

Rostrum

How to Treat Patients with Chronic Spontaneous Urticaria with Omalizumab: Questions and Answers

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Omalizumab is an effective treatment for patients with chronic spontaneous urticaria (CSU). In routine clinical practice, physicians often face complex cases of CSU and need to decide whether patients are suitable for omalizumab treatment and how to manage this therapy. Here, we provide evidence and experience-based answers to the most common and important questions on omalizumab treatment of CSU. At 4 large urticaria centers, questions on the use of omalizumab in the treatment of patients with CSU were collected and then ranked by frequency and importance and grouped into top 5 domains using an interactive consensus approach. We suggest that omalizumab can be used to treat patients with CSU with any of the 3 CSU phenotypes (wheals only, angioedema only, wheals and angioedema), with comorbid chronic inducible urticaria, with cancer, who receive other biologics or cyclosporine, or who are pregnant or want to become pregnant, or are breast-feeding. Omalizumab treatment should be started with 300 mg every 4 weeks, monitored with validated patient-reported outcome measures, and maintained, in responders, until remission of CSU. Finally, partial responders or non responders can benefit from omalizumab up dosing or adding or switching to cyclosporine. We believe our suggestions on the use of omalizumab in CSU will help to inform clinical decision making. Follow-up efforts should increase, systematically review, and profile the data available and provide evidence-based recommendations on how to best use omalizumab in

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INTRODUCTION

Chronic spontaneous urticaria (CSU) is a heterogeneous disease characterized by the development of transient (usually <24 hours) pruritic wheals, angioedema, or both, which are not related to specific triggers, for longer than 6 weeks. CSU causes severe impairment in patients' quality of life (QOL).^{1,2} The international guideline on CSU recommends to "treat CSU until it is gone." It also recommends using pharmacotherapy "as much as needed and as little as possible," to first move patients to effective treatment and to then establish long-term therapy with an optimal risk/benefit profile.³

The use of a second-generation antihistamine (sgAH) at the licensed dose is recommended as the first-line treatment of CSU, and up dosing of this sgAH up to 4-fold is recommended in treatment-resistant patients.⁴ In antihistamine-resistant patients, the humanized anti-IgE mAb omalizumab is recommended as the only third-line treatment option.³

The clinical efficacy and safety of omalizumab in CSU has been shown in several clinical trials and real-life studies,⁵⁻¹² and multiple mechanisms have been suggested for the therapeutic effects of omalizumab in CSU.^{13,14} Several recent studies have helped to understand how and why patients with CSU respond when treated with omalizumab (complete, partial, or no response; fast vs slow response), with important insights on relevant mechanisms and potential predictors of treatment outcome.¹⁵⁻¹⁷ However, many questions on how to use omalizumab in CSU remain unanswered. Here, we review the most frequent and important questions on the use of omalizumab in CSU grouped into 5 domains, and we provide, on the basis of available evidence and our experience, suggestions (Table I) and a practical approach (Figure 1) for answers and solutions.

METHODS

At 4 large urticaria centers in Germany, Turkey, Russia, and Portugal, questions encountered on the use of omalizumab in the treatment of patients with CSU were collected and grouped by domains, which were then ranked by frequency and importance using an interactive consensus approach. For the top 5 domains of questions, we first performed a PubMed and Google Scholar search to identify the most recent relevant studies. We then selected and reviewed studies that provide applicable information for our selected questions. Finally, we used the evidence from these studies together

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Abbreviations used

AAS-Angioedema activity score
 CIndU-Chronic inducible urticaria
 CSU-Chronic spontaneous urticaria
 QOL-Quality of life
 RCT-Randomized controlled trial
 SD-Symptomatic dermographism
 sgAH-Second-generation antihistamine
 UAS7-Urticaria activity score for 7 consecutive days
 UCT-Urticaria control test

with our clinical experience for the development of suggestions for answers and solutions, using a consensus-based approach.

QUESTIONS AND ANSWERS**Domain 1: Which patients with CSU should be considered for omalizumab treatment?**

What do we know? Omalizumab is licensed for the treatment of patients with CSU and recommended by the international urticaria guideline for patients with CSU unresponsive to antihistamine treatment.³ What do we need to know? Can all patients with CSU be treated with omalizumab? Can omalizumab be expected to be safe and well tolerated in all patients with CSU and can all patients with CSU be expected to benefit?

In the phase III trials and all other randomized controlled trials (RCTs) on omalizumab performed so far, the presence of wheals was an inclusion criterion, thus excluding patients with CSU with exclusively angioedema. Along the same line, the exclusion criteria of many RCTs included “a clearly defined underlying cause of chronic urticaria, e.g. physical urticaria,” thus excluding patients with CSU with comorbid inducible urticaria (CIndU). CIndU is known to be a risk factor for severe CSU. Finally, malignant diseases and treatment with cyclosporine or other biologics, pregnancy, or breast-feeding were exclusion criteria in most controlled trials of omalizumab in CSU, and children younger than 12 years were also excluded. Is there enough evidence and experience to recommend the use of omalizumab in these patient populations with CSU?

Should omalizumab be used in all 3 CSU phenotypes—wheals and angioedema, wheals but no angioedema, and angioedema but no wheals? Three CSU phenotypes have been described: (1) 33% to 67% of patients with CSU experience wheals and angioedema, (2) 29% to 65% of patients with CSU exhibit wheals but no angioedema, and (3) up to 13% of patients with CSU have angioedema but no wheals.¹⁸ Although there is strong evidence of efficacy of omalizumab in patients with CSU who have wheals, with or without angioedema, no controlled trials have been performed in patients with CSU with angioedema but without wheals. However, the use of omalizumab for the treatment of angioedema in patients with CSU is supported by the results from controlled studies involving patients who had angioedema and wheals, as well as case reports of patients with angioedema but no wheals.

