



Critical appraisal of the unmet needs in the treatment of chronic spontaneous urticaria with omalizumab: an Italian perspective

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Purpose of review

The humanized anti-IgE antibody omalizumab has been available for patients with chronic spontaneous urticaria (CSU) in Italy since 2015. This review summarizes the unresolved issues and unmet therapeutic needs associated with omalizumab and discusses practical recommendations for its use in the management of CSU.

Recent findings

Although modern second-generation H₁-antihistamines are the standard of care for patients with CSU, adjunctive treatments (including omalizumab) may be required for effective control of symptoms in many patients. Evidence from clinical trials and experience from daily clinical practice suggest that the use of omalizumab in patients with CSU who have inadequate response to H₁-antihistamines remains challenging.

Summary

Based on current international guidelines, omalizumab labelling information and our experience in clinical practice, we provide treatment recommendations regarding the use of omalizumab in patients with CSU. These include: optimal treatment duration, the use of concomitant antihistamine therapy, the definition and management of disease relapse after treatment, and the management of patients with late or no response to treatment.

Keywords

chronic spontaneous urticaria, omalizumab, second-generation H₁-antihistamines, treatment recommendations

INTRODUCTION

Urticaria is a skin disorder that is characterized by the appearance of wheals (hives), angioedema, or both [1,2]. Chronic urticaria is defined as wheals (with or without angioedema) that persists for at least 6 weeks, and is further classified into two subtypes: chronic spontaneous urticaria (CSU) and chronic inducible urticaria [2]. CSU is the most common type of chronic urticaria [3,4], although few epidemiologic data are available. The prevalence of CSU has been reported to range from 0.1 to 0.8% [5–7], and in Italy, the annual prevalence increased from 0.02 to 0.38% between 2002 and 2013 [8^{***}]. Adults aged 20–40 years are most frequently affected, and CSU is twice as common in women as in men [4,9].

The pathogenesis of CSU is not fully elucidated; however, a combination of mechanisms is thought to be involved [9,10]. The release of histamine from mast cells in the skin is thought to be a key factor in

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KEY POINTS

- Although H₁-antihistamines are the standard of care for patients with CSU, add-on omalizumab therapy may be required in many patients.
- Practical recommendations for omalizumab use in patients with CSU are suggested.
- Patients should receive omalizumab for at least 6 months to establish treatment response.
- Concomitant H₁-antihistamines should be initially maintained, then tapered or discontinued in patients with partial or complete response to treatment.
- Repeated cycles or extended treatment may be necessary in patients with disease relapse or late treatment response.

urticaria pathogenesis [9,11,12[•]]. CSU is considered to have an autoreactive aetiology in a large portion of patients, with production of functional (histamine releasing) autoantibodies against the high-affinity IgE receptor (FcεRI) and IgE, and other autoantibodies against autoantigens, such as thyroid peroxidase and many others that are being studied [9,13].

Despite advances in the management of CSU, treatment remains challenging with a number of unresolved issues and unmet needs [14^{••},15[•],16]. H₁-antihistamines are the mainstay of treatment in patients with CSU, but a significant number of patients show insufficient response to H₁-antihistamine, with poor control of wheal appearance even at high doses [4]. In these patients with therapy-resistant CSU, few treatment options are available, including systemic corticosteroids, ciclosporin, and the anti-IgE antibody omalizumab. This review summarizes the treatment options for patients with CSU, and discusses recommendations regarding the use of omalizumab for the management of patients with CSU in clinical practice.

MANAGEMENT OF CHRONIC SPONTANEOUS URTICARIA

Assessment of disease activity and quality of life

Disease activity in patients with CSU is usually assessed using the urticaria activity score (UAS) over 7 days (UAS7), which is based on patient wheals and pruritus severity scores on each day over 1 week (total score 0–42) [2,17]. Other methods of assessing disease activity include the Angioedema Activity Score, which is based on patient daily diary records

where the number of angioedema episodes per week and the severity of each episode are reported [18^{••}], and the urticaria control test, which is a validated protocol for assessing disease control in patients with CSU [19].

