Position statement for the use of omalizumab in the management of chronic spontaneous urticaria in Indian patients

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ABSTRACT

Chronic spontaneous urticaria (CSU) affects 1% of the world population and also their quality of life, and 50% of these patients are refractory to H_1-antihistamines. Omalizumab is a humanized monoclonal anti-IgE antibody that binds with free IgE antibodies and reduces the circulating levels of free IgE. This reduction in free IgE prevents mast-cell degranulation. The EAACI/GA2LEN/EDF/WAO guidelines recommend omalizumab as the third-line of therapy as an add-on to antihistamines. The recommended dose of omalizumab is 300 mg, 4 weekly in the management of CSU refractory to standard of care with H_1-antihistamines in adults and adolescents ≥12 years of age. In some patients, a dose of 150 mg may be acceptable. Omalizumab has a good safety profile. However, due to the biologic nature of the drug, all patients administered omalizumab must be observed for 2 h after administration for anaphylactoid reactions. There have been no studies on the effect of impaired renal or hepatic function on the pharmacokinetics of omalizumab. While no particular dose adjustment is recommended, omalizumab should be administered with caution in these patients.

Key words: Chronic spontaneous urticaria, omalizumab, guidelines

INTRODUCTION

Chronic spontaneous urticaria (CSU), also known as chronic idiopathic urticaria (CIU), is characterized by wheals (hives) or angioedema or both. It affects the quality of life (QOL) of patients, and half of these patients are refractory to standard of care with H_1-antihistamines. International guidelines such as the EAACI/GA2LEN/EDF/WAO recommend omalizumab as the third-line of therapy as an add-on to antihistamines for treatment of CSU. Omalizumab was approved by the Health Authority of India for management of CSU in October 2014. Although the consensus statements on the management of urticaria have been published earlier in 2011, considering that omalizumab is a new molecule, there is a need to drive its usage appropriately in the management of CSU for better patient outcomes. Such clarity is currently lacking in India. To address this need, a meeting of the Urticaria Expert Forum, which comprises dermatology experts across India, was held on April 5, 2015, to develop a position statement for the use of omalizumab in the management of refractory CSU. The objective was also to identify the right patient for omalizumab and apply available guidelines on urticaria management in the Indian scenario with focus on omalizumab. This will help simplify the usage of anti-IgE therapy with omalizumab in CSU.

DEFINITION OF CHRONIC SPONTANEOUS URTICARIA

As per the EAACI/GA2LEN/EDF/WAO guidelines,[1] CSU is defined as spontaneous (without external physical triggers), sudden appearance of wheals, and/or angioedema lasting more than 6 weeks duration. Chronic urticaria

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which is not inducible can also be called as CSU. Inducible urticaria includes symptomatic dermographism (urticaria factitia), cold urticaria, delayed pressure urticaria, solar urticaria, heat urticaria, vibratory angioedema, cholinergic urticaria, and aquagenic urticaria.[2]

DEFINITION OF REFRACTORY CHRONIC SPONTANEOUS URTICARIA

CSU, which does not respond to standard of care, can be labeled as refractory urticaria.[1] The standard of care for CSU is the nonsedating H_1-antihistamines (cetirizine, loratadine, fexofenadine, etc.). Four-fold doses of antihistamines have been reported to be safe in many studies.[3] The duration of nonresponse to standard of care has to be at least 2 weeks to classify the patient as refractory CSU [Figure 1].

EPIDEMIOLOGY AND IMPACT OF CHRONIC SPONTANEOUS URTICARIA ON QUALITY OF LIFE

The global prevalence for CSU is 0.5–1.0%[3] though the prevalence in India has not been reported, and there is a need to estimate the prevalence of CSU in India. Among the patients of chronic urticaria (CU), more than 60% patients have CSU.[3] Although people of all age groups can be affected with CSU, peak incidence is seen between 20 and 40 years of age which is the most productive age group, and the prevalence of CSU is twice in females as compared to males.[3] The exact cause of increased prevalence in females is not known, but menstrual cycle and pregnancy can trigger urticaria in women.[4] Occurrence of CSU is less common in children.

