE strategies [101–107]. DARPins (designed ankyrin repeat protein) are genetically engineered antibody mimetic proteins, which are small, inexpensive, rapidly acting, and can be used as oral drugs [108]. DARPins bi53_79 and E2_79 have shown to be promising inhibitors of IgE-mediated MC activation [108]. DARPins are promising candidates for the treatment of allergic diseases as well as CSU but their potential for use in humans should be confirmed [109].

15.3.1.3 Molecules that Target Intracellular Signalling Pathways in Mast Cells
The heightened releasability of mast cells and basophils in patients with urticaria might indicate potential treatment targets at this pathway [49]. Spleen tyrosine kinase (Syk) is a promoter, while Src homology 2 containing inositol phosphatases (SHIP-1 and SHIP-2) are inhibitors of histamine release and cytokine, leukotriene and prostaglandin synthesis [110]. Phosphatidylinositol 3-kinase (PI3K) is not only

involved in IgE-dependent MC activation, but is also important for KIT-mediated (and other stimulatory receptor) signals [111]. Syk-inhibitors, SHIP-activators, and PI3K inhibitors can block the release of all mediator types from mast cells and might have implications in treating disorders where mast cells play a role. PI3K inhibitors CAL-101 and CAL-263 have been evaluated for allergic rhinitis [(NCT00836914) and (NCT01066611) and a SHIP-1 activator (AQX-1125) is evaluated for patients with atopic dermatitis (NCT02324972). A Syk inhibitor GSK2646264 is currently being evaluated in a cream formulation in a randomized, double blinded study to assess its safety, tolerability, pharmacodynamics, and pharmacokinetics in healthy controls and patients with cold urticaria or CSU (NCT02424799) [112]. The study was completed in November 2017 but no study results published yet.

15.3.1.4 Other Targets on Mast Cells

The surface inhibitory receptors on mast cells could also be targets of treatment for CSU and allergic disorders. The inhibitory receptors, CD300a, FcγRIIB, and Siglec-8 were shown expressed on mast cells and basophils [113]. AK002 is a humanized non-fucosylated immunoglobulin G1 (IgG1) monoclonal antibody targeting Siglec-8, a member of the CD33-related family of sialic acid-binding, immunoglobulin-like lectins (Siglecs) [114]. A Phase 2a, pilot study is now assessing the efficacy and safety of AK002 (Siglec-8) in subjects with antihistamine-resistant CU (NCT03436797). The drug will be given as monthly intravenous infusions at up to 3 mg/kg for 3 doses. All patients enrolled in the study will receive 6 monthly infusions of AK002 and will then be followed for another 8 weeks.

15.3.2 T Cells

The histopathology of CU wheals is characterized by a perivascular mixed infiltrate composed of predominantly CD4+T lymphocytes similar to allergen-mediated late-phase skin reactions, but the cytokine profile is characterized by an increase in IL-4, IL-5, and interferon-gamma, which is suggestive of a mixed Th1/Th2 response [115–117]. Interventions targeting T cells and T cell cytokines could provide benefit for the treatment of CSU.

15.3.2.1 Abatacept

Abatacept is a fusion protein, which inhibits T cell activation by blocking the specific interaction of CD80/CD86 receptors with CD28 and thereby inhibiting T cell proliferation and B cell immunological response [118]. A pilot study of the safety and efficacy of abatacept in patients with CU (NCT00886795) has been completed and 4 of the 4 participants provided a clinically detectable improvement with none of them reporting serious adverse events.

15.3.2.2 Anti-IL-4/IL-13

The inhibition of the cytokines IL-4 or IL-13 suppresses IgE synthesis. Dupilumab is a fully humanized monoclonal antibody (mAb) which blocks the effects of IL-4 and IL-13 by binding to the common α-chain of the IL-4 receptor and it decreases IgE levels by approximately 40% [119, 120]. Approved by the FDA for the treatment of moderate-to-severe atopic dermatitis in 2017 [121]. Biologicals directed against IL-4Rα receptors are AMG-317, dupilumab, and pitrakinra [122]. Anti-IL-13 mAbs are ABT-308, anrukinzumab, IMA-026, lebrikizumab, CNTO, 5825, GSK679586, QAX576, and tralokinumab [123]. Given the effectivity of these agents in lowering IgE levels and the Th1/Th2 mixed infiltrate shown in wheals, dupilumab targeting IL-4 and IL-13 is now being investigated in a phase 2 clinical trial (NCT03749135) for the treatment of CSU patients who are symptomatic despite H1-antihistamine treatment.

15.3.2.3 Anti-IL-1 Therapies

Different types of urticaria including delayed pressure urticaria and cold urticaria could benefit from IL-1 blocking therapies [124, 125]. The efficacy of canakinumab (human monoclonal antibody that specifically targets IL-1β is now being evaluated in patients with moderate-to-severe CU (URTICANA)) (NCT01635127) while rilonacept (is a soluble decoy receptor, neutralizes either IL-1α or IL-1β) is being investigated for cold contact urticaria (NCT02171416). The latter study has been completed but no results have been posted yet.