Analyses of the pooled data from 3 omalizumab phase III trials revealed that treatment with 300 mg/4 wk of omalizumab led to a marked reduction in days per week with angioedema as

compared with placebo at 12 and 24 weeks.¹⁹ Among patients with baseline angioedema, those treated with 300 mg had a greater clinical benefit (defined by the improvement in the QOL and frequency of angioedema episodes) as compared with the omalizumab 150-mg and, especially, 75-mg groups.¹⁹

The double-blind RCT X-ACT included only those patients with CSU who had 4 or more angioedema episodes during the 6 months before inclusion.^{20,21} Treatment with 300 mg of omalizumab significantly decreased the angioedema activity as assessed by the angioedema activity score (AAS), number of angioedema-burdened days per week, the frequency and size of angioedema, and the median time to the first recurrence of angioedema. Furthermore, patients treated with 300 mg omalizumab had significant improvement in QOL.^{19–22} Finally, omalizumab treatment decreased depression scores and fear of suffocation due to angioedema.^{20,21}

In several case reports and case series, omalizumab was successfully used in a total of 28 patients with angioedema but no wheals (Table II). In most patients, 300 mg/4 wk was used, and the onset of effect was seen during the week after the first injection. In all patients, angioedema ceased to occur while on omalizumab treatment, and corticosteroids were stopped in patients who had received them (Table II). In the largest case series reported, AAS decreased to 0 in 8 patients after the start of treatment with omalizumab.²³

In summary, patients with CSU with antihistamine-resistant angioedema with/without wheals should be considered for treatment with omalizumab 300 mg/4 wk. Importantly, the differential diagnoses of recurrent angioedema due to CSU include bradykinin-mediated forms and, in rare cases, idiopathic angioedema (ie, not mediated by bradykinin or mast cell mediators). Bradykinin-mediated angioedema including hereditary angioedema and angiotensin-converting enzyme inhibitor-mediated angioedema need to be excluded before omalizumab treatment is considered. This should be done by a detailed history (eg, early onset of angioedema?, abdominal attacks?, other family members affected?, unresponsive to antihistamine and corticosteroid treatment?), and patients suspected to have hereditary angioedema should be assessed for blood levels of C1-inhibitor function, C1-inhibitor protein, and C4.^{24,25}

Should omalizumab be used in patients with CSU

with CIndU? In 10% to 50% of patients, CSU occurs in combination with CIndU, primarily symptomatic dermographism (SD) and delayed pressure urticaria.¹⁸ Some physicians are hesitant to administer omalizumab in patients with CSU with comorbid CIndU for several reasons. First, omalizumab is not licensed for the treatment of patients with CIndU. Second, patients with CSU with comorbid CIndU were excluded from the omalizumab phase III trials and several other RCTs.²⁶ Third, trials that compare the efficacy and safety of omalizumab in patients with CSU with/without CIndU are lacking. However, comorbidity of CIndU is held to be linked to longer CSU duration²⁷ and more severe CSU.²⁸

There is increasing evidence that omalizumab treatment is effective in patients with CSU plus CIndU. In a retrospective study, 5 patients with CSU plus delayed pressure urticaria and 1 patient with CSU plus SD had complete symptom control after the first use of omalizumab.²⁹ In another report, a 37-year-old woman with CSU plus pressure urticaria plus SD experienced complete remission of her 3 urticarias after the first injection of

TABLE I. The most common and frequent questions on the use of omalizumab in CSU, grouped in 5 domains, and recommendations based on the available evidence and our experience

