Eur J Dermatol 2020; 30(6): 716-22

Zoe APALLA[1]
Theodoros SIDIROPOULOS[1]
Evaggelia KAMPOUROPOULOU[1]
Marina PAPAGEORGIOU[1]
Aimilios LALLAS[2]
Elizabeth LAZARIDOU[3]
Maria SMARAGDI[1]
Florentina DELLI[1]

[1] State Dermatology Department, Hippokratio General Hospital of Thessaloniki, Greece
[2] First Dermatology Department, Aristotle University of Thessaloniki, Greece
[3] Second Dermatology Department, Aristotle University of Thessaloniki, Greece

Reprints: Zoe Apalla <zoimd@yahoo.gr>

Article accepted on 24/05/2020

Real-life, long-term data on efficacy, safety, response and discontinuation patterns of omalizumab in a Greek population with chronic spontaneous urticaria

Background: Omalizumab is approved for the treatment of chronic spontaneous urticaria (CSU) not responding to antihistamines. Data on omalizumab use in real-world settings and in different populations are lacking. *Objectives:* To record our five-year experience of omalizumab use in patients with refractory CSU in a real-world setting. *Materials & Methods:* A retrospective analysis of medical records of 80 patients with refractory CSU was performed. Demographic, and clinical characteristics, patterns of response, discontinuation strategies and rate of recurrence were analysed. *Results:* Eighty individuals were included. UAS7 and DLQI significantly decreased from baseline. Complete response was achieved in 86.3%. Late response was observed at 27.5% of the patients. After discontinuation, 21.7% of patients reinitiated omalizumab due to relapse. The mean number of omalizumab administrations up to first discontinuation was 6.8 (based on an approach to shorten the treatment interval). Only 15.0% of patients experienced adverse events during treatment. *Conclusion:* Omalizumab, with long-term management, was highly effective and safe in achieving control of refractory CSU, with more favourable responses compared to Phase III clinical trials.

Key words: chronic spontaneous urticaria, urticaria, omalizumab, angioedema, allergy, IgE inhibitors

Chronic spontaneous urticaria (CSU) is defined as the spontaneous occurrence of pruritic wheals (hives), angioedema, or both, for a period of at least six weeks with no apparent induction by any external specific trigger [1, 2]. The severity and duration of CSU may vary greatly among patients, whilst the impact on quality of life can be significant [3-5].

According to the EAACI/GA2LEN/EDF/WAO international urticaria guidelines [6], the "gold-standard" treatment for CSU is second-generation H1-antihistamines, with dose-escalation (up to four times the licensed dose) as a second-line approach in those not responding to low doses. However, based on literature data, the licensed doses of H1-antihistamines result in complete remission of symptoms in fewer than 50% of patients with CSU [1, 6, 7]. In addition, increased efficacy with H1-antihistamines updosing is observed in only 38% of patients, and it is mainly restricted for the control of itch, and not used to decrease the number of hives [8, 9]. Omalizumab is a recombinant, humanized anti-immunoglobulin-E antibody, approved for the treatment of CSU in adults and adolescents, who do not respond to antihistamines [6, 10].

Previous trials of the omalizumab clinical programme for CSU demonstrated safety and efficacy of omalizumab for CSU [3, 10-12]. Real-world experience of safety and efficacy of omalizumab for CSU from different populations and in various settings is beginning to emerge, generally showing that the benefits and safety of omalizumab in the real-world setting meet or even exceed the results gleaned from clinical trials [13]. Furthermore, other clinically significant aspects of CSU management, such as prediction of time of response, patterns of response, as well as strategies for omalizumab discontinuation or up-dosing have only recently started to be explored [2, 9, 14-21].

