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Guideline of Chronic Urticaria Beyond

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Urticaria is a relatively common condition that if chronic can persist for weeks, months or years and affect quality of life significantly. The etiology is often difficult to determine, especially as it becomes chronic. Many cases of chronic urticaria are thought to be autoimmune, although there is no consensus that testing for autoimmunity alters the diagnostic or management strategies or outcomes. Many times, urticaria is easily managed with antihistamines and/or short courses of oral corticosteroids, but too often control is insufficient and additional therapies must be added. For years, immune modulating medications, such as cyclosporine and Mycophenolate Mofetil, have been used in cases refractory to antihistamines and oral corticosteroids, although the evidence supporting their efficacy and safety has been limited. Omalizumab was recently approved for the treatment of chronic urticaria unresponsive to H1-antagonists. This IgG anti-IgE monoclonal antibody has been well demonstrated to safely and effectively control chronic urticaria at least partially in approximately 2/3 of cases. However, the mechanism of action and duration of treatment for omalizumab is still unclear. It is hoped that as the pathobiology of chronic urticaria becomes better defined, future therapies that target specific mechanistic pathways will be developed that continue to improve the management of these often challenging patients.

Key Words: Urticaria; hives; angioedema; guidelines; diagnosis; management

INTRODUCTION

Urticaria is a heterogeneous skin disorder that may be acute or chronic, intermittent or persistent, and may occur alone or in association with other related conditions such as angioedema. During an acute urticaria onset, it is frequently difficult for the clinician to determine whether the urticaria and/or angioedema is self-limiting or part of systemic anaphylaxis. In contrast, chronic urticaria (CU) with or without angioedema is self-limiting, and seldom does it progress to anaphylaxis. Urticaria is commonly defined as the sudden appearance of wheals with central swelling and surrounding erythema in the epidermis that are typically pruritic and resolve within about 24 hours without scarring, although some lesions may last up to 48 hours before resolving.[1-3] They can appear over any part of the body, and lesions are frequently polymorphic. Often, CU is associated with a physical component (a.k.a. physical urticaria or inducible urticaria), and this type of urticaria may lack a late phase response and often resolves much quicker in 2 hours or less.[4] Lesions lasting longer than 24-48 hours, those that leave hyperpigmentation, or those that burn instead of itch may be vasculitic rather than urticarial, and skin biopsy may be necessary to differentiate between these 2 disorders. However, it is important to emphasize that urticarial vasculitis can occur in evanescent lesions lasting less than 48 hours as well.[2]

Angioedema is a less well-circumscribed area of edema that occurs in the deeper dermis; in some circumstances, it can be painful rather than pruritic. Angioedema usually resolves in less than 24-48 hours, and when it persists longer than 72 hours in the absence of hives, non-histaminergic causes should be considered.[5] Nevertheless, in both urticaria with or without angioedema, the wheal or swelling is likely the result of the release of histamine and other bioactive mediators from mast cells and basophils, and the erythema is the result of a neuro-reflex response causing vasodilation.[3] Angioedema may be either histaminergic or non-histaminergic, the latter that could be bradykinin mediated or secondary to other poorly elucidated pathways (idiopathic). Isolated urticaria without angioedema occurs in

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approximately 40% of cases, whereas angioedema occurs concurrently with urticaria in up to 40% of cases. Isolated angioedema occurs in up to 20% of cases. Although angioedema and urticaria may present alone, when they occur together, the angioedema typically represents the extension of urticaria into the deeper dermis.