QOL is affected in CSU due to its impact on the activities of daily living, self-perception, social aspects, leisure activities, treatment-related effects, and most importantly, the psychological status of the patient.[5] The psychological aspects of QOL are important since it also contributes to work productivity, absenteeism and thereby having financial implications. Presence of angioedema further affects the QOL.[6]

The duration of CSU is usually estimated to be 1–5 years, although in about 50% patients, CSU resolves in 6 months irrespective of therapy.[3] However, for some patients, the disease can last longer sometimes up to 20–25 years.[7]

Although studies suggest that the average duration of CIU/CSU is generally 1–5 years, it is likely to be longer in patients with more severe disease,[3,8] presence of angioedema,[9,10] physical urticaria,[10] and those with a positive autologous serum skin test (ASST).[11,12] Thus, CSU causes immense distress to the patients, necessitating effective treatment to improve the QOL.

PATHOGENESIS OF CHRONIC SPONTANEOUS URTICARIA

Although the exact trigger of CIU/CSU is unknown, it is hypothesized that there is a repeated and extensive activation of the dermal mast cells.[13] This leads to degranulation of cutaneous mast cells and the release of histamine (preformed) and other mediators (newly formed) such as prostaglandins, endogenous peptides, endorphins, and enkephalins.[14] This causes wheal formation, vasodilatation, and erythema. Histamine released from the mast cells, prostaglandins, endogenous peptides, endorphins, enkephalins, and also chemoattractant from other cells such as neutrophils also mediate in the process of wheal formation. The threshold for mast-cell activation and degranulation is lowered in patients with CSU. Autoimmune mechanisms are involved in CSU in about 45% cases and remaining 55% remain idiopathic.[15] Either IgG autoantibodies to the alpha subunit of the Fc receptor of the IgE molecule or anti-IgE autoantibodies can activate basophils to release histamine. These antibodies are reported to be specific to CSU [Figure 2].[10] Antithyroid antibodies are reported to be positive in 27.3% (33% males and 25% females) patients with CSU.[16] CSU is rarely due to triggers in food,[16] and bacterial infections rarely account for urticaria.[10,17] Angioedema rarely occurs in isolation in CSU,[3,18] and it results from release of inflammatory mediators (histamine, cytokines) after mast-cell degranulation.[13,14]

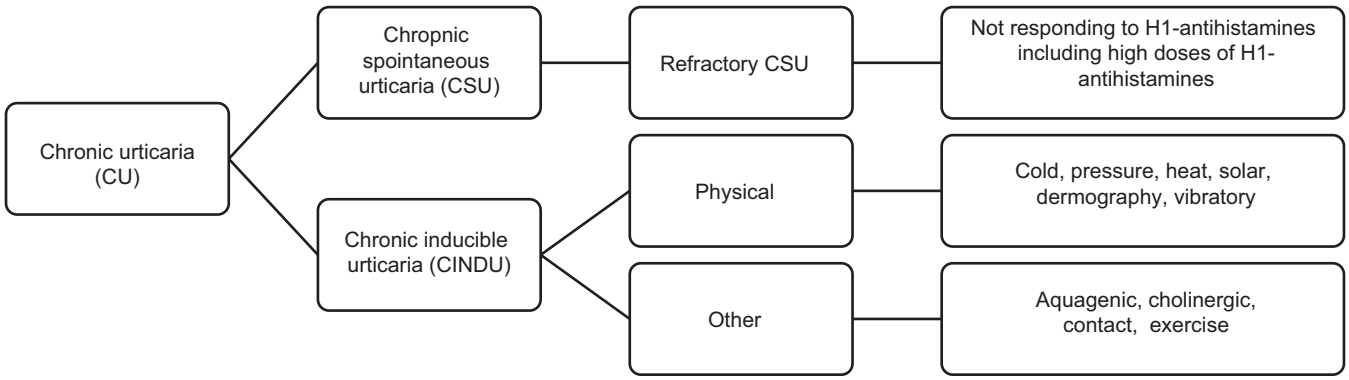

Figure 1: Refractory chronic spontaneous urticaria

DIAGNOSIS OF CHRONIC SPONTANEOUS URTICARIA

A thorough history and physical examination is the most important diagnostic procedure and should include the following questions:[2] timing, frequency and duration of attacks; shape, size, distribution, and associated symptoms of lesions; family and medical history, including allergies; correlation to any triggers, e.g., foods, exercise, drug use; work, hobbies, smoking habits, and stress; previous therapy and response to treatment; use of drugs, e.g. angiotensin converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, physical urticarial and vasculitis, and inducible urticaria should always be excluded to confirm CSU.