Questions	Recommendations
1. Which patients with CSU should be considered for omalizumab treatment?	
Should omalizumab be used in all 3 CSU phenotypes, wheals and angioedema, wheals but no angioedema, angioedema but no wheals?	Patients with CSU with angioedema with/without wheals should be considered for treatment with omalizumab 300 mg/4 wk.
Should omalizumab be used in patients with CSU with CIndU?	Omalizumab can be effective for both CSU and CIndU, although the administration of omalizumab in isolated CIndU is “off-label.”
Can omalizumab be used in patients with CSU with malignant diseases?	Omalizumab can be used for the treatment of CSU in patients with comorbid malignancy.
Can omalizumab be given to patients who receive cyclosporine or other biologics?	A switch from cyclosporine to omalizumab should be offered to all patients. We suggest that omalizumab and other biologics can be used simultaneously, following risk/benefit assessment.
Should omalizumab be used in children with CSU?	Omalizumab is approved in patients with CSU aged ≥ 12 y. In our experience and opinion, omalizumab can be used for the treatment of patients with CSU who are younger than 12 y.
Can omalizumab be used in pregnant patients, in patients who want to become pregnant, or breast-feeding patients?	On the basis of evidence and our experience, pregnant and breast-feeding patients with CSU and patients with CSU who want to become pregnant can be treated with omalizumab (Food and Drug Administration category B).
2. How to start omalizumab treatment in patients with CSU?	
How should the response to omalizumab treatment be defined and evaluated in patients with CSU?	We suggest using the UCT as the primary instrument to assess treatment responses to omalizumab in patients with CSU. Whenever possible, use of the UAS7/AAS and CU-Q ₂ OL/AE-QOL should complement the use of the UCT.
Should any blood tests be done before or during omalizumab treatment?	We suggest to measure blood levels of IgE before and during treatment in patients with CSU on omalizumab therapy, because pretreatment IgE levels of <40 IU/mL and a ratio of <2 of week 4/pretreatment IgE levels may be linked to a higher risk of nonresponse.
What starting dose of omalizumab should be used in patients with CSU?	On the basis of the evidence and our experience, the starting dose of omalizumab in patients with CSU should be 300 mg/4 wk.
Can we discontinue antihistamines in patients with CSU treated with omalizumab?	sgAHs should be taken continuously until the patient shows a complete response to omalizumab. As soon as complete control is achieved, sgAHs can be tapered off.
3. How to manage patients with CSU who are complete responders to omalizumab?	
For how long should omalizumab be continued in patients who show complete response?	The evidence and our experience show that a significant proportion of patients need omalizumab for more than 1 y. Rather than treating patients for a fixed length of time, the focus should be on using omalizumab until the disease is gone.
Can the dose of omalizumab be reduced or the interval of injection be increased in patients with complete response to omalizumab?	At present, we do not reduce the dose of omalizumab in complete responders. We do, however, increase the duration of treatment intervals in some patients with complete control on 300 mg of omalizumab, mainly to assess these patients for their optimal injection intervals and for their need for further treatment.
How should omalizumab treatment be discontinued in patients with complete control of their CSU?	Omalizumab can be stopped at once and the patient kept under surveillance and re-treated if CSU relapses, or omalizumab injection intervals are increased by 1 wk, if tolerated without reappearance of CSU signs and symptoms, until 8-wk intervals are reached, and then treatment discontinuation can be attempted.
When should omalizumab treatment be reinitiated in patients with complete response who experience relapse after discontinuation?	In our experience, relapse of CSU after stopping omalizumab cannot be controlled with antihistamines and omalizumab re-treatment is soon needed.
How should treatment be adapted and managed in patients who show complete response and then experience relapse while on omalizumab treatment?	If exacerbation is mild, sgAHs can be restarted and/or updosed. If this does not work, treatment with glucocorticosteroids for up to 10 d may be considered. If this does not work, we suggest that patients be considered partial responders or nonresponders and treated accordingly.
4. How to manage patients with CSU who are partial responders or nonresponders to omalizumab treatment?	
Should the dose of omalizumab be increased and/or the treatment interval be shortened in patients with CSU with a partial or no response to omalizumab? If so, when and how?	In our experience, in patients with worsening of the symptoms at the end of the interval, we suggest shortening the interval. In patients with uncontrolled symptoms throughout the interval, we updose before shortening the interval.

(continued)

TABLE I. (Continued)

Questions	Recommendations
When should omalizumab be discontinued in patients who do not show a clinical benefit?	On the basis of evidence and our experience, we use omalizumab for a minimum of 6 mo before considering other treatment options.
Can we add cyclosporine to patients receiving omalizumab? When and how?	Combining low-dose cyclosporine with omalizumab might be an option to consider especially in patients who show partial response to omalizumab.
5. How to deal with side effects in patients treated with omalizumab?	
How to deal with side effects in patients treated with omalizumab?	In our experience, mild reactions are usually self-limited. We suggest treatment discontinuation only in severe reactions.

AE-QOL, Angioedema quality of life questionnaire; CU-Q₂OL, chronic urticaria quality of life questionnaire.

omalizumab.³⁰ In addition, a systematic review of 43 trials including 2 RCTs and several case series showed that CIndU improved or resolved in most patients with omalizumab.³¹ The evidence is strongest for SD, cold urticaria, and solar urticaria.^{31,32} Rates of adverse events were low and rarely led to treatment discontinuation. Treatment of patients with CSU plus CIndU is, therefore, very likely to improve both CSU and CIndU, even in patients in whom CIndU is the dominant form of chronic urticaria.

In summary, patients with CSU who also have CIndU, in our opinion, should receive omalizumab if needed. The use of omalizumab, in these patients, is on-label, and there is increasing evidence and experience in support of the substantial benefits of omalizumab in patients with CSU plus CIndU.

Can omalizumab be used in patients with CSU with malignant diseases? This is a question we are frequently asked by patients with CSU and their physicians. There are no reports that the use of omalizumab is less safe or effective in patients with CSU with comorbid malignancy. For now, the only contraindication to omalizumab is a history of hypersensitivity reactions to omalizumab.³³ In patients with asthma, long-term treatment with omalizumab did not increase the risk for malignancies.^{34,35} As of now, there are no published data on the effects of omalizumab in CSU with malignant disease.

In our opinion and experience, omalizumab can be used for the treatment of CSU in patients with comorbid malignancy.

Can omalizumab be given to patients who receive cyclosporine or other biologics? Many patients with CSU who do not respond to antihistamines, today, are treated with cyclosporine, either because guidelines used to recommend both cyclosporine and omalizumab as third-line treatment options, because omalizumab is not available, or because some countries' regulations require patients to fail cyclosporine treatment before omalizumab can be used.^{36,37} The international urticaria guideline recommends that omalizumab should be preferred over cyclosporine for the treatment of antihistamine-resistant patients with CSU. Unlike omalizumab, cyclosporine is not licensed for the treatment of CSU. More importantly, the risk/benefit profiles of both treatments favor the use of omalizumab.^{3,38-40} Patients receiving higher doses of cyclosporine are at increased risk of nephrotoxicity and hypertension, and patients receiving cyclosporine for a long period appear to be at an increased risk of malignancy.³⁷

In line with current guidelines, a switch from cyclosporine to omalizumab should be offered to patients with CSU. In patients

with fully controlled CSU under cyclosporine, reevaluating disease activity and spontaneous remission before starting omalizumab is advisable. In cyclosporine partial responders, we suggest starting omalizumab while maintaining cyclosporine at the lowest effective dose. When complete control with omalizumab is achieved, cyclosporine should be stopped. Once started, omalizumab should be maintained for no less than 6 months, to allow "slow responders" to benefit.⁴¹ In cyclosporine non-responders, we suggest to stop cyclosporine and start omalizumab.³

Patients with CSU have an increased prevalence of autoimmune diseases.^{42,43} Some patients with CSU require treatment of these disorders with biologics. Whether or not omalizumab can be given together with another biologic is, therefore, a common question. There is no published efficacy or safety data on the combined use of omalizumab and other biologics. But there is also no reason to suspect that the use of omalizumab in combination with other biologics is less safe or effective. We suggest that omalizumab and other biologics can be used simultaneously, following risk/benefit assessment.

