Therapeutic Strategy According to Differences in Response to Omalizumab in Patients With Chronic Spontaneous Urticaria

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J Investig Allergol Clin Immunol 2019; Vol. 29(5): 338-348
doi: 10.18176/jiaci.0323

Abstract

Chronic spontaneous urticaria (CSU) is a heterogeneous condition that can severely impact quality of life. Consequently, rapid disease control is essential. First-line treatment of the symptoms of CSU is the licensed dose of second-generation H_1 antihistamines. For second-line treatment, this dose may be increased by up to 4 times. In patients who fail to respond to higher doses of H_1 antihistamines, omalizumab for up to 24 weeks is recommended to achieve disease control. After this 24-week period, the patient's response to omalizumab should be assessed in order to identify refractory patients. Optimal management of refractory patients has not been established. Therefore, the aim of the present consensus document, which was drafted by allergists and dermatologists with specific expertise in treating urticaria, was to define specific patient profiles based on differences in their response to omalizumab. We also developed a treatment algorithm based on the specific response profile. After a comprehensive literature review, a group meeting was held to discuss issues related to the therapeutic management of patients with CSU that had not been addressed in previous studies. The experts considered both the available evidence and their own clinical experience with omalizumab. We believe that implementation of the proposed algorithm will optimize management of CSU patients who are refractory to antihistamines, reduce disease-related costs, and improve quality of life.

Key words: Chronic urticaria. Antihistamines. Omalizumab. Algorithm. Treatment.

Resumen

La urticaria crónica espontánea (UCE) es una afección heterogénea que puede afectar gravemente la calidad de vida, por lo que el control rápido de la enfermedad es esencial. El tratamiento sintomático de primera línea de CSU es la dosis autorizada de antihistamínicos H1 de segunda generación. Para el tratamiento de segunda línea, esta dosis se puede aumentar hasta cuatro veces. En pacientes que no responden a estas dosis más altas de antihistamínicos H1, se recomienda el tratamiento con omalizumab (hasta 24 semanas) para lograr el control de la enfermedad. Después de este período de 24 semanas, se debe definir el perfil de respuesta del paciente a omalizumab para identificar a los pacientes refractarios. El enfoque de manejo óptimo para pacientes refractarios no ha sido establecido. En este contexto, el objetivo del presente estudio de consenso de expertos que involucró a un grupo de especialistas (alergólogos y dermatólogos) con experiencia específica en el tratamiento de la urticaria fue definir perfiles de pacientes específicos en función de sus diferentes respuestas a omalizumab. Otro objetivo fue desarrollar un algoritmo de tratamiento basado en el perfil de respuesta específico. Primero, se realizó una revisión exhaustiva de la literatura. Luego, se llevó a cabo una reunión grupal para discutir todos los temas relacionados con el manejo terapéutico de estos pacientes que no se habían abordado en ningún estudio previo. En todos los casos, los expertos consideraron tanto la evidencia disponible como su propia experiencia clínica con omalizumab. Creemos que la implementación de este algoritmo propuesto ayudará a optimizar la gestión de los pacientes con CSU que son refractarios al tratamiento con antihistamínicos, reduciendo los costos relacionados con la enfermedad y mejorando la calidad de vida de los pacientes.

Palabras clave: Urticaria crónica. Antihistamínicos. Omalizumab. Algoritmo. Tratamiento.

Introduction

Chronic spontaneous urticaria (CSU) is a heterogeneous condition that causes significant morbidity [1,2]. It is characterized by the sudden appearance of wheals and/or angioedema that persist for 6 weeks or longer [2]. In most cases, the average duration of CSU is from 1 to 5 years [3,4]. CSU is estimated to affect between 0.5% and 1% of the general population, with an annual frequency of 1.4% [5]. The annual prevalence of urticaria appears to have increased in recent years. In Italy, the prevalence increased from 0.02% in 2002 to 0.38% in 2013, with a current incidence rate of 0.10-1.50 per 1000 persons per year [6]. CSU imposes a significant economic burden and has a substantial negative impact on patient quality of life (QOL). Therefore, it is crucial to administer effective treatment as soon as possible [7-9].

The management of CSU consists of a 2-pronged approach based on avoiding the triggers (if known) and pharmacological treatment of the symptoms [3]. The current EAACI/GA$_2$LEN/EDF/WAO guidelines recommend second-generation H$_1$ antihistamines as first-line treatment of the symptoms of CSU [2,10]. However, given that approximately 70% of patients remain symptomatic despite the use of antihistamines at the licensed doses [11,12], the guidelines recommend increasing the licensed dose by up to 4 times for second-line treatment [2]. However, a recent systematic review and meta-analysis estimated that up to 36.8% of patients might be refractory to the maximum dose of H$_1$ antihistamines (4-fold the standard dose) [13]. Recent guidelines recommend adding omalizumab to treatment with antihistamines as a third-line treatment. Fourth-line treatment includes the use of cyclosporine A. For exacerbations, the guidelines recommend short courses of oral corticosteroids for no more than 10 days (Figure 1) [2,10].