The primary objective of our study was to describe the response patterns to omalizumab in a real-world population of patients with refractory CSU, based on the experience of our department. The secondary objective was to identify timing of response to omalizumab treatment and patterns of successful discontinuation of therapy, with long-term follow-up. To the best of our knowledge, there are two previous publications reporting real-world experience of omalizumab in Greece, including only 49 patients in total [22, 23]. In the latter studies, however, authors provided no data with regards to long-term management (up to 2.5 years of usage and discontinuation and re-initiation of treatment). The present study provides insight into a large sample of patients that started on omalizumab in a real-life setting in Greece, with long-term efficacy and safety data, with regards to both duration of treatment as well as

doi:10.1684/ejd.2020.3919

To cite this article: Apalla Z, Sidiropoulos T, Kampouropoulou E, Papageorgiou M, Lallas A, Lazaridou E, Smaragdi M, Delli F. Real-life, long-term data on efficacy, safety, response and discontinuation patterns of omalizumab in a Greek population with chronic spontaneous urticaria. *Eur J Dermatol* 2020; 30(6): 716-22 doi:10.1684/ejd.2020.3919

patients' follow-up after discontinuation. Moreover, the criteria taken into consideration for treatment interruption in responders are described, along with the gradual pattern and mean number of administrations associated with handling relevant treatment discontinuation.

Materials and methods

Patient population and study design

This was a retrospective, observational study of 80 patients (>12 years of age) with refractory CSU, who were started on omalizumab as per SpmC label use, after receiving approval from the Greek National Drug Organization for CSU usage in 2015. The patients were recruited through the urticaria outpatient clinic registry of the State Dermatology Department, Hippokratio General Hospital of Thessaloniki, Greece. No time limit was applied. Diagnosis of CSU was made by a team of experienced dermatology experts and was based on previously published guidelines. Patient inclusion criteria were predefined as follows: clinician-confirmed diagnosis of CSU; persistence or recurrence of symptoms for at least 2-4 weeks after up-dosing (up to four-fold the licensed dose) of second-generation non-sedating H1-antihistamines; and omalizumab administration. Patients with inducible urticaria were excluded. The medical records of all 80 identified subjects were reviewed. Extracted data included patients' and disease characteristics at baseline, namely age at diagnosis, gender, disease duration (from onset of symptoms to omalizumab administration), presence of angioedema and previous treatments, as well as data after initiation of omalizumab. The latter included treatment response to omalizumab, duration on omalizumab, concomitant treatment apart from antihistamines, recurrence after discontinuation, patterns of response after re-initiation, duration of follow-up, and adverse events (AEs).

Assessment of CSU activity and definitions of response

As suggested by the EAACI/GA2LEN/EDF/WAO International Urticaria Guidelines 6, the validated weekly urticaria activity score (UAS7) was used to assess urticaria severity prior and post- omalizumab administration, at Weeks 4 and 12, as well as at the last patient visit before the analysis (defined as current score). UAS7 ranges from 0 (no pruritus, no hives for a period longer than seven days/ complete responders) to intermediate values (1-6, 7-15, and 16-27, which were classified as well-controlled, mild, and moderate CSU, respectively), and up to scores of 28-42 (severe CSU with severe pruritus and more than 50 hives/day or large confluent areas of hives) [1, 4, 14]. Patients with complete control or well-controlled disease were classified as responders. Patients were classified, according to the pattern of response, as early responders for those responding within the first month of treatment, and late for those responding after a period of three months. Responses noted within the remaining time frame (second to third month of treatment) were classified as intermediate [24]. The patients were asked to fill in the Dermatology Life Quality Index (DLQI) questionnaire at baseline, Weeks 4 and 12 and at their last visit (current status), before the data analysis.

Statistical analysis

Continuous variables are presented with mean ±standard deviation (SD). Respective *p* values were calculated using the Friedman's test to assess the difference across the whole evaluation period. Quantitative variables are presented with absolute and relative frequencies. Analyses were conducted using Excel and SPSS statistical software (version 25.0).

Results

Demographic and patients' characteristics at baseline

The demographic characteristics of the 80 patients diagnosed with refractory CSU and treated with omalizumab, from January 2015 to June 2019, are presented in *table 1*. The mean age of the population was 44.2 years (range: 16-63 years; SD: ±11.9), with a female predominance of 52/80 (65%). Angioedema was present in 21/80 cases (26%). All patients had a history of chronic urticaria refractory to high doses of antihistamines, with a mean disease duration before omalizumab administration of 10.7 months (range: 2-34 months; SD: ±7.4).