Should omalizumab be used in children with CSU?

Omalizumab is licensed for use in patients with CSU 12 years or older. CSU is as prevalent in childhood as it is in adulthood,⁴⁴⁻⁴⁶ and physicians commonly face the decision on whether or not to use omalizumab in patients with CSU younger than 12 years. Several RCTs have revealed the efficacy and safety of omalizumab in patients with CSU 12 years or older.^{6,7,10,47} As described in a very recent review,⁴⁸ there is evidence from only a couple of case reports on the efficacy and safety of omalizumab in children with CSU younger than 12 years, so far. In a case series, complete remission could be achieved in 4 children with monthly subcutaneous injection of 300 mg (n = 2, 10, and 16 years old) and 150 mg (n = 2, 4, and 5 years old).⁴⁹ In one case, a child initially showed partial remission after 300 mg/4 wk omalizumab but reached complete response after changing the regime to every 2 weeks. In another case report, a rapid total response to 300 mg omalizumab could be achieved within 1 day after the first injection.⁵⁰ As of now, no adverse events have been reported in children with CSU treated with omalizumab. Omalizumab is licensed and used, often at doses higher than in CSU, for the treatment of children with asthma 6 years or older.

In our experience and opinion, omalizumab can be used for the treatment of patients with CSU who are younger than 12 years. Patients/parents and physicians should understand that this is off-label. Studies on omalizumab in children with CSU who are younger than 12 years old must be performed.

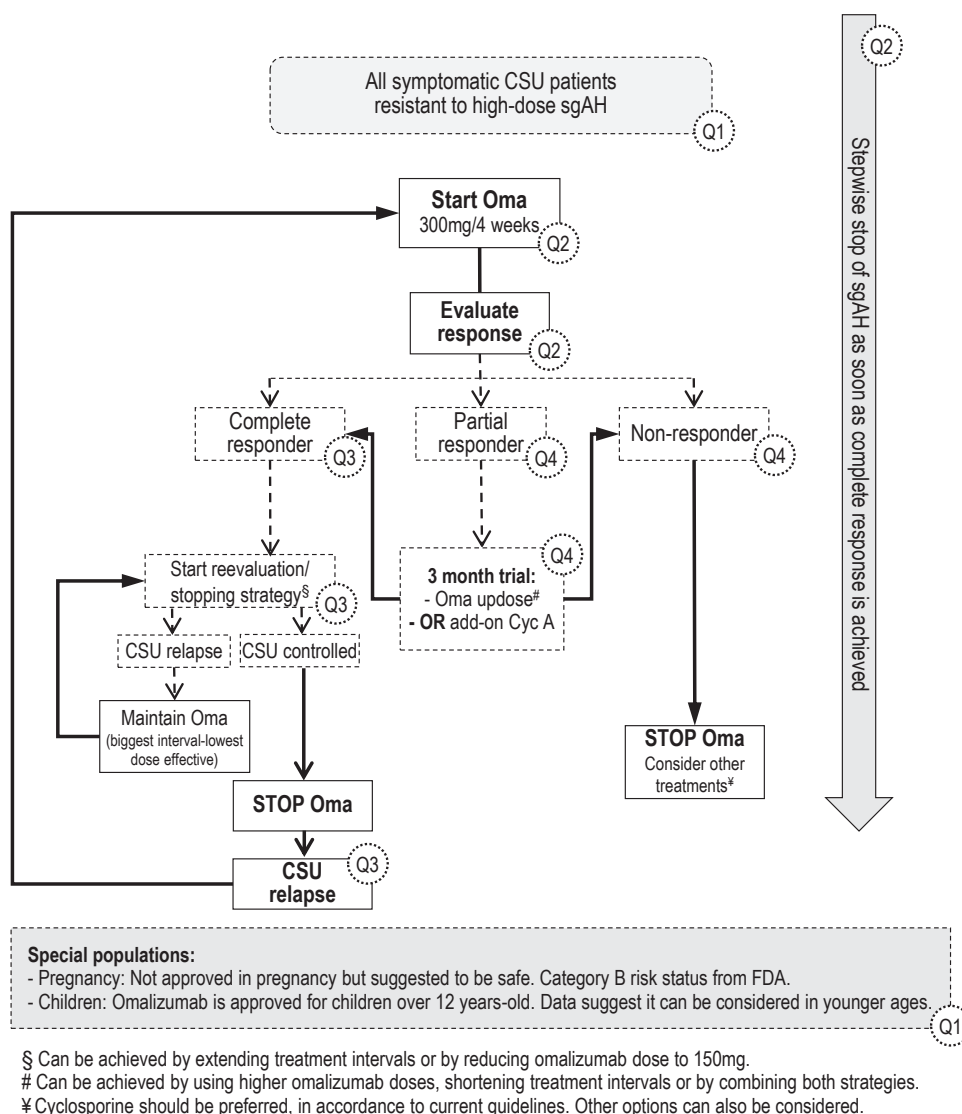


FIGURE 1. Decision making for the treatment of CSU with omalizumab. *Cyc A*, Cyclosporine A; *Oma*, omalizumab.