Phase 3 trials have demonstrated the favorable efficacy and safety profile of omalizumab [3,14,15], which is substantially safer than cyclosporine, particularly with regard to renal toxicity [10]. An expert panel recently drew the same conclusions regarding the favorable safety and efficacy profile of omalizumab compared with cyclosporine [16]. In addition, a recent meta-analysis found that more than 50% of patients

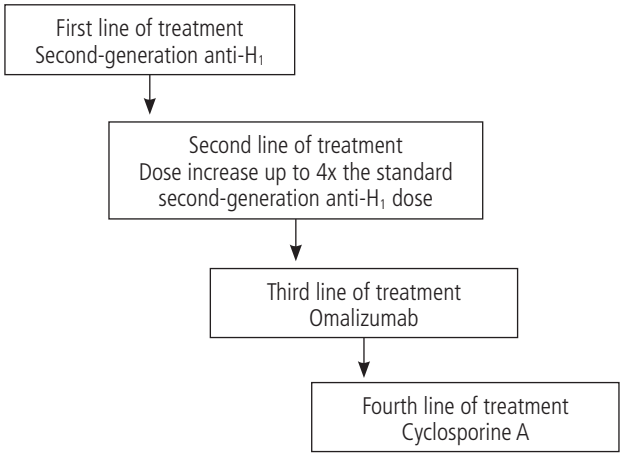


Figure 1. Treatment algorithm for chronic spontaneous urticaria.

who received cyclosporine at doses of 4-5 mg/kg/d presented adverse events [17].

Omalizumab selectively binds to human IgE, thus preventing binding of IgE to its high-affinity receptor (FcεRI) and reducing the amount of free IgE. This process affects the immunological cascade of urticaria on several levels (Figure 2) [18,19]. Both the European Medicines Agency and the United States Food and Drug Administration approved omalizumab for the treatment of CSU in 2014. The favorable efficacy and safety data for omalizumab obtained in clinical trials are further supported by results from real-world clinical studies [1,20,21]. Available evidence supports the use of omalizumab for up to 24 weeks as a third-line treatment for CSU [22]; however, the efficacy of this drug beyond 24 weeks is less well-established [23]. Although most patients respond well to omalizumab, the response profile is highly variable and unpredictable, with some responding quickly and others responding more slowly or not at all. To date, the different response profiles have not been well defined, even though clear

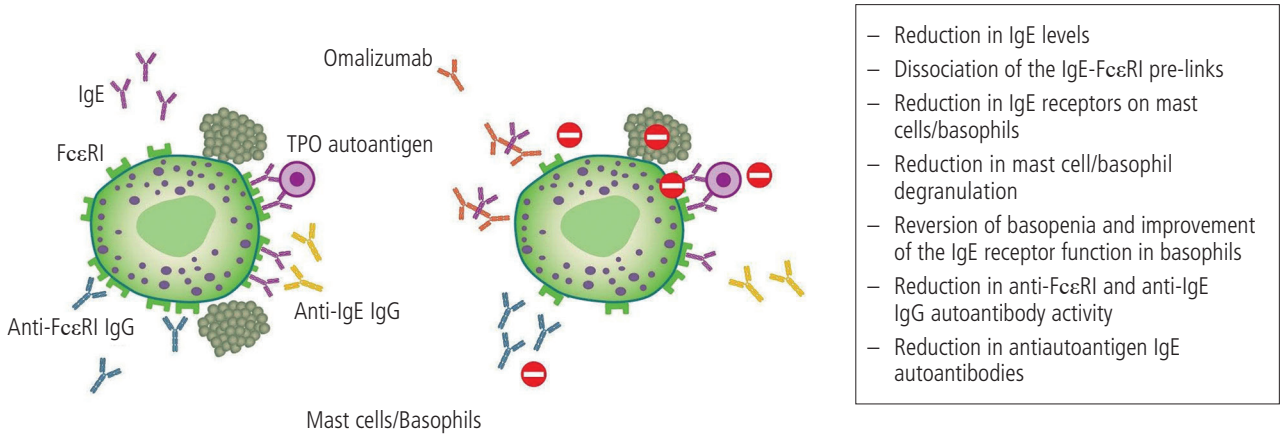


Figure 2. Mechanism of action of omalizumab.

definitions would help to guide the medical management of patients in accordance with their individual response profile.

In this context, an expert working group comprising specialists with broad experience in treating urticaria was convened to define CSU patient profiles depending on the varying responses to omalizumab. We describe these profiles and provide a clear, straightforward therapeutic algorithm to guide the management of patients with CSU according to their specific response to omalizumab.

Methods

We report the consensus opinions of a group of experts in urticaria treatment. The group comprised allergists and dermatologists in Spain with expertise in treating urticaria. This working group met 3 times from 2015 to 2016 to discuss the main unresolved issues regarding therapeutic management of CSU patients.

Initially, the group generated a series of unresolved questions about the optimal use of omalizumab for the treatment of CSU patients that commonly arise in routine clinical practice. The 3 main questions raised were as follows: (*1*) What criteria are taken into consideration when urticaria is "controlled"? (*2*) Can we identify specific patient profiles based on individual differences in the response to omalizumab? (*3*) What is the optimal therapeutic strategy for each of these profiles?