Baseline use of medications

Based on the medical records, at baseline, all patients had received second-generation antihistamines at up to four times the regular dose, with 29.8% (23/80) receiving at least two different types of antihistamines (mean ± SD: 1.3 ±0.5). The proportion of patients that used other medications (apart from H1 antihistamines) for CSU was 62/80 (77.5%) (*figure 1*). About two thirds of them (65.0%) had received oral corticosteroids, whilst only 15.0% had used a leukotriene receptor antagonist (montelukast) and 16.3% cyclosporine prior to omalizumab use.

All patients (100%) received 300 mg of omalizumab, every four weeks. The treatment was administered in the hospital by the physician, or by the patients themselves after establishing sufficient experience and eliminating potential risks to the patient. After achieving successful disease control (UAS7 = 0) for at least two months with omalizumab, the time intervals between two treatments were gradually increased (from 4, to 6, to 8 and up to 10 weeks), in accordance with common clinical practice and previously reported expert opinions [9, 14]. The criteria used for omalizumab discontinuation after the gradual increase in time intervals between drug administrations were: persistence of complete response (UAS7 = 0) after at least three months, minimal antihistamine dose (one pill per day), and patients' preference. The gradual increase started from the approved four weeks at baseline, to 6, 8 and up to 10 weeks. Based on this approach, a group of patients discontinued omalizumab after only a six-week extension, whilst others had an extension with up to 8- and 10-week time intervals. Discontinuation of omalizumab was defined as a time interval of more than 90 days between the last and the next treatment

Table 1. Baseline characteristics of the population.

Baseline variables	Total population ($n = 80$)	
Age, mean (SD)	44.2 (11.9)	
Females, *n* (%)	52 (65)	
Angioedema, *n* (%)	21 (26.3)	
Mean disease duration (SD)	10.7 (7.4)	
	Before omalizumab	**Combined with omalizumab**
UAS7 mean (Min-Max)	27.7 (15-39)	1.1 (0-14)
Medications		
nsAH, *n* (%)	80 (100)	80 (100)
2nd nsAH, *n* (%)	23 (29.8)	21 (26.3)
Cyclosporine, *n* (%)	13 (16.3)	2 (2.5)
Steroids, *n* (%)	52 (65.0)	9 (11.3)
Montelukast *n* (%)	4 (5.0)	0 (0.0)

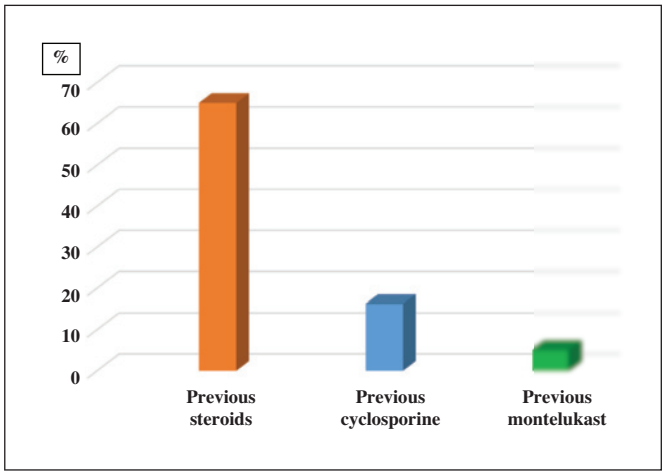

Figure 1. Previous use of concomitant medication (apart from H1 antihistamines) at baseline (%).

(in case of relapse), or between the last day of omalizumab administration and the end of the follow-up period, *i.e.* >90 days between consecutive days of omalizumab administration [25]. The mean time on treatment and the mean number of omalizumab administrations are presented in *table 2*.