Can omalizumab be used in pregnant patients, in patients who want to become pregnant, or in breast-feeding patients? Omalizumab is expected to cross the placenta and be excreted in small amounts in breast milk.³³ No evidence of teratogenicity or embryotoxicity was observed in preclinical studies.³³ Because of ethical reasons, clinical trials with omalizumab are not conducted in pregnant or breast-feeding women. The EXPECT registry on omalizumab treatment in pregnant patients with asthma, a postmarketing, prospective observational study, reported no adverse events in 191 pregnant women with asthma exposed to omalizumab within 8 weeks before conception or during pregnancy.⁵¹ Omalizumab has been assigned pregnancy category B risk status by the Food and Drug Administration.³³

Data on the use of omalizumab in both pregnant and breast-feeding patients with CSU are limited.^{30,52-55} Until now, 10 patients with CSU receiving omalizumab during 12 pregnancies have been reported (Table III).^{30,52-55} All showed complete symptom control after initiation of omalizumab treatment and no adverse effects have been reported. All omalizumab-treated women gave birth to healthy children. There were no abnormalities observed during lactation, though only 5 of 12 children were breast-fed (Table III). The international guideline suggests management of pregnant patients with CSU according to the treatment algorithm used in nonpregnant patients after risk/benefit management.³

On the basis of this evidence and our experience, pregnant and breast-feeding patients with CSU and patients with CSU who want to become pregnant can be treated with omalizumab.^{30,52-55}

TABLE II. Efficacy of omalizumab in patients with isolated angioedema

Author, year	Patients with AE, number, sex (age, y)	Efficacy of prophylactic sgAHS in high doses, daily	Efficacy of on-demand corticosteroids	HAE or AE with known cause excluded	Omalizumab, dose (duration of treatment)	Effective in all patients?	Onset of effect
Brunetta et al, ¹⁰⁰ 2018	2, ♂ (30 and 49)	—	NA	Yes	300 mg/4 wk (6 mo)	Yes	No AE episodes during treatment
Faisant et al, ¹⁰¹ 2017	2, ♀ (35-88) and 3, ♂ (39-49)	—	±	Yes	300 mg/2-4 wk (3-12 mo)	Yes*†	Undefined
Bucher et al, ¹⁰² 2017	2, ♀ (27-67) and 1, ♂ (46)	—	±	Yes	150-300 mg/4 wk	Yes	Soon after omalizumab was initiated
Muñoz et al, ¹⁰³ 2016	1, ♀ (36) and 1, ♂ (55)	—	—	Yes	375 mg/2-4 wk (3 y)	Yes	During the first week
Azofra et al, ²³ 2015	3, ♀ and 5, ♂ (34-70)	—	+	Yes	75-300 mg/3-16 wk (1-3 y)	Yes	2-14 d
Öztürk and Kocaturk, ¹⁰⁴ 2014	1, ♂ (47)	—	+	Yes	300 mg/4 wk (4 mo)	Yes*	No AE episodes during treatment
von Websky et al, ¹⁰⁵ 2013	1, ♂ (68)	—	+	Yes	300 mg/4-8 wk (1 y)	Yes	On the day after the first injection
Büyükoztürk et al, ¹⁰⁶ 2012	1, ♀ (34) and 1, ♂ (46)	—	+	Yes	300 mg/4 wk (10-20 mo)	Yes	Differs‡
Wieczorek et al, ¹⁰⁷ 2011	1, ♀	—	±	Yes	150 mg/4 wk (>1 y)	Yes	Undefined
Sands et al, ¹⁰⁸ 2007	3, ♂ (50-65)	—	±	Yes	300-375 mg/3-4 wk (7 mo)	Yes	Soon after omalizumab was initiated

AE, Angioedema; +, effective; —, not effective; ♀, female; ♂, male; HAE, hereditary angioedema; NA, data are not available or specifically defined.

*Relapse after stopping of treatment in some patients.

†Treatment cycle was shortened.

‡Immediately after the first injection (patient 1) or the symptoms gradually decreased until angioedema disappearance after the fourth dose (patient 2).

Domain 2: How to start omalizumab treatment in patients with CSU?

How should the response to omalizumab treatment be defined and evaluated in patients with CSU?

Patient responses to omalizumab treatment are measured by the use of patient-reported outcome measures such as the urticaria activity score (UAS), the AAS, or the urticaria control test (UCT), and response categories are defined on the basis of these patient-reported outcome measures.⁵⁶⁻⁵⁹ Importantly, the use of urticaria activity score for 7 consecutive days (UAS7) = 0 as the definition of complete response has several limitations: (1) patients with CSU with any itch over the course of a week have a UAS7 of more than 0 and are classified as nonresponders or partial responders, independent of whether the itch is linked to CSU or not; (2) UAS7 does not assess angioedema, a frequent and disabling symptom of CSU.

We suggest using the UCT as the primary instrument to assess treatment responses to omalizumab in patients with CSU. The UCT measures disease control, is easy to use, has high levels of validity, reliability, and reproducibility, and strongly correlates with UAS7 and health-related QOL. The UCT can be used in patients with CSU with and without angioedema, with and without CIndU. Whenever possible, use of the UAS7/AAS and chronic urticaria quality of life questionnaire/angioedema quality of life questionnaire should complement the use of UCT.

Should any blood tests be done before or during omalizumab treatment?