To answer these questions, we performed a bibliographic review of publications on urticaria in the MEDLINE database. Using the PubMed search engine, we searched for various combinations of the following key words in English: *Management, Disease, Urticaria, Chronic Spontaneous Urticaria, Guidelines, Prevalence, Treatment, Therapy, Omalizumab, Antihistamines, Refractory, Cyclosporine, Responders, Non-responders, Activity, UAS, UAS7, QoL, Control, Algorithms, Response predictors, Questionnaire*, and *Impact*.

Questions that were not fully addressed in the literature were addressed based on the extensive clinical experience of the team of experts. Prior to the meetings, the experts were asked to individually prepare their responses to the 3 main study questions in order to facilitate the group discussions. The therapeutic protocol and patient profiles defined in this document are based on available published scientific evidence in conjunction with the consensus expert option of this group of specialists. In addition, a consensus summary of the key points was also developed.

The discussions held to address the aforementioned unresolved issues also yielded several other omalizumab- and CSU-related questions. These issues are addressed in this document.

Discussion

Measurement of the Activity and Impact of CSU

In many cases, it is difficult to precisely assess CSU owing to the heterogeneous nature of the condition and the evanescence of the skin lesions. For this reason, clinical guidelines recommend the use of grading scales in routine clinical practice, and several validated tools are available to monitor disease activity and control and to assess the impact of the condition on patient QOL [2,10]. While it is important to use these scales for the initial assessment, they should also be used for follow-up purposes after initiation of treatment. The scales are particularly useful in patients with poor disease control despite good adherence to treatment. By contrast, these scales may be unnecessary in stable, well-controlled patients [2].

By measuring disease activity, control, and impact, the clinician can identify the patient's individual clinical profile and determine whether his/her CSU is under control. The resulting scores can be used to guide selection of treatment in accordance with the patient's disease status [2].

The Urticaria Activity Score (UAS), particularly the UAS7 version, is recommended for assessment of the symptoms of CSU [2,24]. The UAS7, which was validated in 2008 to measure urticaria symptoms, defines 5 "disease activity categories" according to the score obtained (Supplementary Material, Table 1) [25]. The Spanish versions of the UAS and UAS7 were both recently validated in the EVALUAS trial for use as diagnostic and follow-up tools for patients with CSU [26]. Note, however, that the UAS7 is not suitable for evaluating the activity of chronic inducible urticaria or angioedema. The Angioedema Activity Score is used to assess isolated or CSU-associated angioedema [27].

The consensus opinion of the present expert group is that the Urticaria Control Test (UCT) is the best currently available tool for quantification of disease control in all types of chronic urticaria (which includes both CSU and inducible forms of urticaria). The patient's current treatment should be considered when using these scales, otherwise the scores would not be comparable at different time points.

When evaluating the overall status of a patient with CSU, it is essential to assess the impact of the disease on QOL [2,10]. To date, the only questionnaire specifically developed to measure QOL in CSU patients is the Chronic Urticaria Quality of Life Questionnaire [28].

We recommend using the UAS7 to evaluate the activity of CSU, given that this instrument has proven its value in numerous clinical trials and studies; moreover, the members of this expert group have successfully used this tool for many years. The UAS7 questionnaire is a self-reported instrument that correlates well with the Dermatology Life Quality Index, which is commonly used to assess QOL in dermatology patients [29-31]. Ideally, the UAS7 should be administered weekly to monitor treatment response. It is advisable to use the UCT concomitantly with the UAS7 to ensure that patients have completed both of these instruments correctly during the consultation.

Definition of a Well-Controlled CSU Patient

To accurately determine disease control during follow-up, it is essential to first establish a clear definition of qualitative control to permit the specialist to evaluate response to treatment in daily clinical practice. Moreover, such a definition is important in order to facilitate reliable comparisons of clinical trials.

According to the EAACI/GA2LEN/EDF/WAO guidelines, the aim of treatment in CSU is to achieve complete control of signs and symptoms while ensuring patient safety and QOL [2]. Several scales are available to monitor the variations in different aspects of the disease (Table 1), and a "good" clinical course could be defined based on any of the following: UAS7 activity index <6; a decrease >90% on the UAS7: UCT score >12; or the clinical course based on the clinical criteria of the treating physician.

Given the lack of a specific recommendation regarding the optimal evaluation scale, we believe that a patient whose CSU activity is "well-controlled" should be defined as a stable UAS7 score ≤6 that is sustained over time. Importantly, a UAS7 score ≤6 is closely correlated with the QOL index [32,33].

No clinical trials have yet been performed to establish precisely how long the patient needs to maintain a UAS7 <6 to be considered in remission. Management is patient-specific, both in regard to the type and duration of treatment. Likewise, the best approach to treatment discontinuation (ie, sudden termination or gradual tapering) has not yet been determined.