Treatment outcome

Treatment outcome and patterns are summarized and illustrated in *tables 2, 3*, and *Figures 2, 3*, accordingly.
Omalizumab was an add-on to a second-generation H1-antihistamine, taken at least once a day, in all patients, of whom 77.5% received at least one additional concomitant medication. Importantly, the recorded reduction in other CSU medications, such as cyclosporine and montelucast, dropped from 16.3 and 5.0 at baseline to 2.5% and 0.0%, respectively (*table 1*). The greatest decrease was observed for oral corticosteroids which dropped from 65.0% to 10.0% with omalizumab use.
The mean duration of omalizumab treatment within the observational period was 8.5 months (35.9 weeks; SD ±23.8), with 27.5%, 63.8% and 8.75% of the patients being treated for up to six months, up to one year and for more than one year, respectively (*table 2*). The maximum duration of omalizumab treatment in our population was 3.5 years (192 weeks) in a patient who experienced recurrence of CSU four times, after four unsuccessful attempts of drug discontinuation.
Seventy-nine patients (98.6%) received a dosage of 300 mg every four weeks until full remission of symptoms for at least two months. Based on the favourable response, as described above, we decided to gradually extend the time intervals between treatments until treatment cessation; with 62.5% (50/79) maintaining complete response. In the analysed population, treatment failed in a patient with refractory CSU, in whom the dosage was increased to 600 mg every four weeks, in order to achieve better control of disease activity [9, 14, 19, 26].
At the last follow-up visit, 40 of 80 individuals (50.0%) were still on treatment. In total, 46 patients (57.7%) had ≥one treatment interruption (*table 2*) due to complete remission of disease symptoms as per recent guidelines and expert opinions [6, 14], whilst 10 (21.7%) had to re-initiate the treatment at least once due to recurrence of symptoms. Of the 40 patients who stopped omalizumab treatment due to complete remission and did not experience any relapse, six (15%) were treated with omalizumab for six months and 34 (85%) were treated for longer than six months, with a maximum of 56 weeks.

Evolution of UAS7 score and DLQI

UAS7 before omalizumab ranged from 15 to 39 (mean: 27.7 ±6.6), whilst post-omalizumab mean UAS7 decreased significantly to 1.1 (range: 0 to 14; SD ±2.9) at the end of the observation period (*table 3*, *figure 2*). Response to omalizumab at the end of the observation period was scored as 0 (complete response) in 69/80 patients (86.3%), 1-6 (good responders: well-controlled disease) in 6/80 patients (7.5%), with five patients (6.3%) still experiencing refractory mild disease (partial responders: score of 7-15) (*table 2,*

Table 2. Treatment response to omalizumab.

Mean time on omalizumab in weeks (SD)	36.0 (±23.6)
Mean number of omalizumab administrations to first discontinuation	6.8 (range 4-10)
AEs, *n* (rate)	12 (0.2 per patient)
Patients discontinued treatment, *n* (%)	46 (57.7%)
Patients restarting treatment after discontinuation, *n* (%)	10 (21.7)
Early responders, *n* (%)	27 (33.8)
Intermediate responders, *n* (%)	26 (32.5)
Late responders, *n* (%)	22 (27.5)
Non-responders (mild disease), *n* (%)	5 (6.3)

Table 3. Descriptive statistics for UAS-7 and DLQI during the entire period of evaluation based on Friedman's test.

Variables	Baseline	Week 4	Week 12	Current	*p* value*
UAS7 (0-42)					
Mean ±SD	27.7 ± 6.6	7.8 ± 7.8	3.8 ± 5.4	1.1 ± 2.9	<0.001
Median (min-max)	29 (15- 39)	6 (0-30)	0 (0-24)	0 (0-14)	
[0] %	0	33.8	55.0	86.3	
[1-6] %	0	17.5	17.5	7.5	
[7-15] %	2	32.5	21.3	6.3	
[16-27] %	41.8	13.8	6.3	0	
[28-42] %	56.3	2.5	0	0	
DLQI (0-30)					
Mean + SD	19.2 ± 6.0	7.6 ± 6.0	3.0 ± 4.5	1.6 ± 3.7	<0.001
Median	19.5 (9-28)	6 (0-24)	0 (0-22)	0 (0-16)	