Only routine diagnostic tests such as differential blood count, erythrocyte sedimentation rate, or C-reactive protein are recommended by the EAACI/GA2LEN/EDF/WAO 2013 guidelines. Additional diagnostic tests may be conducted on case-to-case basis. These include test to exclude infectious diseases, Type-I allergy, functional autoantibodies, thyroid hormones and autoantibodies, ASST, skin biopsy of the lesion, basophil test, and stool examination to rule out intestinal parasites. There is no evidence to suggest the benefit of allergy testing (skin prick test, and patch test) for diagnosis of CSU, and these are not recommended routinely. Measurement of serum IgE levels is unnecessary and also not recommended by international guidelines.

ASST is a useful screening test for autoimmune CSU.[18,19] ASST positive patients have more widespread lesions and significantly more severe pruritus and systemic symptoms and these patients are less likely not to respond to standard of care and tend to be refractory[20,21] and more likely to require anti-IgE therapy.[20,21]

The urticaria activity score-7 (UAS-7) is a validated method for assessing disease activity in CSU[22] and is recommended to be used in practice [Table 1].[1] The diagnostic algorithm for CSU recommended for practitioners in India is presented in Figure 3.

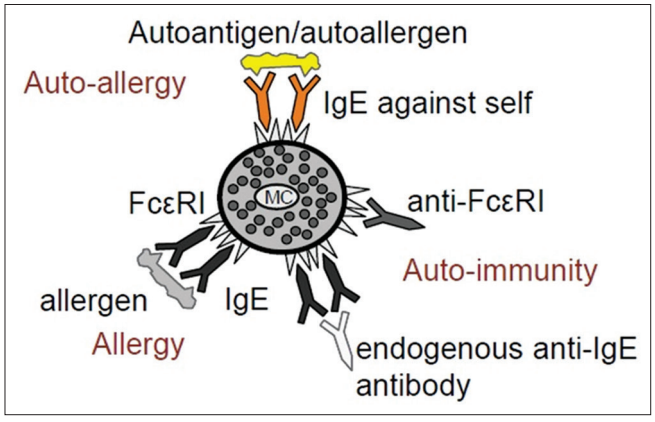

Figure 2: Role of allergens and IgE-mediated autoimmunity through FcεRI receptors in mast-cell degranulation in patients with chronic spontaneous urticaria

Updates in the EAACI/GA2LEN/EDF/WAO 2013 guidelines

As per the 2013 revision in the EAACI/GA2LEN/EDF/WAO guidelines for definition, classification, diagnosis, and management of urticaria, urticaria has been distinctly identified as mast-cell driven disease and it has been classified as CSU and chronic inducible urticaria. The revision recommends the second generation antihistamines as the first-line therapy, with second-line therapy involving dose up-titration of second generation antihistamines to four times the recommended dose; and the use of omalizumab, cyclosporine, and montelukast as the third-line therapy [Figure 4].[2]

STANDARD OF CARE FOR CHRONIC URTICARIA MANAGEMENT

The current standard of care as per the Indian consensus published in 2011 is to begin with second generation antihistamines as the first-line therapy followed by up-titration of the second generation antihistamines to four times the recommended dose, followed by leukotriene receptor antagonists such as montelukast or changing the antihistamine. The use of omalizumab, cyclosporine, methotrexate, dapsone, and H2-antihistamines is recommended as the fourth-line therapy. Steroids are reserved for exacerbations for 3–7 days.[23]

OMALIZUMAB IN CHRONIC SPONTANEOUS URTICARIA

Omalizumab is a humanized monoclonal antibody indicated for adults and adolescents (12 years of age and above) with CSU refractory to standard of care. The recommended dose is 300mg for subcutaneous administration only.[24]

