Therapeutic strategy according to the differing patient response profiles to omalizumab in chronic spontaneous urticaria

Running Title: Omalizumab response profile & management

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ABSTRACT

Chronic spontaneous urticaria (CSU) is a heterogeneous condition that can severely impact quality of life, which is why rapid disease control is essential. Symptomatic first-line treatment of CSU is the licensed dose of second-generation H1 antihistamines. For second-line treatment, this dose may be increased by up to four times. In patients who fail to respond to these higher doses of H1 antihistamines, treatment with omalizumab (up to 24 weeks) is recommended to achieve disease control. After this 24-week period, the patient response profile to omalizumab should be defined in order to identify refractory patients. The optimal management approach for refractory patients has not been established. In this context, the aim of the present expert consensus study involving a group of specialists (allergists and dermatologists) with specific expertise in treating urticaria was to define specific patient profiles based on their differing responses to omalizumab. Another objective was to develop a treatment algorithm based on the specific response profile. First, a comprehensive literature review was conducted. Then, a group meeting was held to discuss all issues related to the therapeutic management of these patients that had not been addressed in any previous studies. In all cases, the experts considered both the available evidence and their own clinical experience with omalizumab. We believe that implementation of this proposed algorithm will help to optimise the management of CSU patients who are refractory to antihistamine treatment, reduce disease-related costs, and improve QoL.

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 periodo de 24 semanas, se debe definir del 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.
1. INTRODUCTION

Chronic spontaneous urticaria (CSU) is a heterogeneous condition that causes significant morbidity [1,2]. CSU is characterised by the sudden appearance of wheals, angioedema, or both 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 from 0.5% to 1% of the general population, with an annual incidence rate of 1.4% [5]. The annual prevalence of urticaria appears to have increased in recent years. In Italy, the prevalence has increased from 0.02% in 2002 to 0.38% in 2013, with a current incidence rate of 0.10 – 1.50 per 1000 persons/year [6]. CSU imposes a significant economic burden and also has a substantial negative impact on patient quality of life (QoL). For these reasons, it is crucial to administer effective treatment as soon as possible [7-9].

The management of CSU consists of a two-pronged approach: 1) avoiding the triggering factors (if known) and 2) pharmacological treatment of the symptoms [3]. For the symptomatic treatment of CSU, current EAACI/Ga2LEN/EDF/WAO guidelines recommend second-generation H1 antihistamines as first-line treatment [2,10]. However, given that approximately 70% of patients remain symptomatic despite the use of antihistamines at the licensed doses [11,12], these guidelines recommend increasing the licensed dose by up to four 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 (four-fold the standard dose) of H1 antihistamines [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 [2,10] (figure 1).

Phase III trials have demonstrated the good efficacy and safety profile of omalizumab [3,14,15], which has a substantially better safety profile than cyclosporine, particularly with regard to renal toxicity [10]. Recently, a group of experts reached these same conclusions regarding the good safety and efficacy profile of omalizumab versus
cyclosporine [16]. Moreover, a recent meta-analysis found that more than 50% of patients who received cyclosporine at doses of 4-5 mg/kg/day presented adverse events [17].

Omalizumab selectively binds to human IgE, preventing binding of IgE to its high-affinity receptor (FcεRI), thus reducing the amount of free IgE. This process affects the urticaria immunological cascade on several different levels (figure 2) [18,19]. Both the European Medicines Agency and the Food and Drug Administration approved Omalizumab in 2014 for the treatment of CSU. The good efficacy and safety data for omalizumab obtained in clinical trials are further supported by results from real-world clinical studies [1,20,21]. Although the available evidence supports the use of omalizumab for up to 24 weeks as a third-line treatment for CSU [22], 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 more slowly or not at all. To date, these different response profiles have not been well-defined even though clear definitions would help to guide the medical management of these patients in accordance with their individual response profile.

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

2. METHODS

The present study describes the consensus opinions of a group of experts in urticaria treatment. The group was comprised of allergists and dermatologists in Spain with expertise in treating urticaria. This working group met three times from 2015 to 2016
to discuss the major unresolved issues regarding therapeutic management of CSU patients.

Initially, the group generated a series of unresolved questions that commonly arise in routine clinical practice about the optimal use of omalizumab for the treatment of CSU patients. Three main questions were raised, as follows: 1) What are the criteria to determine 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 different patient profiles?


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

During the discussions held to address the aforementioned major unresolved issues, several other omalizumab- and CSU-related questions arose. Consequently, we also address those issues in this document.
3. DISCUSSION

Measurement of CSU activity and impact.