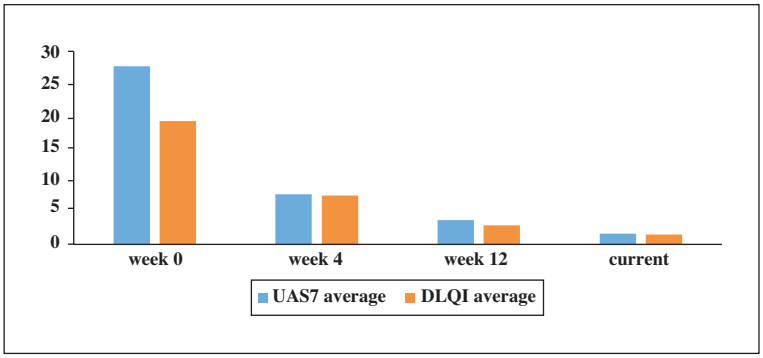

Figure 2. Response to omalizumab with regards to disease control and improvement in quality of life.

figure 3). Fourteen were identified as non-responders (no change in baseline UAS7 score and sustained scores >16). DLQI scores followed a similar pattern of improvement (*table 2*, *figure 2*). The mean DLQI score of 19.2 ± 6.0 before omalizumab declined to 1.6 ± 3.7, reflecting the marked improvement in quality of everyday life of the patients.

Among all responders (75/80, 93.8%), a third (27/80, 33.8%) showed an "early" pattern of response to omalizumab after the first dose (UAS7 = 0 at four weeks), 26 (32.5%) showed an "intermediate" pattern of response after the second dose (1-3 months), while 27.5% (22/80) responded after the fourth or fifth dose ("late" responders) (9/20 cases; 45.0%) (*table 2*). The optimal response in the group of refractory cases (late responders and non-responders) was observed after five or four doses of omalizumab.

Adverse events (AEs)

Overall, 12 AEs were reported (0.2 AEs per patient) by 11 patients (13.8% of the total population) (*figure 3*). The most common was a reaction to the site of injection in six patients, whilst four patients experienced headache and another two joint pain. All the reported AEs were in line with the safety profile of the drug [11], and no serious AE occurred throughout the observation period. None of the patients discontinued omalizumab due to AEs.

Discussion

Based on the analysis of our CSU patients in a real-life setting, omalizumab proved to be highly effective, with

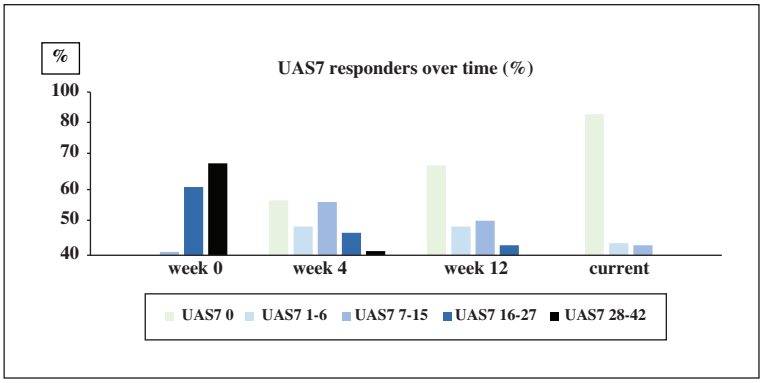

Figure 3. Response rates to omalizumab based on UAS7 throughout the evaluation period.

86.3% of the individuals achieving complete response and a corresponding improvement in their quality of life. These results exceed those retrieved from Phase III clinical trials [3, 10, 11], and are in line with the observations based on previously released real-world data [2, 21-23, 25, 27]. In addition, a recent metanalysis of 76 real-world reports [13] showed that the benefits in terms of efficacy and safety of omalizumab as real-world treatment for patients with CSU generally exceed results gleaned from clinical trials, with complete and partial response rates of approximately 72.2% and 17.8%, respectively. The latter meta-analysis highlights the importance of long-term evidence emerging from a real-world setting, since it may enrich our knowledge in terms of patterns of response and safety issues, and may subsequently influence treatment expectations and policy decision-making.