Classification and quality of life (QoL)

Acute urticaria is defined as urticaria persisting less than 6 weeks, whereas CU persists 6 weeks or longer.[1,5] Acute and chronic urticaria affect up to 20% and 5% of the general population, respectively. In children and adolescents, CU may be more common in boys than girls, while it is more prevalent in middle-aged women than men in adults.[6] CU includes physical urticaria (cold, pressure, vibratory, UV light and others) and both chronic idiopathic urticaria (CIU) and autoimmune urticaria (a.k.a. autoantibody associated urticaria). Since the functional relevance of autoantibodies to the FcER1 alpha subunit or antibodies associated with autoimmune diseases remains unclear, the latter category has been included under the classification of CIU.[2,7] Regardless of the population affected, CU can have a significant impact on quality of life.[2,8] Quality of life has recently become a major focus in CU research. It is specifically addressed by the EAACI/WAO CU guidelines as an important target for disease management. Quality of life can be assessed in urticaria patients by using the urticaria activity score (UAS), a validated scoring system that considers severity of pruritus and wheals to create a daily score ranging from 0 to 6.[9-11] The daily score can be summed over 7 consecutive days to create the UAS7 for that patient, with a possible total score of 0-42. It was recently used as a primary or secondary endpoint in clinical trials assessing omalizumab for the treatment of CU unresponsive to H1-antihistamines.[12-14] It can also be used in clinical practice to determine disease activity and response to treatment for CU. Regardless of whether the UAS7 instrument is used or some other form of a visual analogue scale (VAS) and itch severity score (ISS) that assesses the extent of the body covered in hives and the degree of associated itching, respectively, it is important to objectively assess hives during each office visit to determine the patient's response to treatment and the need to adjust their regimen. The CU-Q2oL is another instrument, validated in multiple languages, that is available for assessing severity of CU quality of life impairment.[1,11,15-17] The 2014 updated AAAAI/ACAAI Joint Task Force practice parameter does not specifically address quality of life or the assessment of impairment in quality of life in urticaria as these instruments had not been adequately validated at the time of publication, but it does recommend objective assessment of hives and itching using a VAS and ISS.[2]

Patients with CU have been found to have an impaired quality of life comparable to patients with other severe chronic skin conditions, such as psoriasis and atopic dermatitis. In fact, patients with CU scored worse than those with these other chronic skin conditions especially in the QoL categories of self-perception, social functioning, leisure activity and treatment-induced restrictions.[15,18,19] Future clinical trials investigating novel therapies for CU will likely continue to incorporate standardized instruments like the UAS7 and CU-Q2oL as endpoints for evaluating clinical efficacy.

Pathophysiology, etiology and prevalence

Acute or chronic urticaria may occur as a result of mast cell and basophil release of bioactive mediators, such as histamine and leukotrienes, after activation of either the innate or adaptive immune system. Therefore, urticaria can result from activation of mast cells by specific IgE, IgM or IgG antibody activating the classical complement pathway. It is also possible for other mediators (neuropeptides, such as substance P, calcitonin gene related peptide and neurokinin A) and medications (opiates) to directly activate mast cells or basophils through specific receptors and for cyclooxygenase inhibitors (*i.e.*, ASA, NSAIDS) to induce hives through non-IgE mediated pathways. While allergic triggers, such as stinging insects, foods and medications, are frequently considered and sometimes confirmed for causing acute urticaria, there are other well-defined culprits for causing acute urticaria, such as viral infections and food toxins (Scombroid poisoning). In pediatric studies investigating the cause of acute urticaria, there is no clear consensus regarding the most common etiology. Many studies find infections, such as urinary tract infections and upper respiratory infections, to be the main cause with rates as high as 81%,[1,2,6,20] while others have found foods, food additives and infections to be equally as common (11%-13% each).[21] Infections, such as urinary tract infections and sinusitis, are some the most common diagnoses associated with the CU evaluation, although other disorders, such as thyroid disease and hepatitis, have also been reported. It is important to emphasize that many of these diagnoses are associations, and establishing a true cause and effect can be very difficult and often not possible. Implicating NSAIDs as an underlying cause is very common that depending on the temporal relationship and patient history, may require a simple challenge or graded oral challenge once the hives are controlled to confirm this association. Otherwise, this class of medications, that is especially important for patients suffering from pain, such as osteoarthritis or headache, are frequently avoided unnecessarily. While the true etiology of CU may not be identifiable or obvious in many cases, if there is clinical suspicion of an underlying cause, such as infection or food allergy, limited testing guided by a thorough history and physical exam may be warranted.[2]