We suggest to measure blood levels of total IgE before and during treatment in patients with CSU started on omalizumab, because recent reports and our experience show that baseline and follow-up total IgE levels are linked to omalizumab treatment responses.^{16,60} Jörg et al⁶¹ found that partial/nonresponders had the lowest baseline total IgE levels in a *post hoc* analysis. Another study found that nonresponders had lower baseline total IgE than complete responders.⁶² Nettis et al⁶³ also found that high baseline total IgE was the only important predictor of response in multivariate analysis. More importantly, Ertas et al⁶² found that nonresponders to omalizumab not only had lower baseline total IgE but also had lower increase in total IgE levels at the fourth week of treatment. They showed that the ratio of IgE at week 4 and IgE at baseline had the highest sensitivity and specificity to predict a response to omalizumab. On the basis of these and other findings, pretreatment total IgE levels of less than 40 IU/mL, a cutoff that was recently found to be linked to autoimmune CSU,⁶⁴ and a ratio of less than 2 of week 4 and pretreatment IgE levels may be linked to a higher risk of nonresponse.

What starting dose of omalizumab should be used in patients with CSU?

The recommended starting dose of omalizumab in patients with CSU is 300 mg/4 wk, according to the current international guideline³; however, phase III trials in CSU demonstrated the efficacy and safety of omalizumab at both 150 mg and 300 mg.^{6,7} On the basis of the pooled analysis of these trials, the 300-mg omalizumab dose was shown to be more effective.²⁶ In addition, doses of 150 mg/4 wk could not control angioedema episodes and particular QOL parameters.^{6,7} Recently, a systematic review of real-world evidence from 84 studies showed that most patients with CSU (62.7%) received

TABLE III. Patients with CSU received omalizumab during pregnancies

Author, year	Patients with CSU	Pregnancies	Dose of omalizumab	Lactation	Safety and efficacy data
Gonzalez-Medina et al, ⁵⁴ 2017	n = 2	n = 2	300 mg/4 wk	n = 1/2	No AdEs; complete symptom control; healthy children
Ensina et al, ⁵⁵ 2017	n = 2	n = 3	1. patient: 150 mg/4 wk; 2. patient: 300 mg/4 wk	n = 3/3	No AdEs; complete symptom control; healthy children
Cuervo-Pardo et al, ⁵³ 2016	n = 4	n = 4	300 mg/4 wk	Not reported	No AdEs; complete symptom control; healthy children
Ghazanfar and Thomsen, ⁵² 2015	n = 1	n = 2	150 mg/2 wk, 2, pregnancy: 300 mg/4 wk	n = 0/2	No AdEs; complete symptom control; healthy child
Vieira Dos Santos et al, ³⁰ 2014	n = 1	n = 1	150 mg/4 wk; exacerbation: 150 mg/2 wk	n = 1/1	No AdEs; complete symptom control; healthy child

AdE, Adverse effect.

300 mg as the starting dose.¹² In the United States, 8 of 10 patients with CSU receive omalizumab 300 mg as a starting dose.⁶⁵ Responder rates in patients with CSU started on 150 mg reportedly range from 15% to 35%, lower than the responder rates of patients started on 300 mg omalizumab.^{17,66} On the basis of these reports and our experience, the starting dose of omalizumab in patients with CSU should be 300 mg/4 wk.

Can we discontinue antihistamines in patients with CSU treated with omalizumab? Omalizumab is considered an add-on treatment to sgAHs in CSU. However, it has been shown to be effective without the need for concomitant sgAH treatment in up to 60% of patients included in 16 studies.¹² Although early responders will show complete response within hours or a few days, late responders can take up to 6 months to achieve it.⁶⁷ Because of their mechanism of action, sgAHs are more effective when taken *before* urticaria symptoms occur.³

If a patient does not have any benefit from sgAHs before omalizumab, we suggest to stop them when omalizumab is started. However, the risk of worsening symptoms should be discussed with patients before this decision is taken, because a small, unrecognized benefit might be present. In a patient who has some benefit from sgAH treatment, this treatment should be continued until the patient shows a complete response to omalizumab. As soon as complete control is achieved, sgAHs can be tapered off.^{3,6,7,68}

Domain 3: How to manage patients with CSU who are complete responders to omalizumab?

For how long should omalizumab be continued in patients who show complete response? Omalizumab, in patients with CSU, is not a curative or disease-modifying treatment.^{3,69} Rather, it very effectively prevents symptoms. CSU, in most patients, is a self-limited disease. It is crucial to not stop omalizumab treatment too soon, making symptoms resurface and subjecting patients to avoidable suffering, and to not stop treatment too late, producing overtreatment and unnecessary health care costs. Complete responders to omalizumab treatment may be free of CSU symptoms because of the omalizumab they receive or because their CSU has gone into spontaneous remission. Thus, guidance on when to stop omalizumab treatment in complete responders is needed.

As of now, there are no studies on when to discontinue omalizumab in complete responders.¹⁷ There are, currently, no biomarkers that can help to assess patients on omalizumab treatment, who have achieved complete symptom control, for CSU remission.⁷⁰ Also, there are no markers to predict, in individual patients, when their CSU will go into spontaneous remission. Higher age at onset, being female, and hypersensitivity to nonsteroidal anti-inflammatory drugs, as well as comorbid CIndU, concomitant recurrent angioedema, thyroid disease, positive autologous serum skin test result, and higher disease severity at presentation have all been reported to be linked to longer CSU duration.^{27,71,72} However, none of these markers, alone or in combination, allows for a meaningful prediction of disease duration in individual patients, and the decision when to discontinue omalizumab should not be based on them. Assessing the need for continued omalizumab treatment in complete responders is, for now, a trial-and-error process.

CSU lasts for more than 1 year in a substantial proportion of patients.^{18,73,74} Omalizumab appears to be safe in patients with CSU when used for 1 year⁶⁹ or more.^{29,75-78} Available data from patients with asthma confirm a remarkable safety profile even when omalizumab is used for much longer periods,⁷⁹ although a possible association with cardiovascular and cerebrovascular events has been reported.⁸⁰ Considering the current evidence, when omalizumab is well tolerated, concerns about its safety should not refrain physicians from using it in CSU for as long as it is needed.