In many cases, it is difficult to precisely assess CSU due to the heterogeneous nature of this 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 also 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 treatment initiation. These scales are particularly useful in patients who present poor disease control despite good treatment compliance. By contrast, these scales may be unnecessary in stable, well-controlled patients [2].

By measuring disease activity, control, and its impact, the clinician can identify the patient’s individual clinical profile and determine whether the CSU is under control. The scores on these questionnaires can be used to guide treatment selection in accordance with the patient’s disease status [2].

The Urticaria Activity Score (UAS), particularly the UAS7 version, is recommended to assess CSU symptoms [2,24]. The UAS7 defines 5 “disease activity categories” according to the score obtained (table 1. Material supplementary). The scale was validated in 2008 to measure urticaria symptoms [25]. The Spanish versions of the UAS and UAS7 were both recently been 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 to evaluate the activity of chronic inducible urticaria (ClndU) nor angioedema. The Angioedema Activity Score (AAS) is used to assess either isolated or CSU-associated angioedema [27].

The consensus opinion of the present expert group is that the Urticaria Control Test (UCT) is the best tool currently available to quantify disease control in all types of
chronic urticaria (CU, which includes both CSU as well as 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.

To evaluate 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 (CU-QoL) [28].

We recommend using the UAS7 to evaluate CSU activity 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 (DLQI), 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 answered 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 treatment response in daily clinical practice. Moreover, such a definition is important to facilitate reliable comparisons among clinical trials.

According to the EAACI/GA2LEN/EDF/WAO guidelines, the aim of treatment in CSU patients is to achieve complete control of the signs and symptoms while also ensuring patient safety and QoL [2]. Several scales are available to monitor different aspects of the disease (table 1), and a "good" clinical course could be defined by any of the following: UAS7 activity index < 6; a decrease > 90% on the UAS7: UCT score > 12; or the clinical course could be judged by the clinical criteria of the treating physician.
Due to 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 in order to consider the patient to be in remission. Patient management is specific to each individual, both in regard to the type and duration of treatment. Likewise, the best approach to treatment discontinuation (i.e., sudden termination or gradual tapering) has not yet been determined.

**Antihistamine-refractory Patients**

CSU activity 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% of cases were refractory to H₁ 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 that CSU patients of this studies, who have been seen mostly at third level clinical centers, do not represent necessarily the general population of patients with the disease. Most CSU patients that respond properly to a second-generation antihistamine at a licensed dose prescribed by the family doctor probably do not present at academic clinics.

CSU has an important 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/CIU on health-related QoL in refractory patients. The results of that study showed that not only did CSU interfere with QoL but it also had both direct (i.e., health) and indirect (i.e., social) costs.
Given the good safety profile of most second-generation antihistamines, it is widely accepted 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 licensed dose of H1 antihistamines responded well to higher doses. Furthermore, the increased dose significantly improved both itch and wheal control in the 49% of patients that 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 shows that measurement of the histamine-induced wheal can predict which patients will have a strong clinical response to antihistamines but has limited utility for identifying nonresponders [38].

The off-label indication for antihistamine dose recommendations should be revised in light of the availability of new, highly effective treatments such as omalizumab and other emerging biologics [39], although it is important to consider their cost too. In this context, the data on the relative value of high dose antihistamines versus 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 to treat CSU**

The efficacy and safety of omalizumab for the treatment of CSU has been demonstrated in several phase III pivotal trials, including ASTERIA I [14], ASTERIA II [3], and the GLACIAL trial [15,40] (table 2. material supplementary). 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 treatment efficacy of omalizumab over 6 months.
Pivotal trials also confirm the good safety profile of omalizumab. Those trials have 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 (regardless of the omalizumab dose) and placebo groups [3,14,15].

Importantly, in real-world observational studies, the efficacy and safety of omalizumab in CSU patients was similar or even better than observed in pivotal trials [20,21,41-43]. Of those real-world studies, of particular interest is the retrospective, descriptive analysis in one study involving 110 CSU patients treated with omalizumab at 9 Spanish hospitals; in that study [1], 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**

Clearly, it would be beneficial, if possible, to identify the clinical predictors of response to omalizumab. This would also enable physicians to provide patients with more accurate information about the expected course of the disease. Based on the findings of the three aforementioned pivotal trials, the response pattern is dose-dependent. Thus, the standard 300 mg/4 weeks dose results in a higher percentage of complete (UAS=0) or good (UAS≤6) response; moreover, higher doses resulted in faster response and more sustained disease control [44]. In the pooled analysis of the trials, good (UAS7 ≤6) or complete (UAS7=0) disease control were achieved in 58% and 40% of patients, respectively 12 weeks after administration of three, 300 mg doses of omalizumab [40]. However, disease control was not achieved in all patients over that period. An analysis [44] of the three pivotal trials revealed that of the patients with uncontrolled (UAS7 ≤6) urticaria at week 12, 58% subsequently achieved disease control between weeks 13 and 24. 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 from 12 - 16 weeks of treatment could be considered "slow responders" [45] (table 2).