Patient demographic characteristics described in the present study were representative of the general population of patients with CSU and comparable with those previously reported in the literature [3, 10, 11, 25]. In contrast, the prevalence of angioedema that represents an unfavourable prognostic factor and an indicator of more severe disease [1] was lower in our study (26.3%) compared to other trials and settings which ranged from 28% to 54% [3, 5, 10, 11]. Moreover, pre-omalizumab use of LTRAs in our patients was significantly more frequent; 5% compared to 57.5% in the Glacial study [10]. However, this is expected since it reflects the beginning of adherence to the updated 2017 CSU treatment Guidelines, in which LTRAs have been removed from the CSU treatment algorithm with cyclosporine as a fourth step choice after omalizumab [6]. On the other hand, the use of oral corticosteroids by 65.0% of our CSU population is comparable to the 57.9% of the Glacial study [10]. The long duration experienced by CSU patients from symptom onset to diagnosis and omalizumab treatment was confirmed in our findings with a mean disease duration of almost one year (10.7 months) before omalizumab initiation, suggesting that better approaches are needed in order to shorten the long period from symptom onset to diagnosis and adequate treatment.

One third (33.75%) of our studied cases reached optimal response to omalizumab after administration of the first omalizumab dose, indicating an early pattern of response. On the other hand, delayed patterns of response, requiring at least 12 weeks (late responders) [14], were noted in 27.5% of the individuals. The latter findings are in accordance with those reported by previous investigators, suggesting that the majority of patients will respond to omalizumab within one to three months of treatment, yet it is important to wait up to 12 weeks for about one third of the patients to show a significant response [2, 9, 14, 22]. Besides the identical clinical expression amongst CSU patients, the diverse patterns of response to omalizumab may indicate different immunological/pathogenic profiles. The possible latter diversity suggests that patients can be classified into two different phenotypes/immunotypes, namely responders versus non-responders and fast versus slow responders [2]. Early and intermediate responders have been correlated with a Type I autoimmune reaction (IgE to auto-allergens), whilst late responders have been correlated with a Type II (IgG autoantibodies to IgE or FcεRI) causality [28]. Early recognition of the pattern of response in a CSU patient is of paramount importance for adequate control of the disease [9]. There are huge efforts towards identification of novel biomarkers that could be used as predictors of response [16, 20, 29, 30]. For the moment, it seems that positive tests for auto-antibodies, both *in vitro* (basophil histamine release assay) and *in vivo* (autologous serum skin test), correlate with slow responders, hypothetically due to higher levels of autoantibodies [21], whilst high FcεRI expression and IgE levels at baseline, as well as after four weeks into therapy, are predictive of an early or intermediate response pattern [18, 20, 29]. The value of total IgE as a useful biomarker response pattern for omalizumab in patients with CSU may be somewhat controversial, because of the wide range of overlapping values observed in the categories of responders [15, 18]. Moreover, late response to omalizumab has also been correlated with shorter disease duration [22]. The latter may be attributed to the presence of more active disease among patients with more recent onset of symptoms. Finally, yet importantly, a lack of basophil CD203c-upregulating activity in the serum of patients with CU has also been found to correlate with good clinical response to omalizumab, which might prove a useful future biomarker of response to treatment [21, 31]

As suggested by the current analysis, response to omalizumab may require continuous long-term dosing, which may increase the percentage of responders. As CSU has a variable and unpredictable course, there may be no optimal treatment duration for omalizumab. In this context, real-world experience from long-term use of omalizumab, such as in our study extending up to 3.5 years of treatment, is extremely helpful in establishing not only the safety profile, but also the long-term efficacy in disease control. Moreover, adjustments of the time intervals between treatments

may benefit some patients who respond early or late to omalizumab, requiring longer or shorter intervals between administrations, respectively [9, 18] As reimbursement for omalizumab in Greece applies only for 300 mg of omalizumab with a four-week interval, there is limited flexibility with regards to administration. In complete responders, although both therapeutic strategies of dose reduction and increasing the treatment interval are described [14], we only used the gradual longer interval approach, starting from the licensed 4 weeks at baseline, to 6, to 8 and up to 10 weeks, which permitted a more stable step-wise approach to reducing the dosage.