As in many conditions of CU with an autoimmune component, the majority are women.[22,23] Patients with CU are at increased risk of having autoimmune conditions, such as thyroid disorders (hypothyroidism more than hyperthyroidism), DM type I, SLE and RA. Although the function and mechanistic rel-

evance of autoantibodies associated with autoimmune diseases remains unclear it has been hypothesized that the inflammatory processes associated with these autoimmune conditions may lead directly to urticaria or increase the individual's susceptibility to CU.[23]

Approximately 40%-50% of adults and children with CU have evidence of an autoantibody directed against the FcER1 alpha subunit of the high-affinity IgE receptor.[24,25] *In vitro* studies have demonstrated that these IgG antibodies can cross-link the high-affinity IgE FcER1 of mast cells and basophils or by binding to IgE antibodies already occupying these receptors.[26,27] The presence of circulating antibodies can be assessed by various *in vitro* tests, including Western blot analysis for anti-FcεRI autoantibodies, histamine release assays, flow cytometry or *in vivo* autologous serum or plasma skin tests.[27,28] Although these autoantibodies are of significant academic interest, their clinical relevance remains unclear as most therapies used to treat hives (*i.e.*, omalizumab or cyclosporine) have been demonstrated to be effective in the presence or absence of these antibodies.

Evaluation

Since common causes of acute urticaria include infection and food allergy, investigation for these underlying causes should be guided by the history and physical exam. Extensive laboratory testing without clinical guidance or suspicion are not recommended.[1,2] In general, skin testing to aeroallergens is not indicated in the evaluation of CU unless the patient has concomitant allergic rhinitis and/or asthma. Skin testing to foods should not be performed unless the patient relates a good clinical history implicating a specific food. Even then, skin testing would not be preferred as these patients are frequently on H1 antihistamines which interfere with test results. It is also often difficult to interpret a wheal and flare response in patients who are having regular bouts of urticaria. Thus, serologic testing to specific foods would be preferred if there is a strong suspicion for food triggers. Unfortunately, the exact cause of acute urticaria is frequently not identified, and many cases will progress for longer than 6 weeks, at which time they become reclassified as chronic. Once urticaria becomes chronic, it is even less likely that the underlying etiology will be identified.

The evaluation of CU should also be guided by a detailed history and physical exam. Guidelines recommend that the initial laboratory evaluation be limited to CBC with differential and ESR and/or CRP. Additional testing, such as liver function testing and TSH, may be appropriate depending on the patient's history. However, a limited number of diagnostic tests are recommended as random testing rarely identifies an underlying cause or has an effect on management or outcomes. Several studies have shown that thyroid autoimmunity in euthyroid patients with chronic angioedema and/or urticaria is more prevalent than in the general population.[29,30] One recent retrospective study found a high correlation between CU and various thyroid disorders. As most subjects were diagnosed with thyroid dysfunction after the diagnosis of CU, the authors suggested that long-term monitoring of symptoms and/or labs for thyroid dysfunction may be appropriate in these patients.[31] The presence of thyroid autoantibodies may also indicate a poorer prognosis with longer symptomatic periods and requirement for oral corticosteroids and higher doses of antihistamines.[32] Skin biopsies are not routinely recommended but may be appropriate to assess for the presence of vasculitis or neutrophils both of which have been demonstrated to be more resistant to conventional therapies, such as H1-antihistamines.[1,2]