According to a recent study [43], the following factors are predictors of a favourable response to omalizumab: 1) diagnosis of CSU vs. CIndU; 2) no prior treatment with immunosuppressant drugs, 3) older age, 4) shorter duration of symptoms, 5) absence of angioedema, and 6) negative histamine release test (HRT). Over 85% of patients who present these characteristics achieve a complete response to treatment. In addition, both HRT negativity and absence of angioedema predict a good response to omalizumab and correlate with previous trial results showing that autologous serum skin test (ASST) positivity is associated with a longer duration and more severe CSU [46,47]. In addition, patient in which angioedema is a significant component of the 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 omalizumab treatment in patients with elevated baseline D-dimer levels has also been shown to predict response [48].

Deza et al. [49] recently demonstrated the predictive value of baseline basophil expression of high-affinity IgE receptors (FcεRI) for response to omalizumab. Those authors found that FcεRI expression levels in CSU patients are usually significantly higher than in healthy controls. Moreover, after administration of the first treatment with omalizumab, FcεRI expression levels drop immediately, while UAS7 scores decrease and UCT scores rise. In their study, Deza and colleagues observed that baseline FcεRI expression less than an MFI (mean fluorescence intensity) of 4743 in the peripheral blood basophils is a significant predictor of non-response 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]. Recently, Gericke et al. described a slower response to omalizumab in ASST-
basophil histamine release assay (BHRA) positive patients, which could suggest that patients presenting with anti-IgE or anti-FcεRI IgG respond more slowly than those presenting with IgE autoantibodies against autoantigens (e.g., TPO, IL-24) [51].

Even though omalizumab provides an early benefit in many patients [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 weeks) are administered, the opportunity to achieve symptom control in a non-responder (UAS7 ≤ 6) could be lost [44].

Regarding the prediction of symptoms return after stopping omalizumab treatment, it has recently published a study [52] that analyzed data from two clinical trials, including 642 patients. The authors studied the predictive potential of 746 variables, which included baseline (i.e. start of treatment) patient characteristics and disease measures, such as IgE levels, weekly urticaria activity score (UAS7), and pre- and post-baseline medications.

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

4. THERAPEUTIC STRATEGY ACCORDING TO THE PATIENT’S RESPONSE PROFILE

It would be useful to define patient profiles according to their response to omalizumab. Such an approach would have two main benefits: first, it would facilitate medical management of the patient and second, it would improve treatment selection to allow the clinician to select the most appropriate therapeutic plan based on the individual’s response profile. Unfortunately, to date, no such categorisation has been reported in the published literature.
CSU patients can be either fast or slow responders to omalizumab [44,51]. In slow responders, the available evidence indicates that omalizumab treatment should continue for 24 weeks to obtain a good (UAS7 ≤ 6), sustained response over time [44]. In patients with severe symptoms (i.e., UAS7 > 28 with unbearable symptoms), the therapeutic scheme 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 one of four different response profiles—non-responders, partial responders, good responders, and complete responders—depending on their response to omalizumab treatment (300 mg every 4 weeks) 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.

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

According to a study by Curto et al. involving patients treated in routine clinical practice, 16% of patients required a dose increase to 450 mg/4 weeks while 4% required an increase to 600 mg/4 weeks to obtain complete disease control. In that study, which included 286 patients treated at 15 hospitals, 21% of patients required up-dosing; in addition, several factors—body mass index ≥ 30, age > 57 years, and previous cyclosporine use were strongly correlated with a need for up-dosing to obtain good disease control [12].

The standard dose and administration interval of omalizumab is 300 mg/4 weeks. However, the frequency could be increased to every 2 weeks at the same dose (300 mg) [3]. The increase in the treatment interval of omalizumab should be determined by the physician, but the dose interval should never be longer than 8 weeks, except in
cases in which treatment with the medication is being discontinued [57].