Furthermore, real-world studies such as ours may contribute to identifying suggestive prognostic indicators of possible relapse, as a significant proportion of patients in real-world studies, including the present study, experience relapses after treatment cessation (50% of patients experienced relapse after discontinuation at six months) [11]. It has been suggested that a higher baseline UAS7 score and slower speed of response (low UAS7 AAC) are predictive of a relapse after discontinuation of omalizumab treatment [9, 14, 17].

In conclusion, the results of our retrospective, observational, real-world data analysis confirm the long-term safety and efficacy of omalizumab, in terms of control of disease activity, as well as an improvement in quality of life for severe refractory CSU. The data also provide meaningful insight into patients' treatment in Greek clinical practice, even in challenging situations. Moreover, as performed in the present study, it is important to follow patients after the end of omalizumab cycles in order to evaluate true remission of CSU. Finally, additional regional and worldwide prospective cohorts of patients with severe refractory CSU, with long-term real-life experience, are needed in order to answer questions that are commonly raised by the attending physician which have not yet been answered by clinical trials and identify potential independent predictors of response and timing of response to omalizumab. ■

Disclosure. *Funding sources: none. Conflicts of interest: none.*

References

1. Maurer M, Weller K, Bindslev-Jensen C, *et al*. Unmet clinical needs in chronic spontaneous urticaria. A GA2 LEN task force report? *Allergy* 2011; 66: 317-30.

2. Larenas-Linnemann DES, Parisi CAS, Ritchie C, *et al*. Update on omalizumab for urticaria: what's new in the literature. *Curr Allergy Asthma Rep* 2018; 18: 33.

3. Kaplan A, Ledford D, Ashby M, *et al*. Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. *J Allergy Clin Immunol* 2013; 132: 101-9.

4. Mlynek A, Zalewska-Janowska A, Martus P, *et al*. How to assess disease activity in patients with chronic urticaria? *Allergy* 2008; 63: 777-80.

5. Maurer M, Sofen H, Ortiz B, *et al*. Positive impact of omalizumab on angioedema and quality of life in patients with refractory chronic idiopathic/spontaneous urticaria: analyses according to the presence or absence of angioedema. *J Eur Acad Dermatol Venereol* 2017; 31: 1056-63.

6. Zuberbier T, Aberer W, Asero R, *et al*. The EAACI/GA(2)LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. The 2017 revision and update. *Allergy* 2018; 73: 1393-414.

7. Sharma M, Bennett C, Carter B, Cohen SN. H1-antihistamines for chronic spontaneous urticaria: an abridged Cochrane Systematic Review. *J Am Acad Dermatol* 2015; 73: 710-6.

8. Ferrer M, Sastre J, Jauregui I, *et al*. Effect of antihistamine updosing in chronic urticaria. *Inv Allergol Clin Immunol* 2011; 21: 34-9.

9. Ferrer M, Boccon-Gibod I, Goncalo M, *et al*. Expert opinion: defining response to omalizumab. *Eur J Dermatol* 2017; 27: 455-63.

10. Maurer M, Rosern K, Hsieh HJ, *et al*. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med* 2013; 368: 924-35.

11. Saini SS, Bindslev-Jensen C, Maurer M, *et al*. Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic on H1 antihistamines: a randomized, placebo-controlled study. *J Invest Dermatol* 2015; 135: 65-75.

12. Zhao ZT, Ji CM, Yu WJ, *et al*. Omalizumab for the treatment of chronic spontaneous urticaria: a meta-analysis of randomized clinical trials. *J Allergy Clin Immunol* 2016; 137: 1742-50.

13. Tharp M, Bernstein JA, Kavati A, *et al*. Benefits and harms of omalizumab treatment in adolescent and adult patients with chronic idiopathic (spontaneous) urticaria. *JAMA Dermatol* 2019; 155: 29-38.

14. Giménez Arnau AM, Valero Santiago A, Bartra Tomás J, *et al*. Therapeutic strategy according to differences in response to omalizumab in patients with chronic spontaneous urticaria. *J Investig Allergol Clin Immunol* 2019; 29: 338-48.