15.3.3 B Cells

15.3.3.1 Bruton's Tyrosine Kinase (BTK) Inhibitor GDC-0853

Bruton's tyrosine kinase (BTK) is critically involved in the signalling cascades of B cell antigen receptor (BCR) activation in B cells, some toll-like receptor (TLR) signalling events in B cells, myeloid cells, and dendritic cells as well as Fc receptor binding of immune complexes in myeloid cells [126]. Preclinical studies have indicated that inhibition of BTK activity might offer a potential treatment in autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus. GDC-0853 (fenebrutinib) is a small, highly selective, orally administered inhibitor of BTK which is now being evaluated in an ongoing phase IIA, multicenter, randomized, double-blind, placebo-controlled pilot study in patients with refractory CSU (NCT03137069). A long-term safety and efficacy study of fenebrutinib is also running (NCT03693625) in which participants will receive open-label fenebrutinib at a dose of 200 milligram (mg) orally twice a day. Other BTK inhibitors for CSU are in development.

15.3.4 Eosinophils

15.3.4.1 Anti- IL-5 Pathway

The eosinophils role in CU pathophysiology, by means of triggering the tissue factor pathway of coagulation cascade and as a source of vascular endothelial growth factor, was postulated [127]. IL-5 induces the maturation, activation, and

recruitment of eosinophils. Successful use of anti-IL-5 inhibitors, mepolizumab and reslizumab has been reported in two patients with CSU [128, 129]. Benralizumab binds to the α-chain of the IL-5 receptor present on both eosinophils and basophils, resulting in depletion of these key inflammatory cells through antibody-dependent cell-mediated cytotoxicity [17]. The efficacy of benralizumab is now being evaluated in a Phase 4 study in CSU patients who are refractory to treatment with H1-antihistamines (NCT03183024). The drug will be given once a month for 3 months and the estimated study completion date will be June 2018. A phase 1 study (NCT03494881) now evaluates the efficacy of 100 mg subcutaneous injections of mepolizumab at week zero, 2, 4, 6, and 8 for a total of 5 doses in CSU patients.

15.3.5 Other Targets that Might have Implications for the Future

As the role of neuroinflammation has been repeatedly reported for CSU [130, 131], therapies that target neuropeptide induced inflammation such as aprepitant, serlopitant, tradipitant, and orvepitant could be future treatment options especially for patients showing stress induced exacerbations [132]. Cellular adhesion molecules such as ICAM-1, ELAM-1, VCAM-1, and P-selectin shows an upregulation in CU and cell adhesion inhibitors such as natalizumab (monoclonal antibody against α-4-integrin) might have a role in the treatment of CSU in the future [133–135]. TSLP is an epithelial-cell-derived cytokine that drives allergic inflammatory responses by acting through the innate immune system and has been shown to be increased in lesional but not non-lesional skin of CSU patients [120, 136]. Drugs such as Tezepelumab (AMG 157) which is a humanized monoclonal antibody that binds TSLP and prevents interaction with its receptor could also be an option to treat CSU patients. C5a receptor blockade of basophils or complement depletion has been shown to reduce the histamine-releasing function of autoantibody-positive sera from CSU patients in vitro [137], this observation might open a new approach like targeting C5 with antibodies such as eculizumab [138]. The discovery of the histamine H4 receptor (H4R) provided a new drug target for the development of novel antihistamines. H4 receptors have been shown to modulate the function of mast cells and basophils, and in experimental models they show some promise in alleviating histamine-evoked itch [139–141]. An H4R antagonist, toreforant has been tested in clinical studies in patients with rheumatoid arthritis, asthma, or psoriasis and it could be a promising target for the future approach in CSU treatment [142]. TNF-α antagonists have been reported to be effective in 60% of 20 CSU patients of a retrospective case series [143], including some omalizumab non-responders, and therefore TNF-α antagonists could be an option in patients not responding to omalizumab and cyclosporine.

As the biologicals market extend, more drugs will be tested in clinical trials and a precision medicine approach will be available in CU patients which will consider the comorbidities and pathomechanisms enrolled in an individual patient.

15.4 Unmet Needs for Chronic Urticaria, Looking Forward

Looking forward in CU implies to improve some unmet needs, as it is, the early identification of such patients that are not medically controlled because the implementation of effective treatments as soon as the CSU or CIndU episodes start is crucial. With this objective a continuous effort in medical education can improve guidelines implementation in daily medical assistance. Active CU networks would help to increase CU knowledge solving global clinical and epidemiologic dilemmas. Phenotype and genotype approach started but genotype expression and its further correlation with CSU phenotypes are still unknown. The identification and validation of reliable biomarkers in CSU would be useful in CU to define the patient's disease status leading to a more individualized and personalized treatment and follow-up. This individual management plan improving symptoms control and quality of life would decrease the burden of CU. Ongoing new therapeutic developments to improve CU management are based on the principle defined by efficacy and safety with the objective to obtain as fast as possible the complete control of symptoms.