Antihistamine-Refractory Patients

The activity of CSU may fluctuate between low- and high-activity periods, when the condition is considered severe. Even when the maximum accepted antihistamine dose is prescribed, this is insufficient to control the clinical manifestations of CSU in a substantial proportion of patients (63%) [11]. The UCREX trial [34] showed that more than 75% of CSU patients remain symptomatic even after 6 months of antihistamine treatment. Likewise, the REG-MAR trial [12], carried out in a cohort of 549 CSU patients, showed that 77.3% were refractory to H_1 antihistamines at the licensed dose. Importantly, antihistamine treatment can exacerbate urticaria, although this reaction is rare [35,36]. However, these data should be interpreted taking into account the fact that patients with CSU in these studies, who were seen mostly at tertiary centers, do not necessarily represent the general population of patients with the disease. Most CSU patients who respond properly to a second-generation antihistamine at a licensed dose prescribed by their family doctor probably do not attend specialized units in urticaria.

CSU has a major negative impact on QOL and health care costs [7,8]. The recent ASSURE-CSU trial [11] highlighted the financial burden and negative impact of CSU/chronic inducible urticaria on health-related QOL in refractory patients. The results of that study showed that not only did CSU interfere with QOL, but that it also had both direct (ie, health) costs and indirect (ie, social) costs.

The favorable safety profile of most second-generation antihistamines means that these drugs can be used as second-line therapy at doses higher than the licensed doses [2,37]. A recently published meta-analysis and systematic review [13] found that 63.3% of CSU patients who did not respond to the licensed dose of H_1 antihistamines responded well to higher doses. Furthermore, the increased dose significantly improved control of wheals and itching in the 49% of patients who required a dose increase.

Nevertheless, there is no effective method to predict whether an antihistamine will have a beneficial clinical effect or not. A recent study showed that measurement of the histamine-induced wheal can predict which patients will have a strong clinical response to antihistamines, although its utility for identifying nonresponders is limited [38].

The off-label indication for antihistamine dosing should be revised in light of the availability of new, highly effective treatments such as omalizumab and other emerging

Table 1. Activity, Control, and Quality of Life Scales for Urticaria and Angioedema Patients

Activity measure	UAS7 AAS	– Patients with wheals – Patients with wheals and angioedema – Patients with angioedema	– Exact clinical picture of the current frequency and severity of the CSU symptoms (daily evaluation, weekly score)	– Prospective PRO measure – Patient must complete daily (not always feasible) – Valid only for patients with CSU, not for patients with CIndU – Has been validated for use in adults only
Control measure	UCT	– Patients with wheals, angioedema, or both	– Retrospective PRO measure – Short and simple structure – Simple scoring system – Results available immediately after completion – Can be applied to all the forms of CU	– The information is not well explained
QOL measure	CU-Q2oL	– Patients with wheals or with wheals and angioedema	– Validated in many languages – Good validity and reliability level – Good sensitivity to change	– Slight variations among versions in different languages – Applicable to CSU but not to CindU – Comparatively complicated scoring system – Not perfectly adapted to CSU patients in whom angioedema predominates

Abbreviations: AAS, Angioedema Activity Score; CIndU, chronic inducible urticaria; CSU, chronic spontaneous urticaria; CU, chronic urticaria; CU-Q2oL, Chronic Urticaria Quality of Life Questionnaire; PRO, patient-reported outcome; QOL, quality of life; UAS, Urticaria Activity Score; UAS7, Urticaria Activity Score 7; UCT, Urticaria Control Test.

biologics [39], although it is also important to consider their cost. In this context, data on the relative value of high-dose antihistamines compared with alternative treatments should be clear and rigorous. Given the proven efficacy and safety of omalizumab, it is our expert opinion that clinicians should consider using this medication to shorten and simplify the gradual treatment approach that is typically used in antihistamine-refractory CSU patients [13].

Omalizumab for Treatment of CSU

The efficacy and safety of omalizumab for the treatment of CSU has been demonstrated in several phase 3 pivotal trials, namely, ASTERIA I [14], ASTERIA II [3], and the GLACIAL trial [15,40] (Supplementary Material, Table 2). The improvements observed in all efficacy variables at week 12 were still present at week 24 in the ASTERIA I and GLACIAL trials [14,15]. Overall, the findings from these trials support the efficacy of omalizumab over 6 months.

Pivotal trials also confirm the favorable safety profile of omalizumab. The authors found that the incidence rate for adverse events, the severity of those events, and the incidence of serious adverse events were all similar in the treatment group (regardless of the omalizumab dose) and placebo group [3,14,15].

Importantly, in real-world observational studies, the efficacy and safety of omalizumab in CSU patients was similar or even better than in pivotal trials [20,21,41-43]. Of particular interest is the retrospective, descriptive analysis of 110 CSU patients treated with omalizumab at 9 Spanish hospitals [1]. The authors found that 81.8% of patients had a complete or significant response to treatment, with only 7.2% not responding to treatment. Moreover, 60% of the patients in that study remained asymptomatic while receiving omalizumab alone (that is, they were able to discontinue antihistamine therapy), and no serious adverse events were reported.