15. Weller K, Ohanyan T, Hawro T, *et al*. Total IgE levels are linked to the response of chronic spontaneous urticaria patients to omalizumab. *Allergy* 2018; 73: 2406-8.

16. Deza G, Ricketti PA, Giménez-Arnau AM, Casale TB. Emerging biomarkers and therapeutic pipelines for chronic spontaneous urticaria. *J Allergy Clin Immunol Pract* 2018; 6: 1108-17.

17. Ferrer M, Giménez-Arnau A, Saldana D, *et al*. Predicting chronic spontaneous urticaria symptom return after omalizumab treatment discontinuation: exploratory analysis. *J Allergy Clin Immunol Pract* 2018; 6: 1191-7.

18. Deza G, Bertolín-Colilla M, Sánchez S, *et al*. Basophil FcεRI expression is linked to time to omalizumab response in chronic spontaneous urticaria. *J Allergy Clin Immunol* 2018; 141: 2313-6.

19. Curto-Barredo L, Spertino J, Figueras-Nart I, *et al*. Omalizumab updosing allows disease activity control in patients with refractory chronic spontaneous urticaria. *Br J Dermatol* 2018; 179: 210-21.

20. Deza G, Bertolín-Colilla M, Pujol RM, *et al*. Basophil FcεRI expression in chronic spontaneous urticaria: a potential immunological predictor of response to omalizumab therapy. *Acta Derm Venereol* 2017; 97: 698-704.

21. Giménez-Arnau AM, Toubi E, Marsland AM, Maurer M. Clinical management of urticaria using omalizumab: the first licensed biological therapy available for chronic spontaneous urticaria. *J Eur Acad Dermatol Venereol* 2016; 30: 25-32.

22. Syrigos N, Grapsa D, Zande M, Tziotou M, Syrigou E. Treatment response to omalizumab in patients with refractory chronic spontaneous urticaria. *Int J Derm* 2018; 57: 417-22.

23. Kyriakou A, Trigoni A, Sotiriadis D, Patsatsi A. Efficacy of omalizumab in severe chronic spontaneous urticaria: Real life from a Greek tertiary center. *Dermatol Ther* 2018; 31: 12739.

24. Kaplan A, Ferrer M, Bernstein JA, *et al*. Timing and duration of omalizumab response in patients with chronic idiopathic/spontaneous urticaria. *J Allergy Clin Immunol* 2016; 137: 474-81.

25. Eghari-Sabet J, Sher E, Kavati A, *et al*. Real-world use of omalizumab in patients with chronic idiopathic/spontaneous urticaria in the United States. *Allergy Asthma Proc* 2018; 39: 191-200.

26. Kocaturk E, Deza G, Kiziltac K, Gimenez-Arnau AM. Omalizumab updosing for better disease control in chronic spontaneous urticaria patients. *Int Arch Allergy Immunol* 2018; 177: 360-4.

27. Lapeere H, Baeck M, Stockman A, *et al*. A retrospective analysis omalizumab treatment patterns in patients with chronic spontaneous urticaria: a real-world study in Belgium. *J Eur Acad Dermatol* 2020; 34: 127-34.

28. Kolkhir P, Church KM, Weller K, Meltz M, Schmetzer O, Maurer M. Autoimmune chronic spontaneous urticaria: what we know and what we do not know. *J Allergy Clin Immunol* 2017; 139: 1772-82.

29. Ertas R, Ozyurt K, Atasoy M, Hawro T, Maurer M. The clinical response to omalizumab in chronic spontaneous urticaria patients is linked to and predicted by IgE levels and their change. *Allergy* 2018; 3: 705-12.

30. Gericke J, Metz M, Ohanyan T, *et al*. Serum autoreactivity predicts time to response to omalizumab therapy in chronic spontaneous urticaria. *J Allergy Clin Immunol* 2017; 3: 1059-61.e1.

31. Palacios T, Stillman I, Borish I, Lawrence M. Lack of basophil CD203c -upregulating activity as an immunological marker to predic response to treatment with omalizumab in patients with symptomatic chronic urticaria. *J Allergy Clin Immunol Pract* 2016; 4: 529-30.