The exact mechanism of action of omalizumab in CSU is unknown. One hypothesis for the mechanism of action of omalizumab in CSU is that it lowers free IgE levels in the blood and subsequently in the skin [Figure 5]. This leads to downregulation of surface IgE receptors, thereby decreasing downstream signaling via the FcεRI pathway, resulting in suppressed cell activation and inflammatory responses. As a consequence, the frequency and severity of

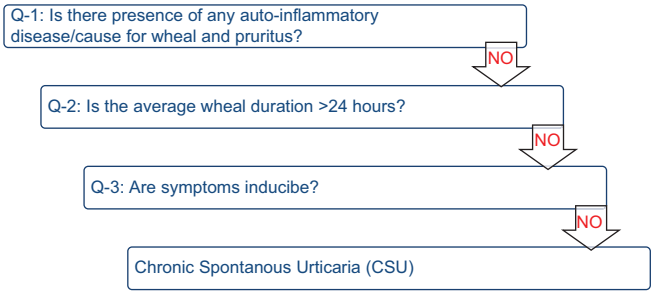

Figure 3: Diagnostic algorithm for chronic spontaneous urticaria

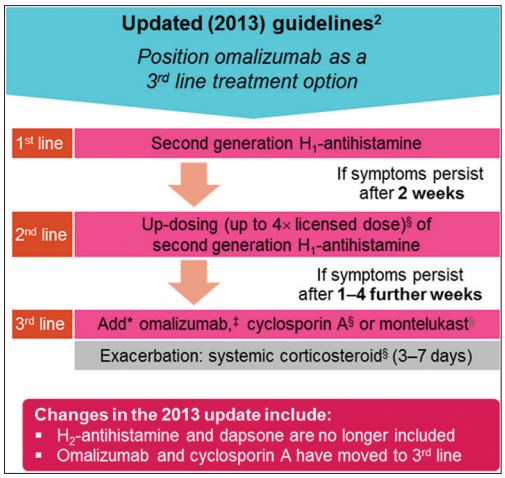

Figure 4: Algorithm for management of chronic urticaria (international guidelines). *The order of third-line treatments does not reflect preference; ‡Licensed in Europe, US, and India; §Not licensed for treatment in chronic spontaneous urticaria

Table 1: Urticaria activity score-7

UAS-7	Score	Details
Wheal assessment	0	No wheal
	1	Mild (<20 wheals/24 h)
	2	Moderate (20-50 wheals/24 h)
	3	Intense (>50 wheals/24 h or large confluent areas of wheals)
Pruritus assessment	0	No pruritus
	1	Mild (present, but not annoying or troublesome)
	2	Moderate (troublesome, but does not interfere with normal daily activity or sleep)
	3	Intense (severe pruritus, which is sufficiently troublesome to interfere with normal daily activity or sleep)

Sum of score: 0-6 for each day is summarized over 1 week, maximum score: 42. UAS-7: Urticaria activity score-7

symptoms of CSU are lessened. Another hypothesis is that lowering circulating free IgE levels leads to a rapid and nonspecific desensitization of cutaneous mast cells. Downregulation of FcεRI may help to sustain the response.[24]

In clinical studies in CSU patients, omalizumab treatment led to a dose-dependent reduction of free IgE and an increase of total IgE levels in serum, similar to the observations in allergic asthma patients. Maximum suppression of free IgE was observed 3 days after the first subcutaneous dose. After repeated dosing once every 4 weeks, predose serum free IgE levels remained stable between 12 and 24 weeks of treatment. Total IgE levels in serum increased after the first dose due to the formation of omalizumab: IgE complexes which have a slower elimination rate compared with free IgE. After repeated dosing once every 4 weeks at 75 mg to 300 mg, average predose serum total IgE levels at week 12 were two-to three-fold higher compared with pretreatment levels and