If the aim of the therapeutic strategy is to increase either the dose or to shorten the administration interval, it is crucial to first determine the most appropriate change suitable to the patient's particular case. However, it should be noted that in most cases—such as in patients in which 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, the evidence base to support an increase in the administration interval at the same dose is scant, and the sample sizes in the few available studies are small [56]. Nonetheless, this strategy may be considered in certain cases: 1) when the usual strategy (i.e., up-dosing) fails to produce any improvement; 2) when the symptoms recurrently worsen and the UAS7 score increase during the two weeks prior to receiving the next omalizumab dose; 3) when the pattern of response is better during the first two weeks after dose administration; or 4) in cases in which the patient expresses a clear preference for this strategy.

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

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

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

After careful consideration and much discussion about the advantages of using either the UCT and the 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 omalizumab response (table 2).

4.1. Non-responders

Patients classified as “non-responders” 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 weeks (table 2).

Given that some patients are late responders—that is, only achieving disease control between 13 and 24 weeks after treatment initiation—our recommendation is to re-evaluate the patient after 6 months on omalizumab [45]. However, if the non-responder shows symptoms of intolerance, the therapeutic plan may be changed after 3 months of omalizumab treatment instead of 6 months.

In non-responders, there are two possible therapeutic strategies: 1) increase the omalizumab dose while maintaining the same treatment interval or 2) reduce the treatment interval while maintaining the original dose. The selection of the strategy will depend on the patient's weekly UAS7 scores over the four-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 the two first weeks after omalizumab 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 response does not improve, then we recommend withdrawing omalizumab and performing another medical evaluation to reassess the treatment approach.
4.2. Partial responder

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 six months before altering the therapeutic 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 therapeutic scheme. As with non-responders, 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 three 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 the 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 six-month follow up assessment. If disease control remains good, then a strategy change may be considered in an attempt to identify the minimum effective dose for good disease control. In these cases, three different strategies are possible, as follows: 1) dose reduction at the same treatment interval; 2) increased treatment interval but same dose, or 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 three and six 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 then re-evaluated after another three and six months.
Similarly, in patients in whom no change is made to the standard therapy, the patient should be re-evaluated at a maximum of six months.

4.4. Complete responders

Patients considered “complete responders” are those with sustained UAS7 scores of 0, without any 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 H1 antihistamines nor any salvage medications (table 2). In fact, we recommend reducing the dose or even complete withdrawal of H1 antihistamines in these patients.

Prolongation of the standard prescription of omalizumab beyond six months is not recommended in complete responders. However, a change in the therapeutic approach may be considered three months after initiation of omalizumab therapy in complete responders. In these cases, the strategy change would involve a dose reduction while maintaining the treatment interval; alternatively, another option would be to increase the treatment interval 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 strategy modification, a return to the standard dose and frequency (300 mg/4 weeks) is recommended, followed by re-evaluation three to six months later. Discontinuation of omalizumab should be considered in patients who maintain a sustained response lasting ≥ 8 weeks to determine if the patient has achieved disease remission.

Although the implementation of the suggested omalizumab therapeutic strategies may involve, in some cases, an increase of therapeutic cost, these costs may be compensated by a decrease in concomitant medication use, the improvement patients’ quality of life, and the reduction of disease-related health care costs achieved with this treatment [42].
5. CONCLUSION

The European guidelines support the use of omalizumab as a third-line treatment for patients with CSU. Patients typically show a response to omalizumab within the first 4-8 weeks of treatment initiation, and response is often evident within the first week. Importantly, even patients who do not initially respond to treatment (non-responders) can obtain a significant reduction in disease activity and even 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 four different patient response profiles described in this study.

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CONFLICTS OF INTERESTS

1. In relation to this talk, 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.
2. 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 urticarial patients. He has also accepted invitations to international meetings and travel grants from Novartis and other companies.
3. Joan Bartra reports having served as a consultant to, Novartis, FAES FARMA, Hal Allergy and UCB; having been paid lecture fees by Novartis, Stallergenes, Hal Allergy, FAES FARMA and Thermofisher.
4. 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 also from Novartis, Leti and Roxall. He has received advisory, speaker and medical writer fees from Novartis, Sanofi, MSD, FAES FARMA and Roxall. He reports no other conflicts of interest related to this paper.

5. Moises Labrador has received speaker and consulting fees from Novartis.

6. 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 urticarial patients and has accepted invitations to meetings and travel grants from Novartis, Leo Pharma, Astellas, Janssen, and Almirall. He also has participated in advisory boards from Novartis.

7. Javier Ortiz de Frutos has served as a consultant to Novartis, Uriach, Astellas, Sanofi, Viñas, BDF and GSK; having been paid lecture fees by Sanofi, Novartis, BDF, GSK and Astellas; as well as having received grant support for research from Astellas.