References

1. Labrador-Horrillo M, Ferrer M. Profile of omalizumab in the treatment of chronic spontaneous urticaria. Drug Des Devel Ther. 2015;9:4909–15.
2. Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B, Bernstein JA, Bindslev-Jensen C, Brzoza Z, Buense Bedrikow R, Canonica GW, Church MK, Craig T, Danilycheva IV, Dressler C, Ensina LF, Giménez-Arnau A, Godse K, Gonçalo M, Grattan C, Hebert J, Hide M, Kaplan A, Kapp A, Katelaris CH, Kocatürk E, Kulthanan K, Larenas-Linnemann D, Leslie TA, Magerl M, Mathelier-Fusade P, Meshkova RY, Metz M, Nast A, Nettis E, Oude-Elberink H, Rosumeck S, Saini SS, Sánchez-Borges M, Schmid-Grendelmeier P, Staubach P, Sussman G, Toubi E, Vena GA, Vestergaard C, Wedi B, Werner RN, Zhao Z, Maurer M. The EAACI/GA^{2}LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. The 2017 revision and update. Allergy. 2018;73(7):1393–414.
3. Maurer M, Rosén K, Hsieh HJ, Saini S, Grattan C, Gimenéz-Arnau A, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. N Engl J Med. 2013;368(10):924–35.
4. Beltrani VS. An overview of chronic urticaria. Clin Rev Allergy Immunol. 2002;23(2):147–69.
5. Bernstein JA, Lang DM, Khan DA, Craig T, Dreyfus D, Hsieh F, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. J Allergy Clin Immunol. 2014;133(5):1.270–7.
6. Lapi F, Cassano N, Pegoraro V, Cataldo N, Heiman F, Cricelli I, et al. Epidemiology of chronic spontaneous urticaria: results from a nationwide, population-based study in Italy. Br J Dermatol. 2016;174(5):996–1.004.
7. Yosipovitch G, Greaves M. Chronic idiopathic urticaria: a "Cinderella" disease with a negative impact on QoL and health care costs. Arch Dermatol. 2008;144(1):102–3.
8. Ferrer M. Epidemiology, healthcare, resources, use and clinical features of different types of urticaria. Alergológica 2005. J Investig Allergol Clin Immunol. 2009;19(Suppl 2):21–6.
9. Maurer M, Abuzakouk M, Bérard F, Canonica W, Oude Elberink H, Giménez-Arnau A, et al. The burden of chronic spontaneous urticaria is substantial: real-world evidence from ASSURE-CSU. Allergy. 2017;72(12):2005–16.

10. Maurer M, Abuzakouk M, Bérard F, Canonica W, Oude Elberink H, Giménez-Arnau A, Grattan C, Hollis K, Knulst A, Lacour JP, Lynde C, Marsland A, McBride D, Nakonechna A, de Frutos JO, Proctor C, Sussman G, Sweeney C, Tian H, Weller K, Wolin D, Balp MM. The burden of chronic spontaneous urticaria is substantial: real-world evidence from ASSURE-CSU. Allergy. 2017;72(12):2005–16. https://doi.org/10.1111/all.13209. Epub 2017 Jul 10.
11. Maurer M, Metz M, Bindslev-Jensen C, Bousquet J, Canonica GW, Church MK, Godse KV, Grattan CE, Hide M, Kocatürk E, Magerl M, Makris M, Meshkova R, Saini SS, Sussman G, Toubi E, Zhao Z, Zuberbier T, Gimenez-Arnau A. Definition, aims, and implementation of GA(2) LEN Urticaria Centers of Reference and Excellence. Allergy. 2016;71(8):1210–8.
12. Giménez-Arnau A, Curto-Barredo L, Nonell L, Puigdecanet E, Yelamos J, Gimeno R, Rüberg S, Santamaria-Babi L, Pujol RM. Transcriptome analysis of severely active chronic spontaneous urticaria shows an overall immunological skin involvement. Allergy. 2017;72(11):1778–90.
13. Metz M, Torene R, Kaiser S, Beste MT, Staubach P, Bauer A, Brehler R, Gericke J, Letzkus M, Hartmann N, Erpenbeck VJ, Maurer M. Omalizumab normalizes the gene expression signature of lesional skin in patients with chronic spontaneous urticaria: a randomized, double-blind, placebo-controlled study. Allergy. 2019;74(1):141–51. https://doi.org/10.1111/all.13547. [Epub ahead of print].
14. Curto-Barredo L, Archilla LR, Vives GR, Pujol RM, Giménez-Arnau AM. Clinical features of chronic spontaneous urticaria that predict disease prognosis and refractoriness to standard treatment. Acta Derm Venereol. 2018;98(7):641–7.
15. Giménez Arnau AM, Valero Santiago A, Bartra Tomás J, Jáuregui Presa I, Labrador-Horrillo M, Miquel Miquel FJ, de Frutos JO, Sastre J, Silvestre Salvador FJ, Ferrer Puga M. Therapeutic strategy according to the differing patient response profiles to omalizumab in chronic spontaneous urticaria. J Investig Allergol Clin Immunol. 2019;29:338–48.
16. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther. 2001;69:89–95.
17. Casale TB. Biologics and biomarkers for asthma, urticaria, and nasal polyposis. J Allergy Clin Immunol. 2017;139:1411–21.
18. Kasperska-Zajac A, Grzanka A, Misiolek M, Mazur B, Machura E. Pentraxin-3 as a local inflammatory marker in chronic spontaneous urticaria. Cytokine. 2015;76:566–8.
19. Grzanka A, Machura E, Mazur B, et al. Relationship between vitamin D status and the inflammatory state in patients with chronic spontaneous urticaria. J Inflamm (Lond). 2014;11:2.
20. Aleem S, Masood Q, Hassan I. Correlation of C-reactive protein levels with severity of chronic urticaria. Indian J Dermatol. 2014;59:636.
21. Rajappa M, Chandrashekar L, Sundar I, Munisamy M, Ananthanarayanan PH, Thappa DM, et al. Platelet oxidative stress and systemic inflammation in chronic spontaneous urticaria. Clin Chem Lab Med. 2013;51:1789–94.
22. Ucmak D, Akkurt M, Toprak G, Yesilova Y, Turan E, Yıldız I. Determination of dermatology life quality index, and serum C-reactive protein and plasma interleukin-6 levels in patients with chronic urticaria. Postepy Dermatol Alergol. 2013;30:146–51.
23. Kasperska-Zajac A, Grzanka A, Machura E, Misiolek M, Mazur B, Jochem J. Increased serum complement C3 and C4 concentrations and their relation to severity of chronic spontaneous urticaria and CRP concentration. J Inflamm (Lond). 2013;10:22.
24. Tedeschi A, Asero R, Lorini M, Marzano AV, Cugno M. Serum eotaxin levels in patients with chronic spontaneous urticaria. Eur Ann Allergy Clin Immunol. 2012;44:188–92.
25. Takahagi S, Mihara S, Iwamoto K, et al. Coagulation/fibrinolysis and inflammation markers are associated with disease activity in patients with chronic urticaria. Allergy. 2010;65:649–56.
26. Tedeschi A, Asero R, Lorini M, Marzano AV, Cugno M. 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.
27. Kasperska-Zajac A, Sztylc J, Machura E, Jop G. Plasma IL-6 concentration correlates with clinical disease activity and serum C-reactive protein concentration in chronic urticaria patients. Clin Exp Allergy. 2011;41:1386–91.