If urticaria appears to be inducible, specific provocation tests, such as ice cube challenge for cold-induced urticaria and sand bag weights for delayed pressure urticaria, can be performed to confirm a diagnosis. If there is a suspicion that a particular medication is inducing the urticaria, a trial of withholding the drug can be performed. Although infections, such as *Helicobacter pylori*, Hepatitis B and C, bacterial (*i.e.*, *Staphylococcus*), viral (*i.e.*, *norovirus*, *parvovirus 19*) and helminthic, have been reported to be associated with some cases of CU, routine evaluation for these infections can be expensive and are not recommended unless guided by history and physical.[1,2,33]

The basophil activation test and the autologous serum skin test (ASST) are *in vitro* and in vivo methods, respectively, that can identify the presence of autoantibodies in CU patients.[34,35] Basophil activation testing has been recently reviewed in detail[36] and is not well supported by evidence-based literature in the evaluation and management of CU.[1,2] In addition, skin testing for autoantibodies to the high-affinity IgE receptor or to IgE is not recommended. Although the presence of these antibodies, like in thyroid autoimmunity, may suggest a more severe phenotype, the clinical relevance has not been strongly established and currently the treatment recommendations do not differ based on results of these tests.[27] However, 1 recent report found that response to treatment may vary based on biopsy results, presence of thyroid antibodies, dermatographia and other distinguishing factors.[37] Therefore, there may be additional CU phenotypes that predict response or poor response to therapies. Further research may help guide management based on these specific phenotypic features.

Treatment

Two major groups have published guidelines for the evaluation and management of urticaria.[1,2] Their recommendations, that are based on the published evidence and expert opinion regarding various treatment options are extensively reviewed in these guidelines.[1,2] For the purpose of this review, discussion of treatment will focus on the US JTF Practice Parameter which advocates a 4-step approach to management (Fig. 1) in addition to the EAACI guidelines which advocates a 3-step approach (Fig. 2). Both guidelines agree that first-line management of acute or chronic urticaria should focus on the use of H1

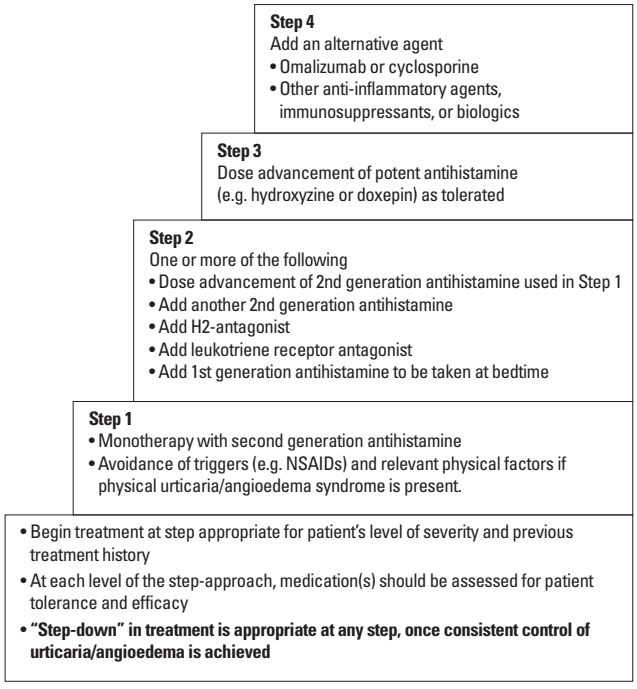

Fig. 1. Adapted from JTF Practice Parameters "The diagnosis and management of acute and chronic urticaria: 2014 update".