CSU is often associated with a considerable disease burden, which causes substantial reductions in quality of life (QoL) [3,15[•],20]. Patient-related outcomes, including the impact of disease on QoL, should, therefore, be considered when managing patients with CSU. The Chronic Urticaria QoL Questionnaire is a validated method for assessing QoL and evaluating treatment outcomes in patients with chronic urticaria [21]. The Angioedema QoL Questionnaire (AE-QoL) has also been developed and validated and is the first specific patient-reported outcome method available to evaluate the impairment of QoL in patients with CSU and recurrent angioedema [22[•]].

Treatment options

The international treatment guidelines recommend a stepwise approach for the pharmacological management of CSU [2]. Modern second-generation H₁-antihistamines are recommended as the first-line therapy; if symptoms persist for more than 2–4 weeks (or earlier in patients with intolerable symptoms) the antihistamine dosage may be increased by up to four-fold (second-line therapy). Third-line therapy involves addition of omalizumab to second-generation H₁-antihistamines, and may be considered if symptoms persist after a further 2–4 weeks (or earlier if symptoms are intolerable). If symptom control remains inadequate after 6 months of treatment, fourth-line therapy with a trial of ciclosporin as add-on therapy to second-generation H₁-antihistamines is recommended. Corticosteroids may be used for up to 10–20 days at any stage if disease exacerbations occur (2; unpublished data from the 5th Consensus Conference on the Update and Revision of the European Academy of Allergy and Clinical Immunology (EAACI)/Global Allergy and Asthma European Network (GA²LEN)/European Dermatology Forum (EDF)/World Allergy Organization (WAO) Guideline for Urticaria, December 2016).

The efficacy and safety of subcutaneous omalizumab for the adjunctive treatment of CSU has been established in several randomized, placebo-controlled trials [18^{••},23–27], and confirmed in real-world clinical studies [28,29], with no safety concerns identified. A systematic review and *Grading of Recommendations Assessment, Development and Evaluation* assessment [30], and a meta-analysis of randomized, controlled studies ($n=1312$) [31[•]] have

provided further evidence supporting the use of omalizumab (300 mg every 4 weeks) in patients with CSU. In 2014, omalizumab was approved for use in patients with CSU with inadequate response to second-generation H₁-antihistamines, both in the United States [32] and Europe [33].

Unresolved issues in the management of chronic spontaneous urticaria with omalizumab

Based on a review of selected relevant literature and our experience in clinical practice, we agreed that there are several issues related to the management of patients with CSU that remain challenging in daily clinical practice in Italy: CSU duration and treatment duration; treatment with antihistamines in patients receiving omalizumab; definition and management of disease relapse following omalizumab discontinuation; and management of patients with a late or no response to omalizumab.

These issues are discussed in the following sections, and recommendations on how to manage these in clinical practice are provided. These practical recommendations are summarized in Table 1.

Chronic spontaneous urticaria duration and treatment duration

What is the optimal treatment duration for omalizumab?

CSU has a variable and unpredictable disease course, with its duration varying from 3 to 12 months in most patients, whereas others may be affected for more than 5 years [4,5]. Data concerning the duration of CSU are limited and vary considerably between studies, most likely because of differences in patient selection criteria. Other factors that may contribute to this variability include the heterogeneity of treatments received for CSU, differences in the characteristics of the treatment centers, and the incidence of disease relapse or concomitant infections. Overall, the evidence indicates that CSU can last for more than 1 year in a substantial proportion of patients [5,34–39]. Factors that appear to be associated with a prolonged duration of CSU, include increased disease severity, the presence of angioedema, autoreactivity, and the combination of CSU with physical urticaria [4]. Population-based epidemiological studies of CSU are clearly needed, and registries of patients with CSU may also provide useful epidemiological data.

In the three pivotal, randomized controlled trials of omalizumab in patients with CSU and inadequate response to H₁-antihistamines, treatment

Table 1. Summary of practical recommendations concerning unresolved issues related to omalizumab treatment in patients with chronic spontaneous urticaria