28. Kolkhir P, Pogorelov D, Olisova O. CRP, D-dimer, fibrinogen and ESR as predictive markers of response to standard doses of levocetirizine in patients with chronic spontaneous urticaria. Eur Ann Allergy Clin Immunol. 2017;49:189–92.
29. Rasool R, Ashiq I, Shera IA, Yousuf Q, Shah ZA. Study of serum interleukin (IL) 18 and IL-6 levels in relation with the clinical disease severity in chronic idiopathic urticaria patients of Kashmir (North India). Asia Pac Allergy. 2014;4:206–11.
30. Magen E, Mishal J, Zeldin Y, Feldman V, Kidon M, Schlesinger M, et al. Increased mean platelet volume and C-reactive protein levels in patients with chronic urticaria with a positive autologous serum skin test. Am J Med Sci. 2010;339:504–8.
31. Aleem S, Masood Q, Hassan I. Correlation of mean platelet volume levels with severity of chronic urticaria. J Dermatol Dermatol Surg. 2015;19:9–14.
32. Chandrashekar L, Rajappa M, Sundar I, et al. Platelet activation in chronic urticaria and its correlation with disease severity. Platelets. 2014;25:162–5.
33. Puxeddu I, Pratesi F, Ribatti D, Migliorini P. Mediators of inflammation and angiogenesis in chronic spontaneous urticaria: are they potential biomarkers of the disease? Mediators Inflamm. 2017;2017:4123694.
34. Cugno M, Tedeschi A, Borghi A, et al. Activation of blood coagulation in two prototypic autoimmune skin diseases: a possible link with thrombotic risk. PLoS One. 2015;10:e0129456.
35. Baek YS, Jeon J, Kim JH, Oh CH. Severity of acute and chronic urticaria correlates with D-dimer level, but not C-reactive protein or total IgE. Clin Exp Dermatol. 2014;39:795–800.
36. Asero R, Cugno M, Tedeschi A. Activation of blood coagulation in plasma from chronic urticaria patients with negative autologous plasma skin test. J Eur Acad Dermatol Venereol. 2011;25:201–5.
37. Wang D, Tang H, Shen Y, Wang F, Lin J, Xu J. Activation of the blood coagulation system in patients with chronic spontaneous urticaria. Clin Lab. 2015;61:1283–8.
38. Lu T, Jiao X, Si M, et al. The correlation of serums CCL11, CCL17, CCL26, and CCL27 and disease severity in patients with urticaria. Dis Markers. 2016;2016:1381760.
39. Farres MN, Refaat M, Melek NA, Ahmed EE, Shamseldine MG, Arafa NA. Activation of coagulation in chronic urticaria in relation to disease severity and activity. Allergol Immunopathol (Madr). 2015;43:162–7.
40. Triwongwaranat D, Kulthanan K, Chularojanamontri L, Pinkaew S. Correlation between plasma D-dimer levels and the severity of patients with chronic urticaria. Asia Pac Allergy. 2013;3:100–5.
41. Criado PR, Antinori LCL, Maruta CW, dos Reis VMS. Evaluation of D-dimer serum levels among patients with chronic urticaria, psoriasis and urticarial vasculitis. An Bras Dermatol. 2013;88:355–60.
42. Zhu H, Liang B, Li R, et al. Activation of coagulation, anti-coagulation, fibrinolysis and the complement system in patients with urticaria. Asian Pac J Allergy Immunol. 2013;31:43–50.
43. Takeda T, Sakurai Y, Takahagi S, et al. Increase of coagulation potential in chronic spontaneous urticaria. Allergy. 2011;66:428–33.
44. Asero R, Tedeschi A, Riboldi P, Griffini S, Bonanni E, Cugno M. Severe chronic urticaria is associated with elevated plasma levels of D-dimer. Allergy. 2008;63:176–80.
45. 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.
46. Asero R, Tedeschi A, Riboldi P, Cugno M. Plasma of patients with chronic urticaria shows signs of thrombin generation, and its intradermal injection causes wheal-and-flare reactions much more frequently than autologous serum. J Allergy Clin Immunol. 2006;117:1113–7.
47. Rauber MM, Pickert J, Holiangu L, Möbs C, Pfützner W. Functional and phenotypic analysis of basophils allows determining distinct subtypes in patients with chronic urticaria. Allergy. 2017;72:1904–11.
48. Oliver ET, Sterba PM, Saini SS. Interval shifts in basophil measures correlate with disease activity in chronic spontaneous urticaria. Allergy. 2015;70:601–3.
49. Saini SS. Basophil responsiveness in chronic urticaria. Curr Allergy Asthma Rep. 2009;9:286–90.