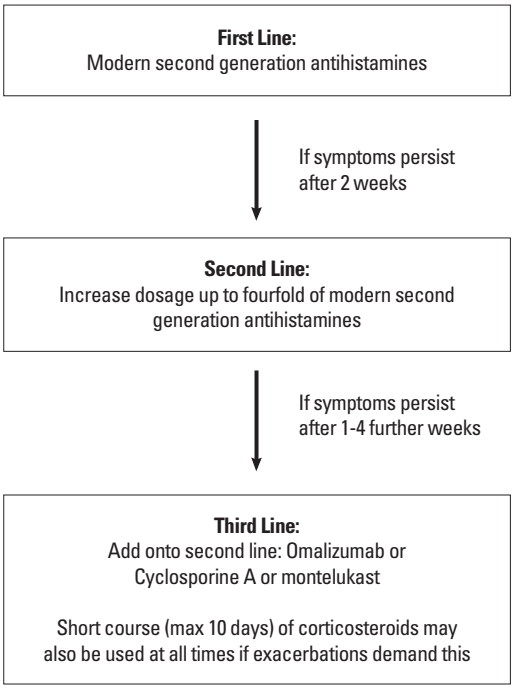

Fig. 2. Adapted from EAACI Urticaria Guideline for the definition, classification, diagnosis and management of urticaria: the 2013 revision and update.

Table. Comparison of the JTF and EAACI urticaria guidelines step treatment

	Step 1	Step 2	Step 3	Step 4	Oral steroids OK?
JTF	Antihistamine monotherapy	One or more: 1) Dose escalation of 2nd generation antihistamine 2) Add another 2nd generation antihistamine 3) Add H2 antagonist 4) Add leukotriene receptor antagonist 5) Add 1st generation antihistamine at bedtime	Dose advancement of potent antihistamine as tolerated	Add an alternative agent: 1) Omalizumab or cyclosporine 2) Other anti-inflammatory agents, immunosuppressants or biologics	Yes, short term (1-3 weeks)
EAACI	Modern 2nd generation antihistamine	Increase dosage up to fourfold of modern 2nd generation antihistamine	Add: Omalizumab or Cyclosporine A or Montelukast	N/A	Yes, short term (10 days)

antihistamines. The European guidelines differ from the US guideline in that treatment with sedating H1 antihistamines and H2 antihistamines are not recommended (Fig. 2). In addition, European guidelines relegate leukotriene modifying agents (LTMAs) to a Step 3 treatment, whereas US guidelines recommend these agents be used earlier as adjunctive Step 2 therapy. Table compares the differences between the US and European guidelines.

H1 antihistamines are classified as first-, second-, and third-generation formulations. First- generation H1 antihistamines that include diphenhydramine and hydroxyzine cross the blood-brain barrier and therefore have sedating and anticholinergic drying side effects. Second- generation antihistamines include fexofenadine, loratadine and cetirizine that are pharmacologically more selective to H1 receptors and have been pharmacologically engineered not to cross the blood-brain barrier resulting in fewer sedative side-effects. Cetirizine, a metabolite of hydroxyzine, was shown in a double-blind placebo-controlled study to be as effective as hydroxyzine in controlling urticaria without significant sedation when used in doses ranging from 5 to 20 mg.[38] Fexofenadine, the acid metabolite of terfenadine, has been shown to significantly improve symptoms scores and pruritus most effectively at doses of 120 mg daily or greater.[39-41] Loratadine, which is structurally similar to azata-

dine, has also been shown to be better than placebo for control of urticaria.[42,43] Although all 3 have been proven to be effective in control of CU, none are consistently superior and response varies among patients.[44-46]

Third-generation antihistamines include desloratadine and levocetirizine, isomeric forms of loratadine and cetirizine, respectively. They may be more appropriate in patients who are sensitive to the sedating effects associated with first-generation and on occasion second- generation antihistamines. Desloratadine is superior to placebo for control of urticaria at a dose of 5 mg daily.[47] However, when compared to levocetirizine, doses of 5-20 mg of desloratadine have been demonstrated to be not as effective to comparable doses of levocetirizine.[48,49] When second- and third- generation antihistamines are used, there is evidence that doses can be safely titrated up to 4 times the FDA recommended dose as indicated. First-generation sedating H1 antihistamines have been advocated for use by US guidelines as Step 2 therapy at night and can be titrated up to higher doses as Step 3 therapy if tolerated by the patient. EAACI guidelines recommend use of second-generation H1 antihistamines as first-line therapy with the same up titration to higher doses as Step 2 of therapy.[1,2] Many clinicians chose to combine H1 antihistamines, such as loratadine, fexofenadine and cetirizine, rather than up titrate a single H1 antihistamine as recommended as Step 3 therapy. The vast majority of studies have evaluated effect of uptitration of a single antihistamine rather than combination of H1 antihistamines that likely explains why combination of different H1 antihistamines is not recommended by the US or the EAACI guidelines.