Treatment duration
Recommendation
At least six doses of 300 mg of monthly omalizumab should be administered to establish whether or not there is treatment response
Treatment with antihistamines in patients receiving omalizumab
Recommendation
Maintain antihistamine therapy for the first 4 weeks of add-on omalizumab treatment, after which antihistamines may be:
Discontinued or used as needed in patients with complete response
Tapered to the lowest effective dosage in patients with partial response
Maintained without change in patients with limited/no response
Definition of disease relapse following omalizumab discontinuation
Recommendation
Disease relapse is defined as the gradual recurrence of CSU symptoms, as measured by UAS >3 or UAS7 >16 after 30 days of H ₁ -antihistamines at maximum approved dosages
Management of disease relapse
Recommendation
Administer a second cycle of omalizumab (five doses of 300 mg every 4 weeks) in patients with disease relapse, repeating the cycle of six and five doses in patients with a further relapse
Management of patients with a late response to omalizumab
Recommendation
Extend omalizumab treatment for up to 6 months in patients with partial response to omalizumab (i.e., >50% to <90% improvement in UAS7) before discontinuation
Management of patients with no response to omalizumab
Recommendation
Discontinue omalizumab in patients who do not respond after 6 months of treatment, and consider ciclosporin treatment

CSU, chronic spontaneous urticaria; UAS, urticaria activity score; UAS7, urticaria activity score over 7 days

durations ranged from 12 to 24 weeks [23,25,27]. Across these trials, the median time to achieve well controlled urticaria (UAS7 ≤6) with omalizumab 300 mg every 4 weeks (the approved dose) was 3–6 weeks, and the median time to achieve complete response (UAS7 = 0) was 8–13 weeks [40^{***}]. Of note, among patients who were receiving omalizumab 300 mg who had not achieved UAS7 6 or less at week 12, 58% achieved UAS7 6 or less between weeks 13 and 24 (vs. 38% of those receiving placebo) [40^{***}]. In a meta-analysis of seven randomized trials, the rate of complete response (i.e., UAS7 = 0) with omalizumab 300 mg was 36% [31[†]]. These data, along with the experience in clinical practice, indicate that patients who fail to achieve rapid response to omalizumab can respond later and may,

therefore, need prolonged treatment (>3 months) to achieve a clinically meaningful response.

Omalizumab has been available in Italy for the management of patients with CSU since September 2015. According to the Italian Medicine Agency (AIFA) labelling information, omalizumab 300 mg (as 2×150 -mg injections) should be administered once every 4 weeks for 3 months and a further 3 months in cases with clinical response, for a total of 12×150 -mg subcutaneous injections (6-month treatment duration), as add-on to H₁-antihistamines at approved dosages [41]. This first cycle of treatment should be followed by an 8-week treatment interruption. If symptoms recur, a second cycle of five additional doses of omalizumab 300 mg every 4 weeks (5 months) can be administered (total treatment duration 13 months).

As omalizumab is not a disease-modifying agent, repeated treatment cycles will likely be required in several patients. Effective, long-term treatment with omalizumab has been described [42–46], but clinical experience with extended treatment durations and/or repeated treatment cycles remains limited. Taking into account the limitations imposed by current regulations, the best method of long-term management for these patients still remains unknown. It should be noted that the lack of a standard definition of response to omalizumab and of a consensus regarding appropriate treatment targets adds to the challenge of establishing optimal treatment duration in patients with CSU [47]. Based on our experience, we do not have a specific recommendation regarding the optimal omalizumab treatment duration, but the AIFA labelling information should be followed.

Treatment with antihistamines in patients receiving omalizumab

Should concomitant antihistamine treatment be modified or discontinued during treatment with omalizumab?

In the pivotal clinical trials of omalizumab, H₁-antihistamine therapy was maintained at stable prandomization dosages during the treatment period [25]; at approved dosages for the first 12 weeks (after which an additional H₁-antihistamine could be introduced) [27]; or at stable prandomization dosages in combination with H₁-antihistamines, leukotriene receptor antagonists, or both [23]. A meta-analysis of treatment response by antihistamine dosage (standard vs. high dosage) indicated that increasing the antihistamine dose in patients with CSU can improve pruritus control, but does not significantly affect response rates or number of wheals [48*]. According

to the international guidelines, a trial of omalizumab added to high-dose H₁-antihistamines (i.e., up to four-fold increase) is recommended as third-line treatment for CSU [2]. In contrast, the Italian prescribing information recommends addition of omalizumab to approved dosages of H₁-antihistamines [41]. The lack of consistent guidelines regarding antihistamine dosages may complicate decisions concerning antihistamine treatment in patients with CSU in clinical practice in Italy.