50. Grattan CEH, Dawn G, Gibbs S, Francis DM. Blood basophil numbers in chronic ordinary urticaria and healthy controls: diurnal variation, influence of loratadine and prednisolone and relationship to disease activity. Clin Exp Allergy. 2003;33:337–41.
51. Baker R, Vasagar K, Ohameje N, Gober L, Chen SC, Sterba PM, et al. Basophil histamine release activity and disease severity in chronic idiopathic urticaria. Ann Allergy Asthma Immunol. 2008;100:244–9.
52. Curto-Barredo L, Yelamos J, Gimeno R, Mojal S, Pujol RM, Giménez-Arnau A. Basophil activation test identifies the patients with chronic spontaneous urticaria suffering the most active disease. Immun Inflamm Dis. 2016;4:441–5.
53. Ye YM, Yang EM, Yoo HS, Shin YS, Kim SH, Park HS. Increased level of basophil CD203c expression predicts severe chronic urticaria. J Korean Med Sci. 2014;29:43–7.
54. Vohra S, Sharma NL, Mahajan VK, Shanker V. Clinicoepidemiologic features of chronic urticaria in patients having positive versus negative autologous serum skin test: a study of 100 Indian patients. Indian J Dermatol Venereol Leprol. 2011;77:156–9.
55. George M, Balachandran C, Prabhu S. Chronic idiopathic urticaria: comparison of clinical features with positive autologous serum skin test. Indian J Dermatol Venereol Leprol. 2008;74:105–8.
56. Caproni M, Volpi W, Giomi B, Cardinali C, Antiga E, Melani L, et al. Chronic idiopathic and chronic autoimmune urticaria: clinical and immunopathological features of 68 subjects. Acta Derm Venereol. 2004;84:288–90.
57. Alyasin S, Hamidi M, Karimi AA, Amiri A, Ghaffarpasand F, Ehsaei MJ. Correlation between clinical findings and results of autologous serum skin test in patients with chronic idiopathic urticaria. South Med J. 2011;104:111–5.
58. Asero R. D-dimer: a biomarker for antihistamine-resistant chronic urticaria. J Allergy Clin Immunol. 2013;132:983–6.
59. Huilan Z, Bihua L, Runxiang L, Jiayan L, Luyang L, Zhenjie L. Features of antihistamine-resistant chronic urticaria and chronic urticaria during exacerbation. Indian J Dermatol. 2015;60:323.
60. Asero R. Plasma D-dimer levels and clinical response to ciclosporin in severe chronic spontaneous urticaria. J Allergy Clin Immunol. 2015;135:1401–3.
61. Grattan CE, O'Donnell BF, Francis DM, Niimi N, Barlow RJ, Seed PT, et al. Randomized double-blind study of cyclosporin in chronic "idiopathic" urticaria. Br J Dermatol. 2000;143:365–72.
62. Iqbal K, Bhargava K, Skov PS, Falkencrone S, Grattan CE. A positive serum basophil histamine release assay is a marker for ciclosporin-responsiveness in patients with chronic spontaneous urticaria. Clin Transl Allergy. 2012;2:19.
63. Altrichter S, Hawro T, Hänel K, Czaja K, Lüscher B, Maurer M, et al. Successful omalizumab treatment in chronic spontaneous urticaria is associated with lowering of serum IL-31 levels. J Eur Acad Dermatol Venereol. 2016;30:454–5.
64. Deza G, Bertolín-Colilla M, Pujol RM, Curto-Barredo L, Soto D, García M, et al. Basophil FcεRI expression in chronic spontaneous urticaria: a potential immunological predictor of response to omalizumab therapy. Acta Derm Venereol. 2017;97:698–704.
65. Deza G, Bertolín-Colilla M, Sánchez S, Soto D, Pujol RM, Gimeno R, Giménez-Arnau AM. Basophil FcεRI expression is linked to time to omalizumab response in chronic spontaneous urticaria. J Allergy Clin Immunol. 2018;141(6):2313–6.
66. Ertas R, Ozyurt K, Atasoy M, Hawro T, Maurer M. The clinical response to omalizumab in CSU patients is linked to and predicted by IgE levels and their change. Allergy. 2018;73(3):705–12. https://doi.org/10.1111/all.13345. [Epub ahead of print].
67. Palacios T, Stillman L, Borish L, Lawrence M. Lack of basophil CD203c-upregulating activity as an immunological marker to predict response to treatment with omalizumab in patients with symptomatic chronic urticaria. J Allergy Clin Immunol Pract. 2016;4:529–30.
68. Gericke J, Metz M, Ohanyan T, Weller K, Altrichter S, Skov PS, et al. Serum autoreactivity predicts time to response to omalizumab therapy in chronic spontaneous urticaria. J Allergy Clin Immunol. 2017;139:1059–61.e1.