LTMAs and H2 antihistamines are recommended as add-on Step 2 therapies by the US guidelines. LTMAs are recommended in the third and final step in the EAACI guidelines. LTMAs have been found to significantly improve CU symptoms when used in conjunction with H1 antihistamines but are not as effective as H1 antihistamines when used as monotherapy.[50] Montelukast was reported to reduce urticaria activity scores compared to placebo[9,51,52] and when combined with a daily H1 antihistamine, control of symptoms was found to be greater than with either antihistamines or placebo alone.[53] Although H2 antihistamines, such as cimetidine and ranitidine, have been shown to provide control of CU and angioedema when used as monotherapy,[54] they are more typically used as add-on therapy in combination with H1 antihistamines and LTMAs when H1 antihistamines alone are not sufficient.[2,55] The EAACI guidelines do not recommend the addition of H2 antihistamines to treatment for CU.

Oral corticosteroids are commonly used in the management of acute urticaria and prednisone has been shown to significantly improve control of itch associated with acute urticaria compared to antihistamines alone.[56] Short courses of oral corticosteroids are often used to better control CU in patients poorly responsive to H1 and H2 antihistamines until other combinations of medications (*i.e.*, anti-inflammatory, immunosuppressive or biologics) are able to establish control. Their use is supported by both the JTF and EAACI guidelines. Each provides specific length of treatment limits ranging from 10 days to 3 weeks. One large study including subjects with CU not controlled with H1 antihistamines showed that a short course of prednisone provided at least a partial response in 85% of subjects and induced complete remission in approximately 50% of subjects.[57] According to the JTF guidelines, if Step 3 therapy involving dose escalation of sedating H1 antihistamines or addition of a combination antihistamine (doxepin) is ineffective or not tolerated due to excessive sedation, then CU would be considered non-histaminergic. In these cases, advancement to Step 4 therapy is recommended and could include anti-inflammatory medications (hydroxychloroquine, dapsone, sulfasalazine, and colchicine), immunosuppressants (cyclosporine, mycophenolate, tacrolimus, and methotrexate) or biologics, notably omalizumab (Xolair™).[1,2] Similarly, the EAACI guidelines Step 3 recommends the addition of Omalizumab or Cyclosporine if up titration of H1 antihistamines is not sufficient. A review of alternative agents, such as immune modulators in the treatment of CU, has recently been published.[7] Overall, there is poor strength of evidence for the use of these agents, with the exception of omalizumab, as there have been few or no well-powered double-blind placebo-controlled randomized studies supporting their benefit. However, a recent study by Amin *et al.*,[37] which investigated patient-specific characteristics associated with treatment outcomes in CU patients prior to FDA approval of omalizumab, found that hydroxychloroquine completely controlled hives in 15% of treated patients, and colchicine, dapsone and sulfasalazine completely controlled CU in 18%, 22%, and 25% of patients. Overall, with proper monitoring, these therapies were generally well tolerated with minimal side effects. Previous retrospective, open-label or case series studies suggest that these agents may provide significant improvement in control of CU and in some cases induce disease remission, supporting these findings.[6,58-61]