In clinical trials and in real life, relapse rates after stopping omalizumab are high (Table IV). Most patients receiving omalizumab in the context of clinical trials have experienced relapse after stopping omalizumab treatment.^{6,7,10,81} In the XTEND-CIU trial, a relapse rate of 43.4% and 45.1% was observed during the 12 weeks after withdrawing omalizumab in patients treated for either 24 or 48 weeks.⁷⁴ Preliminary results from the OPTIMA study also showed a 44.4% to 50% relapse rate after 6 months of treatment.⁶⁶ A real-life study, including 280 patients, reported that it was rarely possible to stop omalizumab even after 1 to 2 years of treatment.⁷⁶

Taken together, this evidence and our experience show that a significant proportion of patients need omalizumab for several years, and that multiple attempts to stop treatment may be needed. Rather than treating patients for a fixed length of time, the focus should be on using omalizumab until the disease is

TABLE IV. Relapse rates after discontinuation of omalizumab in CSU

Author, year	No. of patients in the study	Duration of CSU	Dosage/interval of omalizumab	Duration of the treatment	Duration of the follow-up	% of relapses in follow-up
Nettis et al, ⁶³ 2018	292 CSU	44.1 ± 64.3 mo	300 mg/4 wk	24 wk	16 wk	40.8%
Mandel et al, ⁹⁹ 2018	18 CSU	65 mo	300 mg/4 wk	24 wk	9.5 mo (range, 1-28)	17.6%
Maurer et al, ⁷⁵ 2018	81 CSU	77 ± 118.8 mo	300 mg/4 wk	24 wk 48 wk	12 wk	43.4% 45.1%
Kulthanan et al, ¹⁰⁹ 2018	15 CSU	2.7 y (n = 3)	150 mg with extended durations	NA	Range, 26-38 wk	2 of 3 (67%)
Türk et al, ⁸⁷ 2018	25 CSU	44 mo	300 mg/4 wk	Median, 6 mo	Range, 8 wk to 18 mo	11 of 18 (61%)
Marcelino et al, ¹¹⁰ 2018	23 CSU	4 y (3-28 range)	NA with extended durations	Mean, 30 mo (range, 5-71)	NA	4 of 11 (36%)
Niemeyer-van der Kolk et al, ⁹⁵ 2018	63 CSU	NA	300-600 mg with extended durations	NA	208 wk	10 of 24 (42%)
Sussman et al, ⁶⁶ 2017	136 CSU	NA	300 mg/4 wk	24 wk	4.7 wk	44 of 88 (50%)
Ghazanfar et al, ³² 2016	154 (CSU = 137, CIndU = 17)	3.8 ± 5.4 y (CSU = 137)	150 or 300 mg with extended durations	1 y	NA	14 of 24 (58%) (CSU + CIndU)
Saini et al, ⁷ 2015	81 CSU	6.2 ± 8.0 y	300 mg/4 wk	24 wk	16 wk	NA
Pinto Gouveia et al, ⁹¹ 2017	13 CSU	19.5 y (n = 3)	150 or 300 mg with extended durations	10-12 administrations	NA	2 of 3 (67%)
Kaplan et al, 2013 ¹⁰	252 CSU	7.0 ± 8.8 y	300 mg/4 wk	24 wk	16 wk	NA
Maurer et al, ⁶ 2013	79 CSU	6.1 ± 7.3 y	300 mg/4 wk	12 wk	16 wk	NA
Labrador-Horrillo et al, ⁹² 2013	110 CSU	NA	150 mg/2 wk or 300 mg/4 wk	11.4 mo (range, 1-48)	NA	20 of 41 (47.5%)

NA, Data are not available or specifically defined.

gone. Health regulators need to avoid establishing rules that restrain treatment duration. In contrast, they should support approaches that allow for individualized omalizumab treatment such as discontinuation of omalizumab by interval extension, as outlined in the answer to the following questions. In our own practice, we maintain patients with CSU on treatment with omalizumab for 1 year after they have reached complete response, before we consider discontinuation.

Can the dose of omalizumab be reduced or the interval of injection be increased in patients with complete response to omalizumab? Some authors have suggested that it is possible to reduce the dose of omalizumab to 150 mg/4 wk in patients with complete response on 300 mg/4 wk.^{12,41,82-84} Omalizumab 150 mg/4 wk was effective in a subset of patients with CSU in the pivotal clinical trials,^{6,7} in the OPTIMA study,⁸⁵ and in real life.⁷⁶ More studies on this are needed. At present, we do not reduce the dose of omalizumab in complete responders. We do, however, increase the duration of treatment intervals in some patients with complete control on 300 mg/4 wk of omalizumab, mainly to assess these patients for their optimal injection intervals and for their need for further treatment.⁸⁶

How should omalizumab treatment be discontinued in patients with complete control of their CSU?

Currently, there are 2 strategies to discontinue omalizumab treatment. (1) Omalizumab can be stopped at once and the patient kept under surveillance and re-treated if CSU relapses, which has been shown to be effective.^{29,66,87} (2) Omalizumab injection intervals are increased by 1 week, if tolerated without reappearance of CSU signs and symptoms, until 8-week intervals are reached, and then the treatment can be discontinued.^{41,86-89} Implementation of this strategy benefits from the recent approval for self-administration of omalizumab in many countries.⁹⁰

On the basis of published evidence and our clinical experience, both strategies are effective. The interval extension strategy has 2 benefits: it can help to identify optimal injection intervals in individual patients and it minimizes time to re-treatment in patients who show relapse.⁹¹ However, extending treatment intervals can become difficult to manage, because it demands appointment flexibility and frequent patient observations.