69. Ertas R, Ozyurt K, Ozlu E, Ulas Y, Avci A, Atasoy M, et al. Increased IgE levels are linked to faster relapse in patients with omalizumab-discontinued chronic spontaneous urticaria. J Allergy Clin Immunol. 2017;140:1749–51.
70. Gangemi S, Saitta S, Lombardo G, Patafi M, Benvenga S. Serum thyroid autoantibodies in patients with idiopathic either acute or chronic urticaria. J Endocrinol Invest. 2009;32:107–10.
71. Woo YR, Jung KE, Koo DW, Lee JS. Vitamin D as a marker for disease severity in chronic urticaria and its possible role in pathogenesis. Ann Dermatol. 2015;27:423–30.
72. Rasool R, Masoodi KZ, Shera IA, Yosuf Q, Bhat IA, Qasim I, et al. Chronic urticaria merits serum vitamin D evaluation and supplementation; a randomized case control study. World Allergy Organ J. 2015;8:15.
73. Kessel A, Helou W, Bamberger E, Sabo E, Nusem D, Panassof J, et al. Elevated serum total IgE—a potential marker for severe chronic urticaria. Int Arch Allergy Immunol. 2010;153:288–93.
74. Netchiporouk E, Sasseville D, Moreau L, Habel Y, Rahme E, Ben-Shoshan M. Evaluating comorbidities, natural history, and predictors of early resolution in a cohort of children with chronic urticaria. JAMA Dermatol. 2017;153:1236–42.
75. Maurer M, Church MK, Weller K. Chronic urticaria in children: still itching for insight. JAMA Dermatol. 2017;153:1221–2.
76. Chansakulporn S, Pongpreuksa S, Sangacharoenkit P, Pacharn P, Visitsunthorn N, Vichyanond P, et al. The natural history of chronic urticaria in childhood: a prospective study. J Am Acad Dermatol. 2014;71:663–8.
77. Sahiner UM, Civelek E, Tuncer A, Yavuz ST, Karabulut E, Sackesen C, et al. Chronic urticaria: etiology and natural course in children. Int Arch Allergy Immunol. 2011;156:224–30.
78. Champion RH, Roberts SO, Carpenter RG, Roger JH. Urticaria and angio-oedema. A review of 554 patients. Br J Dermatol. 1969;81:588–97.
79. Juhlin L. Recurrent urticaria: clinical investigation of 330 patients. Br J Dermatol. 1981;104:369–81.
80. Kozel MM, Mekkes JR, Bossuyt PM, Bos JD. Natural course of physical and chronic urticaria and angioedema in 220 patients. J Am Acad Dermatol. 2001;45:387–91.
81. Hiragun M, Hiragun T, Mihara S, Akita T, Tanaka J, Hide M. Prognosis of chronic spontaneous urticaria in 117 patients not controlled by a standard dose of antihistamine. Allergy. 2013;68:229–35.
82. Lee HC, Hong JB, Chu CY. Chronic idiopathic urticaria in Taiwan: a clinical study of demographics, aggravating factors, laboratory findings, serum autoreactivity and treatment response. J Formos Med Assoc. 2011;110:175–82.
83. Nebiolo F, Bergia R, Bommarito L, Bugiani M, Heffler E, Carosso A, et al. Effect of arterial hypertension on chronic urticaria duration. Ann Allergy Asthma Immunol. 2009;103:407–10.
84. Sánchez-Borges M, Caballero-Fonseca F, Capriles-Hulett A, González-Aveledo L. Aspirin-exacerbated cutaneous disease (AECD) is a distinct subphenotype of chronic spontaneous urticaria. J Eur Acad Dermatol Venereol. 2015;29:698–701.
85. Kim JH, Lee HY, Ban GY, Shin YS, Park HS, Ye YM. Serum clusterin as a prognostic marker of chronic spontaneous urticaria. Medicine (Baltimore). 2016;95:e3688.
86. Guo A, Zhu W, Zhang C, Wen S, Chen X, Chen M, et al. Association of FCER1A genetic polymorphisms with risk for chronic spontaneous urticaria and efficacy of nonsedating H1-antihistamines in Chinese patients. Arch Dermatol Res. 2015;307:183–90.
87. Lin CE, Kaptein JS, Sheikh J. Differential expression of microRNAs and their possible roles in patients with chronic idiopathic urticaria and active hives. Allergy Rhinol (Providence). 2017;8:67–80.
88. 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;132:101–9.
89. 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 Mar;135(3):925.