Predictors of Response to Omalizumab

It would clearly be beneficial, if possible, to identify the clinical predictors of response to omalizumab. Knowledge of these predictors would also enable physicians to provide patients with more accurate information about the expected course of the disease. The findings of the 3 aforementioned pivotal trials show that the response pattern is dose-dependent. Thus, the standard dose of 300 mg/4 wk results in a higher percentage of complete response (UAS=0) or good response (UAS≤6); moreover, higher doses resulted in faster response and more sustained disease control [44]. In the pooled analysis of the trials, disease control was good (UAS7 ≤6) or complete (UAS7=0) in 58% and 40% of patients, respectively, 12 weeks after administration of 3 × 300 mg doses of omalizumab [40]. However, disease control was not achieved in all patients over that period. An analysis of the 3 pivotal trials revealed that of the patients with uncontrolled urticaria (UAS7 ≤6) at week 12, 58% subsequently achieved disease control between weeks 13 and 24 [44]. The mean number of weeks necessary to obtain a score ≤6 or 0 on the UAS7 was, respectively, 6 weeks and 12-13 weeks. These data show that some patients respond quickly to omalizumab, whereas others respond more slowly. Patients who respond within 4-6 weeks could be classified as "fast responders" and those requiring 12-16 weeks of treatment could be considered "slow responders" [45] (Table 2).

Table 2. Patient Profile According to the Response to Omalizumab

Fast responder	Patient who responds in 4-6 weeks
Slow responder	Patient who responds in 12-16 weeks
Complete responder	– Sustained UAS7 score = 0 – Absence of symptoms – Absence of angioedema – Requires neither salvage medication nor H_1- antihistamines
Good responder	– Sustained UAS7 score = 1-6
Partial responder	– Partial improvement in baseline UAS7, with scores ranging from 7-15
Nonresponder	– No change in baseline UAS7 score and sustained scores >16

Abbreviations: UAS, Urticaria Activity Score; UAS7, Urticaria Activity Score 7.

According to a recent study [43], the predictors of a favorable response to omalizumab are as follows: (*1*) diagnosis of CSU with chronic inducible urticaria, (*2*) no prior treatment with immunosuppressive drugs, (*3*) older age, (*4*) shorter duration of symptoms, (*5*) absence of angioedema, and (*6*) negative histamine release test. Over 85% of patients who present these characteristics achieve a complete response to treatment. In addition, a negative histamine release test result and absence of angioedema both predict a good response to omalizumab and correlate with previous trial results showing that a positive autologous serum skin test (ASST) result is associated with a longer duration of and more severe CSU [46,47]. In addition, patients in whom angioedema is a significant component of urticaria tend to relapse faster after treatment is discontinued [10]. Neither the patient's gender nor their smoking habits have been shown to influence the efficacy of omalizumab [43]. A significant reduction in D-dimer values following treatment with omalizumab in patients with elevated baseline D-dimer levels has also been shown [48].

Deza et al [49] recently demonstrated the predictive value of baseline basophil expression of high-affinity IgE receptors (FcεRI) for response to omalizumab. The authors found that FcεRI expression levels in CSU patients are usually significantly higher than in healthy controls. Moreover, after the first treatment with omalizumab, FcεRI expression levels drop immediately, while UAS7 scores decrease and UCT scores rise. Deza et al observed that baseline FcεRI expression with a mean fluorescence intensity of less than 4743 in peripheral blood basophils is a significant predictor of nonresponse to omalizumab (100% sensitivity and 73.2% specificity). Another study showed that the baseline expression level of FcεRI was lower in slow responders than in fast responders [50]. Gericke et al [51] recently reported a slower response to omalizumab in patients with a positive result in the ASST or basophil histamine release assay, thus suggesting that patients presenting with anti-IgE or anti-FcεRI IgG respond more slowly than those presenting with IgE autoantibodies against autoantigens (eg, TPO, IL-24) [51].

Even though omalizumab generally provides an early benefit [3,14,15], some patients have a delayed response, often only after 12 weeks of treatment [14,44]. This finding suggests that if fewer than 3 treatments (300 mg/4 wk) are administered, the opportunity to achieve symptom control in a nonresponder (UAS7 ≤6) could be lost [44].

Prediction of symptom return after stopping omalizumab was recently addressed in a study that analyzed data from 2 clinical trials, including 642 patients [52]. The authors studied the predictive potential of 746 variables, which included baseline patient characteristics and disease measures (ie, start of treatment), such as IgE levels, weekly urticaria activity score (UAS7), and pre- and postbaseline medications.

Only 2, variables, UAS7 and the speed of response to treatment, predicted speed of symptom return. The results suggest that patients with worse symptoms before treatment (ie, higher UAS7 score) and a slow response to omalizumab have a higher probability of rapid symptom return after discontinuation of treatment. In contrast, those with a lower UAS7 score at baseline and fast response to omalizumab have a lower probability of rapid symptom return.

Therapeutic Strategy According to the Patient's Response Profile

Defining patient profiles according to the response to omalizumab would have 2 main benefits: first, it would facilitate medical management of the patient, and second, it would improve treatment selection, thus enabling the clinician to select the most appropriate therapeutic plan based on the individual's response profile. Unfortunately, to date, no such categorization has been reported in the published literature.

CSU patients can be either fast or slow responders to omalizumab [44,51]. Available evidence for slow responders indicates that omalizumab should be continued for 24 weeks to obtain a sustained favorable response (UAS7≤6) over time [44]. In patients with severe disease (ie, UAS7>28 with unbearable symptoms), the therapeutic schedule could be modified prior to administration of the sixth dose.