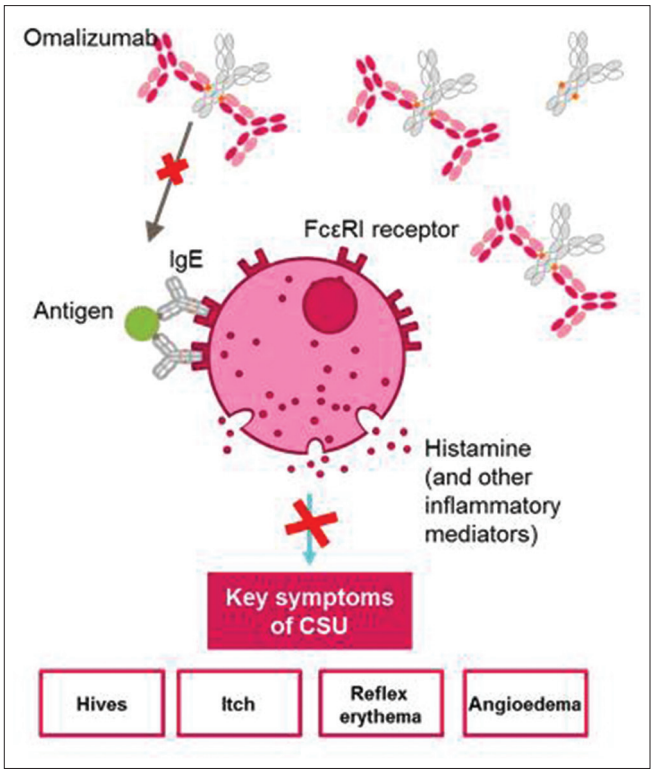

Figure 5: Mechanism of omalizumab (anti-IgE) in preventing mast-cell degranulation

remained stable between 12 and 24 weeks of treatment. After discontinuation of omalizumab, free IgE levels increased and total IgE levels decreased toward pretreatment levels over a 16-week treatment-free follow-up period.[24]

EVIDENCE ON EFFICACY AND SAFETY OF OMALIZUMAB IN CHRONIC SPONTANEOUS URTICARIA

There are three important landmark studies on the use of omalizumab in CSU. First is a 24-week treatment with omalizumab 300 mg (*n* = 81), omalizumab 150 mg (*n* = 80), omalizumab 75 mg (*n* = 78), and placebo (*n* = 80) followed by a 16-week follow-up in CSU management (ASTERIA-I study).[25] The second study was ASTERIA-II study which was a 12-week treatment with omalizumab 300 mg (*n* = 79), omalizumab 150 mg (*n* = 83), omalizumab 75 mg (*n* = 82), and placebo (*n* = 79) followed by 16 weeks follow-up,[26] and the third study was GLACIAL study which was a global, multicenter, randomized, double-blind, placebo-controlled study of safety and efficacy of 24 weeks treatment with omalizumab 300 mg (*n* = 252) versus placebo (*n* = 84).[27] In the above three studies, a total of 733 patients having CSU received omalizumab, and it was found to be effective and safe in the dose of 300 mg 4 weekly injections (subcutaneous). There was a 62–71% reduction in itch with omalizumab from baseline at 12 weeks, 34–44% of patients were itch- and hive-free with omalizumab at 12 weeks, and 73–78% had improvement in

dermatology life quality index scores at 12 weeks, respectively. Common side effects observed were headache, joint pain, injection site reactions, and upper respiratory infections.

In 24 months follow-up study, of the 16 patients with severe CSU using fixed dose omalizumab (150 mg 2–4 weekly), 10 patients (62%) had remission after the first injection of omalizumab, and two patients discontinued therapy.[28] Of the 14 patients, four patients remained in remission for over 9 months after the last injection, and seven patients continued to be in remission with continuing maintenance therapy. In another study presented in the annual conference of the American academy of Allergy, Asthma, and Immunology (20–24 February 2015) in Houston, Texas, 30 patients (15 male/15 female) with treatment-resistant CSU being treated with omalizumab were followed for up to 4 years, with 15 patients completing 4 years treatment.[29] Complete remission was seen in 9/30 (30%) patients after the second dose, and there were significant improvements in UAS between pretreatment and first dose, with mean of 3.9, (95% confidence interval 3.45–4.3) which was maintained throughout the 4th year of therapy. Omalizumab was a safe and effective alternative to corticosteroid for refractory urticaria patients. It is equally effective and safe for long-term use up to 4 years.