When should omalizumab treatment be reinitiated in patients with complete response who experience relapse after discontinuation? Recent studies have shown that up to 61% of patients will experience clinical worsening after omalizumab discontinuation,^{75,87,92} even if the treatment was maintained for 1 year.⁷⁵ Physicians and patients should be aware of this possibility and omalizumab should be restarted as soon as patients experience relapse after discontinuation. In our experience, relapse of CSU after stopping omalizumab cannot be controlled with antihistamines, and, therefore, omalizumab re-treatment is needed. Re-treatment with omalizumab is effective in the vast majority of patients previously responding to the drug,^{29,66,75,87,92} even when more than 1 re-treatment cycle is needed.⁹³

How should treatment be adapted and managed in patients who show complete response and then experience relapse while on omalizumab treatment? In our clinical experience, exacerbation of CSU under omalizumab treatment is very rare and may be due to increased disease activity, loss of omalizumab efficacy, or both. As of now, the development of antibodies to omalizumab that impair its effects has not been described. CSU disease activity can change spontaneously or because of the presence of new and relevant exacerbators such as drugs, foods, stress, or infection. If exacerbation is mild, sgAHs can be restarted and/or updosed. If this does not work, treatment with glucocorticosteroids for up to 10 days may be considered. If this does not work, we suggest that patients be considered partial or nonresponders and treated accordingly.

Domain 4: How to manage patients with CSU who are partial responders and nonresponders to omalizumab treatment?

Should the dose of omalizumab be increased and/or the treatment interval be shortened in patients with CSU with partial or no response to omalizumab? If so, when and how? Omalizumab updosing can be effective in partial responder or nonresponder patients with CSU.^{28,83,94,95} A retrospective observational study reported that at the end of 3-month therapy, UAS7 of 6 or less was achieved in 43 and 16 of the 79 previously partial responder or nonresponder (UAS>7) patients with 450 and 600 mg/4 wk, respectively.²⁸ Twenty patients did not achieve disease control despite high doses. In another study, 50 of 78 patients with CSU with partial response to omalizumab 300 mg/4 wk became responders after up dosing to 450 mg/4 wk.⁷⁶ There are also reports that switching to shorter treatment intervals can lead to complete response in patients with partial or no response.^{83,95}

In our experience, in patients with worsening of the symptoms at the end of the interval, we suggest shortening the interval. In patients with uncontrolled symptoms throughout the interval, we updose before shortening the interval.^{41,96}

When should omalizumab be discontinued in patients who do not show a clinical benefit? Most patients with CSU who are treated with omalizumab show a fast response, within days to several weeks.⁴⁰ Still, some patients are slow responders.^{7,10} In the phase III studies ASTERIA I and GLACIAL, the median time for patients treated with 300 mg/4 wk omalizumab to achieve UAS7 of 6 or less (UAS7 = 0) was 6 weeks (12 and 13 weeks, respectively).⁶⁷ Importantly, patients who do not benefit by week 12 of omalizumab treatment can benefit from longer treatment. In the ASTERIA I and GLACIAL studies, 58% and 48% of the patients who did not respond (UAS7 > 6) to 300 mg/4 wk omalizumab treatment at week 12 responded with a UAS7 of 6 or less at week 24, respectively.⁶⁷ On the basis of these data and our experience, we use omalizumab for a minimum of 6 months before considering other treatment options.

Can we add cyclosporine to patients receiving omalizumab? When and how? The current urticaria guideline recommends cyclosporine as a fourth-line treatment option in patients with CSU if omalizumab is not effective within 6

months or earlier.³ However, in selected patients, combining low-dose cyclosporine with omalizumab might be an option to consider. Although this strategy is not discussed in the current guideline,³ Eghrari-Sabet et al⁶⁵ reported that immunosuppressive agents, including cyclosporine, were combined with omalizumab in 3.2% (17 of 528) of patients with CSU. Furthermore, 4 adult patients achieved complete resolution of their CSU after adding 1.5 to 3.7 mg/kg of cyclosporine daily to omalizumab 300 mg/4 wk.⁹⁷ No significant adverse effects were observed.

We also find cyclosporine to be effective as add-on treatment in patients with CSU who show partial response to omalizumab. In partial responders to omalizumab, we consider cyclosporine/omalizumab combination, that is, adding cyclosporine at 2 mg/kg, after at least 6 months of omalizumab treatment and after using omalizumab at higher than standard doses and/or shorter than standard intervals.

Domain 5: How to deal with side effects in patients treated with omalizumab?

Omalizumab is considered a safe treatment with a low frequency of side effects, and it is licensed for self-administration in some countries.^{17,90} In several studies, the incidence of adverse events in patients with CSU was comparable or even less to that in placebo.^{26,98} Only 4% of patients discontinued treatment because of adverse events.²⁶

Fatigue, asthenia, headache, and exacerbation of urticaria can occur.^{26,68} We find that patients who experience this often do so after the first or the second treatment only. These reactions are usually mild, last for hours up to a few days, resolve spontaneously, and respond to treatment in case this is needed. Our strategy, when this occurs, is to inform patients that these are known responses and to continue omalizumab treatment.

Severe adverse events that have resulted in the discontinuation of omalizumab treatment include thrombocytopenia, hypertension, retroperitoneal infection, pelvic abscess, and anaphylaxis.^{17,26,98,99} In our practice, with hundreds of patients with CSU treated with omalizumab, we have not had a patient with a severe reaction to this treatment and have not stopped omalizumab treatment because of these side effects.

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