Based on our clinical experience and the literature review we conducted for this study, we recommend classifying patients into 1 of 4 different response profiles—nonresponders, partial responders, good responders, and complete responders—depending on their response to omalizumab (300 mg/4 wk) after the first 3 and 6 months of treatment [33]. Based on this classification system, we also propose a specific therapeutic approach for each response profile.

The 4 different approaches mainly involve modification of the omalizumab dose or a change in the treatment interval [33,45]. Dose increases or reductions should be stepwise. Thus, a standard dose of 300 mg/4 wk should be increased to 450 mg/4 wk [33,53-55] and then, if necessary, up to 600 mg/4 wk [33,56]. In cases requiring dose reduction, the dose would be reduced from 300 mg/4 wk to 150 mg/4 wk.

According to a study by Curto et al [12] involving 286 patients treated at 15 hospitals under conditions of routine clinical practice, 16% of patients required their dose to be increased to 450 mg/4 wk, while 4% required an increase to 600 mg/4 wk to achieve complete disease control. The authors found that 21% of patients required updosing; in addition, several factors—body mass index ≥30, age >57 years, and previous cyclosporine use—were strongly correlated with the need for updosing to ensure good disease control [12].

The standard dose of omalizumab is 300 mg administered every 4 weeks; this frequency could be increased to every 2 weeks at the same dose (300 mg) [3], according to the criteria of the attending physician. However, the dose interval should never be longer than 8 weeks, except in cases in which the medication is being discontinued [57].

If the aim of the therapeutic strategy is to increase the dose or to shorten the administration interval, the change must first be tailored to the patient. However, it should be noted that in most cases—such as in patients in whom the UAS7 score remains stable over the 4-week period—the recommended strategy is to increase the dose while maintaining the administration interval, given that this strategy is supported by the strongest scientific evidence [56,58]. By contrast, evidence to support an increase in the administration interval at the same dose is scant, and the samples in the few available studies are small [56]. Nonetheless, this strategy may be considered in certain cases: (*1*) when the usual strategy (ie, updosing) fails to produce an improvement; (*2*) when the symptoms recurrently worsen and the UAS7 score increases during the 2 weeks prior to receiving the following omalizumab dose; (*3*) when the pattern of response is better during the first 2 weeks after administration; and (*4*) when the patient expresses a clear preference for this strategy.

Although administration of omalizumab at >600 mg has proven to be safe and effective in asthmatic patients [59], we suggest that clinicians should not exceed the 600 mg/4 wk dose owing to the lack of clinical evidence to support this dose in CSU patients [56].

Likewise, therapeutic strategies based on dose reduction or shortening of the treatment interval may be combined successively (never simultaneously), as it is important that treatment be withdrawn or reduced gradually. Thus, for example, the dose can first be reduced by 1 step, and then—provided that the patient's condition remains stable—the same dose could be administered over longer intervals until the decision is made to discontinue treatment [3,60].

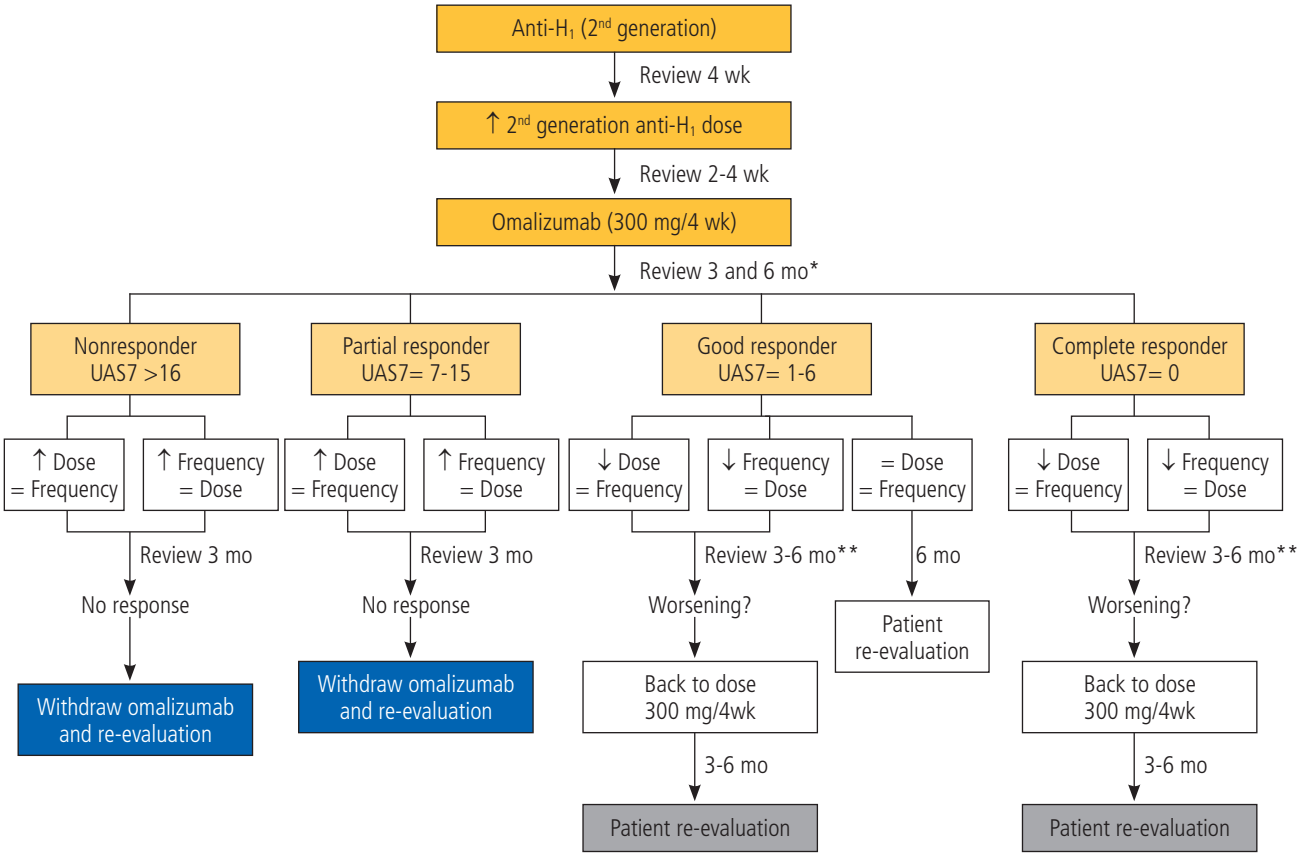
The 4 different patient profiles defined in this study, which are based on the individual response to omalizumab at the standard dose (300 mg/4 wk) after 6 months of treatment, are described in detail below. Figure 3 shows the recommended therapeutic approach according to the specific patient profile.