90. Vadasz Z, Tal Y, Rotem M, et al. Omalizumab for severe chronic spontaneous urticaria: real-life experiences of 280 patients. J Allergy Clin Immunol Pract. 2017;5(6):1743–5.
91. Sussman G, Hebert J, Barron C, et al. Real-life experiences with omalizumab for the treatment of chronic urticaria. Ann Allergy Asthma Immunol. 2014;112:170–4.
92. 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 Jan;73(1):57–62. https://doi.org/10.1016/j.jdermsci.2013.08.011.
93. Ghazanfar MN, Sand C, Thomsen SF. Effectiveness and safety of omalizumab in chronic spontaneous or inducible urticaria: evaluation of 154 patients. Br J Dermatol. 2016;175(2):404–6.
94. Bernstein JA, Kavati A, Tharp MD, Ortiz B, MacDonald K, Denhaerynck K, Abraham I. Effectiveness of omalizumab in adolescent and adult patients with chronic idiopathic/spontaneous urticaria: a systematic review of 'real-world' evidence. Expert Opin Biol Ther. 2018;18(4):425–48.
95. Kolkhir P, Church MK, Weller K, Metz M, Schmetzer O, Maurer M. Autoimmune chronic spontaneous urticaria: what we know and what we do not know. J Allergy Clin Immunol. 2017;139:1772–81.
96. Grattan C. Autoimmune chronic spontaneous urticaria. J Allergy Clin Immunol. 2018;141:1165–6.
97. 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.
98. Maurer M, Gimenez Arnau A, Sussman G, et al. Ligelizumab achieves rapid onset of action, improved and sustained efficacy compared with omalizumab in patients with chronic spontaneous urticaria not adequately controlled by H1-antihistamines. Poster presented at 27th EADV Congress, 12–16 September 2018, Paris, France.
99. http://www.unitedbiopharma.com/UB-221.php.
100. Hu J, Chen J, Ye L, Cai Z, Sun J, Ji K. Anti-IgE therapy for IgE-mediated allergic diseases: from neutralizing IgE antibodies to eliminating IgE+ B cells. Clin Transl Allergy. 2018;8:27.
101. Navinés-Ferrer A, Serrano-Candelas E, Molina-Molina GJ, Martín M. IgE-related chronic diseases and anti-IgE-based treatments. J Immunol Res. 2016;2016:8163803. https://doi.org/10.1155/2016/8163803. Very good review on anti-IgE treatments.
102. Pennington LF, Tarchevskaya S, Brigger D, et al. Structural basis of omalizumab therapy and omalizumab-mediated IgE exchange. Nat Commun. 2016;7:11610.
103. Nyborg AC, Zacco A, Ettinger R. Development of an antibody that neutralizes soluble IgE and eliminates IgE expressing B cells. Cell Mol Immunol. 2016;13:391–400.
104. Lupinek C, Roux KH, Lafer S, Rauter I, Reginald K, Kneidinger M, et al. Trimolecular complex formation of IgE, Fc epsilon RI, and a recombinant nonanaphylactic single-chain antibody fragment with high affinity for IgE. J Immunol. 2009;182:4817–29.
105. Peng X, Wang J, Li X, Lin L, Xie G, Cui Z, et al. Targeting mast cells and basophils with anti-FcεRIα Fab-conjugated celastrol-loaded micelles suppresses allergic inflammation. J Biomed Nanotechnol. 2015;11:2286–99.
106. Kirak ORG. A novel, nonanaphylactogenic, bispecifc IgE-CD3 antibody eliminates IgE(+) B cells. J Allergy Clin Immunol. 2015;136(3):800–2.
107. Chu SY, Horton HM, Pong E, Leung IW, Chen H, Nguyen DH, et al. Reduction of total IgE by targeted coengagement of IgE B-cell receptor and Fc gamma RIIb with Fc-engineered antibody. J Allergy Clin Immunol. 2012;129:1102–15.
108. Kim B, Eggel A, Tarchevskaya SS, Vogel M, Prinz H, et al. Accelerated disassembly of IgE receptor complexes by a disruptive macromolecular inhibitor. Nature. 2012;491:613–7.
109. Kocatürk E. Role of biologics and future perspectives in the treatment of urticaria. Curr Treat Options Allergy. 2017;4:428.
110. Altman K, Chang C. Pathogenic intracellular and autoimmune mechanisms in urticaria and angioedema. Clin Rev Allergy Immunol. 2013;45:47–62.
111. Siebenhaar F, Redegeld FA, Bischoff SC, et al. Mast cells as drivers of disease and therapeutic targets. Trends Immunol. 2018 Feb;39(2):151–62.