INDIAN DATA ON OMALIZUMAB IN CHRONIC SPONTANEOUS URTICARIA

Although there no reports of comparative studies of omalizumab in Indian patients, there are two reports published earlier. First is a single case study of 45 years female who presented with severe CU prevalent since 10 years not responding to antihistamines and steroids.[30] The patient was treated with cyclosporine for sarcoidosis and incidentally her urticaria responded to cyclosporine. Considering the autoimmune etiology for CSU, omalizumab was administered to this patient and the patient's response for CSU was dramatic. The second report is a case study series of omalizumab in five patients with CSU.[31] These five patients had severe urticaria that required multiple antihistamines, steroids, or dapsone to control symptoms and in spite of therapy, they had severe symptoms. In the absence of recommended dose for omalizumab in CSU, the patients were treated with omalizumab according to the dose schedule of asthma. There was a significant improvement in all the patients, with reduction in UAS and need of antihistamines. At the end of 4 months, two patients were free from symptoms and the other three required only antihistamines to control their symptoms. Side effects were recorded in two patients in the form of headache and fatigue.

PRECAUTIONS FOR THE PREVENTION OF ANAPHYLAXIS

In postmarketing experience, anaphylaxis and anaphylactoid reactions have been reported following the first or subsequent administration of omalizumab. Although most of these reactions occurred within 2 h, some occurred beyond 2 h. As per the Omalizumab Joint Task Force report published in 2007 for omalizumab-associated anaphylaxis, patients should be kept under observation for 30 min after each injection. This time should be extended to 2 h after each of the first 3 injections; however, it could be modified based on a physician's clinical judgment after discussing the risks with the patient. In postmarketing spontaneous reports, the frequency of anaphylaxis attributed to omalizumab use was estimated to be at least 0.2% of patients.[24,32-34]

Omalizumab does not necessitate hospital admission for administration. Omalizumab should only be administered by a physician or health care professional, who is trained in the recognition and treatment of anaphylaxis, in a setting where the appropriate medications and equipment are available to respond to an episode of anaphylaxis.[32]

CONSENSUS RECOMMENDATIONS FOR THE USE OF OMALIZUMAB IN CHRONIC SPONTANEOUS URTICARIA IN INDIA

The following recommendations were issued on the use of omalizumab for treatment of CSU in India:

- Omalizumab is approved in adults and adolescents ≥12 years of age with CSU refractory to standard of care by the Health authority of India. Omalizumab is used as an add-on to antihistamine therapy and is currently the only licensed therapy for refractory CSU
- Assessment of the severity of CSU to be done using UAS-7 score
- Serum IgE measurement is not needed before the start of omalizumab therapy for CSU
- It is recommended as the third-line therapy for management of CSU by EAACI/GA2LEN/EDF/WAO 2013 guidelines. The Indian consensus recommends omalizumab as the fourth-line therapy
- Omalizumab should only be administered in a setting where the appropriate medications and equipment are available to respond to an episode of anaphylaxis
- Recommended dose and best response are seen with 300 mg subcutaneous injection once in 4 weeks. Some patients may respond to 150 mg once in 4 weeks and can be tried as per the discretion of treating dermatologist. Because the solution is slightly viscous, the injection may take 5–10 s to administer
- Body weight measurement is not required for calculating the dose of omalizumab
- Ice compress may be applied at site of injection to minimize local reactions
- All patients administered omalizumab to be observed for 2 h after dosage for any allergic reactions

- Dose of omalizumab in patients with hepatic/renal compromised status may remain same (i.e., 300 mg once every 4 weeks)
- Omalizumab should only be used during pregnancy if clearly needed. Caution should be exercised when administering omalizumab to a nursing woman
- Treatment duration for omalizumab is at the discretion of the treating dermatologist. Clinical trial experience for omalizumab is up to 24 weeks (6 months). Real-world data are suggestive of duration of therapy up to 2–4 years with longer remission up to 9 months. Some patients may become refractory and discontinue therapy.

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Conflicts of interest

There are no conflicts of interest.

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