In our experience, patients who respond to add-on omalizumab may gradually reduce and eventually discontinue antihistamines on the basis of their clinical course; antihistamines can be resumed as needed. Indeed, reduced antihistamine requirements are often observed in patients receiving omalizumab in clinical practice [44,45,49]. We suggest that the current antihistamine agent and dosage be maintained during the first 4 weeks of omalizumab treatment (until the first follow-up visit), with reduction or discontinuation of antihistamine therapy at the second omalizumab administration based on treatment response (UAS7 reduction). In patients with a UAS7 reduction of more than 90% (i.e., complete response), antihistamines can be discontinued or used intermittently on an as-needed basis; if UAS7 reduction is 50–90% (partial response), the antihistamine dosage can be tapered to the lowest effective dosage; and if the UAS7 reduction is less than 50% (limited or no response), current antihistamine therapy is maintained without change.

Definition and management of disease relapse following omalizumab discontinuation

How is chronic spontaneous urticaria relapse defined in terms of urticaria activity score over 7 days score?

In the pivotal clinical trials, CSU symptoms (as measured by weekly number of hives and itching-severity scores) gradually recurred at approximately 10–12 weeks after the end of omalizumab treatment [23,25,27]. According to the AIFA labelling information for omalizumab, disease relapse is defined as a UAS score of more than 3 or a UAS7 score of more than 16 after 30 days of H₁-antihistamines at the maximum approved dose [41]. By contrast, international guidelines suggest using H₁-antihistamines at up to four-fold higher than recommended doses as second-line treatment in patients with CSU [2].

Patients with disease relapse should be treated as per the AIFA labelling information (see CSU duration and treatment duration), which recommend a second treatment cycle, consisting of five injections

of omalizumab 300 mg every 4 weeks, in patients with recurrent CSU symptoms.

Management of patients with late or no response to omalizumab

How should treatment response rates be defined?

The lack of standard treatment response definitions and of a consensus regarding treatment targets complicates CSU management [47]. Clear definitions concerning the rate of response (i.e., early responders and late responders) are also lacking (Table 2).

An analysis of responder rates (response defined as a UAS7 ≤ 6) from the pivotal randomized controlled trials of omalizumab has revealed the existence of early (before week 4) and late (after week 12) responders [40^{***}], which suggests that omalizumab may act through distinct mechanisms of action depending on the rate of response [50^{***}]. This finding also indicates that if omalizumab is stopped before administration of at least 6 months of therapy (six doses of 300 mg monthly), potential responders may be missed. According to the AIFA labelling information, omalizumab should be discontinued in patients who do not show significant improvement (i.e., at least moderate response of $>50\%$ improvement in UAS and UAS7 from pretreatment values) after 3 months of therapy (three doses of 300 mg monthly) [41]; however, this approach may exclude late responders. In a study of patients with slow and late response to omalizumab, positive basophil histamine release assay and autologous serum skin test results were significant predictors ($P < 0.01$) of slow response to omalizumab (i.e., complete response after 8 days) [51^{***}]. Patients who do not respond to omalizumab after 6 months may be switched to ciclosporin if there are no contraindications to this drug.

In our opinion, patients who exhibit partial response to omalizumab (i.e., $>50\%$ to $<90\%$

improvement in UAS7 score) should receive extended treatment for up to 6 months before omalizumab is discontinued. Based on a general consensus, a treatment duration of more than 3 months (ideally 6 months) appears to be more adequate for identifying nonresponders.

CONCLUSION

Based on current guidelines, AIFA labelling information, evidence from the literature and clinical experience, we have suggested recommendations regarding some of the unresolved clinical issues associated with use of omalizumab in patients with CSU. These recommendations, include guidance regarding the duration of treatment, the use of antihistamines, and the management of patients with disease relapse after omalizumab, and those with partial or no response to treatment. Further real-world studies on the use of omalizumab in patients with CSU may provide more detailed information regarding the optimal treatment duration and strategies for the management of patients with partial or no response to treatment.

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Table 2. Patterns of response to omalizumab in patients with chronic spontaneous urticaria

Grade of response	UAS7 score
Responder	≤ 6
Partial responder	>6 to ≤ 28
Non responder	>28
Rate of response	Time to response
Early responder	4 weeks
Late responder	5–24 weeks

UAS7, urticaria activity score over 7 days.

Conflicts of interest

There are no conflicts of interest.

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