112. https://adisinsight.springer.com/drugs/800042342.
113. Harvima IT, Levi-Schaffer F, Draber P, et al. Molecular targets on mast cells and basophils for novel therapies. J Allergy Clin Immunol. 2014;134(3):530–44.
114. https://adisinsight.springer.com/drugs/800045646.
115. Elias J, Boss E, Kaplan AP. Studies of the cellular infiltrate of chronic idiopathic urticaria: prominence of T lymphocytes, monocytes and mast cells. J Allergy Clin Immunol. 1986;78(5):914–8.
116. Caproni M, Giomi B, Volpi W, Melani L, Schincaglia E, Macchia D, Manfredi M, D'Agata A, Fabbri P. Chronic idiopathic urticaria: infiltrating cells and related cytokines in autologous serum-induced weals. Clin Immunol. 2005;114:284–92.
117. Smith CH, Kepley C, Schwartz LB, Lee TH. Mast cell number and phenotype in chronic idiopathic urticaria. J Allergy Clin Immunol. 1995;96:360–4.
118. Herrero-Beaumont G, Martínez Calatrava MJ, Castañeda S. Abatacept mechanism of action: concordance with its clinical profile. Reumatol Clin. 2012;8(2):78–83.
119. Wenzel S, Ford L, Pearlman D, et al. Dupilumab in persistent asthma with elevated eosinophil levels. N Engl J Med. 2013;368:2455–66.
120. Manka LA, Wechsler ME. New biologics for allergic diseases. Expert Rev Clin Immunol. 2018;14(4):285–96.
121. Shirley M. Dupilumab first global approval. Drugs. 2017;77:1115–21.
122. Boyman O, Kaegi C, Akdis M, et al. EAACI IG biologicals task force paper on the use of biologic agents in allergic disorders. Allergy. 2015;70(7):727–54.
123. Kocatürk E, Zuberbier T. New biologics in the treatment of urticaria. Curr Opin Allergy Clin Immunol. 2018;18(5):425–31.
124. Lenormand C, Lipsker D. Efficiency of interleukin-1 blockade in refractory delayed pressure urticaria. Ann Intern Med. 2012;157(8):599–600.
125. Bodar EJ, Simon A, de Visser M, van der Meer JW. Complete remission of severe idiopathic cold urticaria on interleukin-1 receptor antagonist (anakinra). Neth J Med. 2009;67(9):302–5.
126. Herman AE, Chinn LW, Kotwal SG, et al. Safety, pharmacokinetics, and pharmacodynamics in healthy volunteers treated with GDC-0853, a selective reversible Bruton's tyrosine kinase inhibitor. Clin Pharmacol Ther. 2018;103(6):1020–8.
127. Asero R, Cugno M, Tedeschi A. Eosinophils in chronic urticaria: supporting or leading actors? World Allergy Organ J. 2009;2(9):213–7.
128. Magerl M, Terhorst D, Metz M, Altrichter S, Zuberbier T, Maurer M, Bergmann KC. Benefit from mepolizumab treatment in a patient with chronic spontaneous urticaria. J Dtsch Dermatol Ges. 2018;16(4):477–8.
129. Maurer M, Altrichter S, Metz M, et al. Benefit from reslizumab treatment in a patient with chronic spontaneous urticaria and cold urticaria. J Eur Acad Dermatol Venereol. 2018;32(3):e112–3.
130. Metz M, Krull C, Hawro T, Saluja R, Groffik A, Stanger C, Staubach P, Maurer M. Substance P is upregulated in the serum of patients with chronic spontaneous urticaria. J Invest Dermatol. 2014;134(11):2833–6.
131. Başak PY, Vural H, Kazanoglu OO, Erturan I, Buyukbayram HI. Effects of loratadine and cetirizine on serum levels of neuropeptides in patients with chronic urticaria. Int J Dermatol. 2014;53(12):1526–30.
132. Kocatürk E, Maurer M, Metz M, Grattan C. Looking forward to new targeted treatments for chronic spontaneous urticaria. Clin Transl Allergy. 2017;7:1.
133. Haas N, Hermes B, Henz BM. Adhesion molecules and cellular infiltrate: histology of urticaria. J Investig Dermatol Symp Proc. 2001;6:137–8.
134. Zuberbier T, Schadendorf D, Haas N, et al. Enhanced P-selectin expression in chronic and dermographic urticaria. Int Arch Allergy Immunol. 1997;114:86–9.
135. Barlow RJ, Ross EL, Macdonald D, Kobza Black A, Greaves MW. Adhesion molecule expression and the inflmmatory cell infiltrate in delayed pressure urticaria. Br J Dermatol. 1994;131:341–7.

136. Kay AB, Clark P, Maurer M, Ying S. Elevations in T-helper-2-initiating cytokines (interleukin-33, interleukin-25 and thymic stromal lymphopoietin) in lesional skin from chronic spontaneous ("idiopathic") urticaria. Br J Dermatol. 2015;172:1294–302.
137. Fiebiger E, Hammerschmid F, Stingl G, Maurer D. Anti-FcεRIα autoantibodies in autoimmune-mediated disorders: identification of a structure-function relationship. J Clin Invest. 1998;101(1):243–51.
138. Horiuchi T, Tsukamoto H. Complement-targeted therapy: development of C5- and C5a-targeted inhibition. Inflammation and Regeneration. 2016;36:11.
139. Hofstra CL, Desai PJ, Thurmond RL, Fung-Leung WP. Histamine H4 receptor mediates chemotaxis and calcium mobilization of mast cells. J Pharmacol Exp Ther. 2003;305:1212–21.
140. Thurmond RL, Desai PJ, Dunford PJ, Fung-Leung WP, Hofstra CL, Jiang W, et al. A potent and selective histamine H4 receptor antagonist with antiinflammatory properties. J Pharmacol Exp Ther. 2004;309:404–13.
141. Shiraishi Y, Jia Y, Domenico J, Joetham A, Karasuyama H, Takeda K, et al. Sequential engagement of FcεRI on mast cells and basophil histamine H(4) receptor and FcεRI in allergic rhinitis. J Immunol. 2013;190:539–48.
142. Thurmond RL, Venable J, Savall B, La D, Snook S, Dunford PJ, Edwards JP. Clinical development of histamine H4 receptor antagonists. Handb Exp Pharmacol. 2017;241:301–20.
143. Sand FL, Thomsen SF. TNF-alpha inhibitors for chronic urticaria: experience in 20 patients. J Allergy (Cairo). 2013;2013:130905.