After careful consideration and much discussion about the advantages of using either the UCT and UAS7 scales or using the percentage decrease from baseline in the UAS7, we believe that the UAS7 should be used as the main, but not the only, indicator of response to omalizumab (Table 2).

4.1. Nonresponders

Patients classified as nonresponders to omalizumab are those whose baseline UAS7 score remains unchanged after treatment and who continue to present a UAS7 score >16 after 6 doses of omalizumab at 300 mg/4 wk (Table 2).

Given that some patients are late responders—that is, only achieving disease control between 13 and 24 weeks after



Short corticosteroid cycles are permitted in exacerbations
*Continue omalizumab up to 6 months, except in nonresponders with intolerable signs and symptoms, and in complete responders, in whom the therapeutic strategy could be adapted 3 months after initiation of omalizumab.
**In those cases in which a sustained response is achieved for ≥8 weeks, omalizumab can be discontinued to evaluate whether the patient continues in remission.

Figure 3. Therapeutic algorithm for the 4 different omalizumab response profiles.

initiation of treatment—our recommendation is to re-evaluate the patient after 6 months on omalizumab [45]. However, if the nonresponder shows symptoms of intolerance, therapy may be changed after 3 months of omalizumab instead of 6 months.

In nonresponders, there are 2 possible therapeutic strategies: increasing the omalizumab dose while maintaining the same treatment interval; and reducing the treatment interval while maintaining the original dose. The strategy selected will depend on the patient's weekly UAS7 scores over the 4-week period. Thus, if the UAS7 score remains >16 at all weekly assessments, then the dose should be increased. However, if the score is >16 only during 2 weeks after administration, then the treatment interval should be reduced.

In cases in which the therapeutic strategy is modified, it is advisable to re-evaluate the patient 3 months after changing the strategy; if the response does not improve, then we recommend withdrawing omalizumab and performing another medical evaluation to reassess the treatment approach.

4.2. Partial Responders

A partial responder to omalizumab is defined a patient whose UAS7 score partially improves over baseline but who maintains a UAS7 score of 7-15 (Table 2). In patients who demonstrate a partial response to the standard omalizumab dose, we recommend waiting 6 months before altering the treatment plan, although this will depend on the patient's symptoms or level of discomfort. If the UAS7 scores remain in the 7-15–point range after 6 months of standard treatment, we recommend modifying the regimen. As with nonresponders, the recommended modification is to either increase the dose while maintaining the same treatment interval or, conversely, to shorten the interval from 4 to 2 weeks while maintaining the original dose. The patient should be re-evaluated after 3 months, and if disease control remains poor, we suggest withdrawing omalizumab and reassessing the patient. However, it is important to consider the patient's opinion with regard to the efficacy of the drug before deciding to discontinue treatment.

4.3. Good Responders

Patients with a sustained UAS7 score ranging from 1 to 6 points are considered good responders (Table 2). In these patients, the standard dose and treatment frequency should continue until the 6-month follow-up assessment. If the disease remains controlled, then the strategy could be modified in an attempt to identify the minimum effective dose for good disease control. In these cases, the 3 possible strategies are as follows: (*1*) dose reduction at the same treatment interval, (*2*) increased treatment interval with the same dose, and (*3*) no change in dose or treatment interval.

If either the dose or the treatment interval is modified, then the patient should be re-evaluated after 3 and 6 months. If this assessment shows a deterioration in the patient's health, then the patient should be returned to the previous standard dose and frequency and re-evaluated after a further 3 and 6 months.

Similarly, when no change is made to standard therapy, the patient should be re-evaluated at a maximum of 6 months.