In the study by Amin *et al.*,[37] they also found that cyclosporine controlled CU in 33% of patients. This finding is consistent with previous studies that have found cyclosporine to be the most effective immune modulating medication used for treatment of CU. There are 2 sentinel randomized-controlled trials that have demonstrated significant improvement with cyclosporine compared to placebo in the treatment of CU[10,62] resulting in remission of hives in 26% of subjects.[10] Mycofenolate mofetil (MMF) has been demonstrated in 1 case series to improve poorly controlled CU and allow discontinuation of oral corticosteroids in patients poorly controlled by H1 antihistamines after 12 weeks of therapy.[10] A retrospective chart review of MMF in CU and autoantibody-associated urticaria showed that the majority of subjects were able to taper off MMF after only 7 weeks, with over 85% achieving remission for up to 16 weeks.[63] Omalizum-

ab, a humanized recombinant IgG1 kappa monoclonal anti-IgE antibody previously approved for treatment of moderate to severe persistent asthma since 2003, was recently approved for the treatment of CU unresponsive to H1 antihistamines in 2014.[64] Whereas dosing of omalizumab for asthma treatment is based on pre-treatment IgE level and patient weight, these prespecifications are not necessary for CU. The FDA approved dose and frequency of administration of omalizumab for CU is 150 to 300 mg subcutaneously every 4 weeks. Two large double-blind, placebo-controlled, randomized dose-ranging Phase 3 pivotal clinical trials demonstrated significant reduction in UAS and itch severity scores after 12 weeks of therapy (3 injections) at the 150 mg and 300 mg doses compared to the 75 mg dose and placebo. Clinical improvement in CU has been reported as quickly as 1 week after the initial injection, but the full clinical effect may not be realized for up to 4-6 months.[12,65] Both studies found that omalizumab established complete control in approximately one-third of patients and partial control in another one-third whereas one-third were unresponsive. After discontinuation of omalizumab the majority of patients experienced a return of their hives to baseline and in some cases worsening of hives from baseline.[2,65] There are reports of long-term remission after treatment with omalizumab for up to 9 months, but given the lack of reproducibility of remission in other studies it is possible that remission could have been spontaneous rather than induced by treatment.[66] The known major risks associated with omalizumab include anaphylaxis, increased risk of cardiac and neurovascular events, and a controversial increased risk of lymphoma.[67-69] However, omalizumab is overall considered very safe and is rated as pregnancy category B. Based on the quality of evidence supporting omalizumab in contrast to the low risk of adverse effects related to its use, both the JTF and WAO/EAACI strongly endorse the use of omalizumab for patients with refractory CU.[1,2,13,14] However, signfiicantly more information regarding the mechanism of action of omalizumab in CU as well as duration of treatment and how to step down once CU is controlled is still required.

Most patients with CU with or without angioedema do not progress to more severe reactions involving the airway or features of anaphylaxis. However, in cases where the clinician is not yet able to differentiate between urticaria as part of systemic anaphylaxis vs a self-limiting condition, patients should be provided with an epinephrine autoinjector until a definite diagnosis can be made.

CONCLUSION

The exact mechanism(s) by which CU occurs remains poorly elucidated, although based on the fact that 50% or more of cases have an identifiable autoantibody, it is still believed by many that autoimmunity plays an important role. In addition, how omalizumab works in CU is unclear. It is speculated that omalizumab may work by reducing levels of serum IgE and cause down- regulation of high-affinity IgE receptors on mast cells and basophils thereby reducing the proliferation, survival, and activation of these cells[70] However, the fact that omalizumab is not effective in all patients suggests involvement of mechanisms/pathways in CU other than blockade of IgE and/or the FcεRI.[13,28,71] Phenotypes of urticaria, including the presence or absence of autoantibodies, the cellular infiltrates seen on skin biopsy, the presence or absence of physical triggers and responsiveness to H1/H2 antihistamines and LTMAs, provide useful information regarding management using existing step care therapy recommendations and long- term prognosis.[37] However, in order to develop more effective therapies for CU in the future, further research is essential to understand the pathobiology of this heterogeneous chronic and often disabling condition.

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