8. Joaquín Sastre: reports having served as a consultant to Thermofisher, MSD, Novartis, Gennetech, Sanofi, Leti, Roche, FAES FARMA, Mundipharma, and GSK; having been paid lecture fees by Novartis, GSK, Stallergenes, LETI, and FAES FARMA; as well as having received grant support for research from Thermofisher.

9. 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.

10. Marta Ferrer served in advisory boards for Genentech, and has received a research grant, advisory and speaker fees from Novartis; speaker fees from FAES, MSD, and Menarini.
REFERENCES


57. Kasperska-Zajac A, Jarząb J, Żerdzińska A, Bąk K, Grzanka A. Effective treatment of different phenotypes of chronic urticaria with omalizumab: Case reports and


FIGURES AND TABLES

FIGURES

Figure 1. Treatment algorithm for chronic spontaneous urticaria.

First line of treatment
- Second-generation anti-H₁

Second line of treatment
- Dose increase up to 4x the standard second-generation anti-H₁ dose

Third line of treatment
- Omalizumab

Fourth line of treatment
- Cyclosporin A

Short corticoid cycles may be used (10 days maximum) should exacerbations require so
**Figure 2.** Mechanism of action of omalizumab.

- Reduction of the IgE levels
- Dissociation of the IgE-FceRI pre-links
- Reduction of the IgE receptors in mast cells/basophils
- Reduction of the mast cell/basophil degranulation
- Basopenia reversion and improvement of the IgE receptor function in basophils
- Reduction of the anti-FceRI and anti-IgE IgG autoantibodies activity
- Reduction of the antiautoantigen IgE autoantibodies
Figure 3. Therapeutic algorithm for the four different omalizumab response profiles.

Short corticosteroid cycles are permitted in exacerbations
*Continue omalizumab up to 6 months, except in non responder patients with intolerable signs and symptoms, and in complete responders, in whom the therapeutical strategy could be adapted after 3 months of omalizumab inception.
**In those cases in which an 8-week or greater interval is attained with response sustainment, omalizumab discontinuation is envisaged to evaluate whether the patients continue remitting.
### TABLES

**Table 1.** Activity, control, and quality of life scales for urticaria and angioedema patients.

**Table 2. Use, advantages and disadvantages of the scales for measuring activity, control and quality of life of patients with CSU and angioedema**

<table>
<thead>
<tr>
<th>PRO</th>
<th>Stipulated use</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| **Activity measure** | UAS7 | Patients with wheals | Exact clinical picture of the current frequency and severity of the CSU symptoms (daily evaluation, weekly score) | • Prospective PRO measure  
• Patient must complete daily (which is not always feasible)  
• Valid only for patients with CSU, not for patients with CIndU  
• Has been validated for use in adults only |
| AAS | Patients with wheals and angioedema  
Patients with angioedema | • Patients with wheals  
• Patients with angioedema  
• Patients with angioedema |  |
| **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-QoL | 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 which angioedema predominates |

AAS: Angioedema Activity Score; CIndU: chronic inducible urticaria; CSU: chronic spontaneous urticaria; CU: chronic urticaria; CU-QoL: Chronic Urticaria Quality of Life Questionnaire; PRO: Patients-reported outcomes tool; QoL: Quality of Life; UAS: Urticaria Activity Score; UAS7: Urticaria Activity Score 7; UCT: Urticaria Control Test.
Table 2. Patient profile according to omalizumab response (technical data sheet).

<table>
<thead>
<tr>
<th>Response Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast responder</td>
<td>Patients who respond in 4-6 weeks</td>
</tr>
<tr>
<td>Slow responder</td>
<td>Patients who respond in 12-16 weeks</td>
</tr>
<tr>
<td>Complete responder</td>
<td>- Sustained UAS7 score = 0</td>
</tr>
<tr>
<td></td>
<td>- Absence of symptoms</td>
</tr>
<tr>
<td></td>
<td>- Absence of angioedema</td>
</tr>
<tr>
<td></td>
<td>- Requires neither salvage medication nor H1-antihistamines</td>
</tr>
<tr>
<td>Good responder</td>
<td>- Sustained UAS7 score = 1-6</td>
</tr>
<tr>
<td>Partial responder</td>
<td>- Partial improvement in baseline UAS7 with UAS7 scores ranging from 7-15</td>
</tr>
<tr>
<td>Non-responder</td>
<td>- No change in baseline UAS7 score and sustained scores &gt; 16</td>
</tr>
</tbody>
</table>

UAS: Urticaria Activity Score; UAS7: Urticaria Activity Score 7