4.4. Complete Responders

Patients considered complete responders are those with sustained UAS7 scores of 0 and no signs or symptoms of urticaria while on the standard omalizumab dose.

Considering add-on treatment, the complete responder profile also includes patients who require neither H_1 antihistamines nor salvage medications (Table 2). In fact, we recommend reducing the dose or even complete withdrawal of H_1 antihistamines in these patients.

Prolongation of the standard prescription of omalizumab beyond 6 months is not recommended in complete responders. However, a change in the therapeutic approach may be considered 3 months after initiation of omalizumab in complete responders. In these cases, the change in strategy would involve a dose reduction while maintaining the treatment interval; alternatively, the treatment interval could be increased while maintaining the dose in order to find the minimum effective dose. If possible, treatment should be withdrawn.

If the patient's condition has worsened at the 3- or 6-month re-evaluation following the modification in strategy, a return to the standard dose and frequency (300 mg/4 wk) is recommended, followed by re-evaluation 3 to 6 months later. Discontinuation of omalizumab should be considered in patients who maintain a sustained response lasting ≥8 weeks to determine whether the patient has achieved disease remission.

Although implementation of the therapeutic strategies for omalizumab suggested may involve an increase in costs, these may be compensated by a decrease in concomitant medication use, improvement in patients' quality of life, and reduced disease-related health care costs [42].

5. Conclusion

European guidelines support the use of omalizumab as a third-line treatment for patients with CSU. Patients typically respond to omalizumab within the first 4-8 weeks of treatment, and the response is often evident within the first week. Importantly, even patients who do not initially respond to treatment (nonresponders) can obtain a significant reduction in disease activity and achieve "good control" (UAS7≤6) or "complete control" (UAS7=0) if treatment is continued for up to 24 weeks.

The therapeutic algorithm presented here is intended to facilitate the clinical management of omalizumab and to help clinicians determine the most appropriate therapeutic strategy based on the 4 different patient response profiles described in this study.

Acknowledgments

We are grateful to Novartis Pharmaceutical S.A. for sponsoring the meetings organized to prepare this article.

Funding

The meetings were financed by Novartis Farmacéutica S.A.

Conflicts of Interest

Ana M Giménez-Arnau declares the following, real or perceived conflicts of interest: medical advisor for Uriach Pharma, Genentech, Novartis, FAES, GSK; research grants supported by Uriach Pharma, Novartis, grants from Instituto Carlos III-FEDER; educational activities for Uriach Pharma, Novartis, Genentech, Menarini, LEO- PHARMA, GSK, MSD, Almirall.

Antonio Valero belongs to the Spanish advisory group in chronic urticaria sponsored by Novartis. He has participated in several observational studies sponsored by Novartis involving chronic urticaria patients. He has also accepted invitations to international meetings and travel grants from Novartis and other companies.

Joan Bartra reports having served as a consultant to Novartis, FAES FARMA, Hal Allergy, and UCB and having been paid lecture fees by Novartis, Stallergenes, Hal Allergy, FAES FARMA, and Thermo Fisher.

Ignacio Jáuregui belongs to the Spanish advisory group in chronic urticaria sponsored by Novartis. He has participated in several observational studies sponsored by Novartis and Circassia. He has accepted invitations to international meetings and travel grants from Novartis, Leti, and Roxall. He has received advisory, speaking, and medical writing fees from Novartis, Sanofi, MSD, FAES FARMA, and Roxall. He reports no other conflicts of interest related to this paper.

Moises Labrador has received speaker and consulting fees from Novartis.

Francisco Javier Miquel Miquel belongs to the Spanish advisory group in chronic urticaria sponsored by Novartis. He has participated as a paid speaker in training activities and meetings organized by the following companies: Novartis Pharmaceutical S.A., Leo Pharma, Astellas, Janssen, and Almirall. He has participated in several observational studies sponsored by Novartis involving chronic urticaria patients and has accepted invitations to meetings and travel grants from Novartis, Leo Pharma, Astellas, Janssen, and Almirall. He has also participated in advisory boards from Novartis.

Javier Ortiz de Frutos has served as a consultant to Novartis, Uriach, Astellas, Sanofi, Viñas, BDF, and GSK and has been paid lecture fees by Sanofi, Novartis, BDF, GSK,

and Astellas. He has also received grant support for research from Astellas.

Joaquín Sastre reports having served as a consultant to Thermo Fisher, MSD, Novartis, Gennetech, Sanofi, Leti, Roche, FAES FARMA, Mundipharma, and GSK and having been paid lecture fees by Novartis, GSK, Stallergenes, LETI, and FAES FARMA. He has also received grant support for research from Thermo Fisher.

JF Silvestre has attended meetings organized by Sanofi, Novartis, Menarini, Almirall, and Galderma. He has also been invited to speak at meetings organized by Sanofi, MSD, Novartis, and Janssen. He participates in advisory boards for Novartis, Sanofi, and Viñas.

Marta Ferrer has served on advisory boards for Genentech and has received a research grant and advisory and speaker fees from Novartis. She has also received speaker fees from FAES, MSD, and Menarini.

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Manuscript received May 29, 2018; accepted for publication September 10, 2018.

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