SECTION 4

Clinical management of urticaria using omalizumab; the first licensed biologic therapy available for chronic spontaneous urticaria

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Abstract

This supplement reports proceedings of the second international Global Urticaria Forum, which was held in Berlin, Germany in November 2015. Omalizumab is approved for the treatment of chronic spontaneous urticaria (CSU) in adult and adolescent (12 years and above) patients with inadequate response to/who remain symptomatic, despite H_1-antihistamine treatment, and has demonstrated good efficacy and safety in the clinical trial setting. Real-life clinical experience with omalizumab can be explored to address important practical questions relating to its use in CSU patients. Some experts have proposed that a consensus algorithm, covering various aspects to consider when using omalizumab in real-life clinical practice for the management of CSU, could answer many of these questions.

Conflicts of interest

- Ana M. Giménez-Arnau has acted as a medical advisor for Uriach Pharma, Genentech and Novartis; received research grants supported by Uriach Pharma and Novartis, and been involved in educational activities sponsored by Uriach Pharma, Novartis, Genentech, Menarini and MSD.
- Elias Toubi has acted as a speaker for Novartis.

- Alexander Marsland has acted as a speaker and/or advisor for Galderma, GSK, Novartis and UCB Pharma.
- Marcus Maurer is, or was recently, a speaker and/or advisor for FAES, Almirall Hermal, Genentech, GSK, Merckle Recordati, Novartis, Sanofi-Aventis MSD, Moxie, Takeda, Shire, UCB and Uriach.

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Introduction

When a new treatment for a challenging target disease is developed, there is a need to determine for whom this treatment is suitable and how the drug should be used. Treatment objectives need to be defined. By assessing a drug's efficacy and safety in clinical trials and in real-life practice we gain valuable knowledge regarding the drug, the disease and the patients. This experience helps us to develop solid criteria that enable us to make recommendations for the clinical management of that drug.

Chronic spontaneous urticaria (CSU) (also called chronic idiopathic urticaria [CIU]), is one such challenging target disease, and omalizumab is the first licensed biologic treatment available.[1,2] The treatment objective is to achieve complete resolution of signs (hives and angioedema) and relief of symptoms (pruritus and pain) as quickly as possible, and to ensure patients have the best possible quality of life until the point at which the signs and symptoms of the disease are no longer present. This objective is defined by consensus in the current EAACI/GA[2]LEN/EDF/WAO urticaria guideline.[3]

Some common principles, valid for any type of active treatment, should be considered when treating CSU. Some CSU phenotypes and patients need months while others will require years of continuous treatment.[4] Different patterns of response to treatment are not necessarily related only to different patients, but also to different disease periods in the same patient.

A three-step treatment algorithm is recommended for urticaria, according to evidence-based criteria **(Fig. 1)**.[3] Following an inadequate response to first- and second-line treatment with H_1-antihistamines at the licensed dose or up to 4-times the licensed dose, respectively, add-on omalizumab, ciclosporin or montelukast are recommended as third-line treatment options.[3] In real-world studies, omalizumab has been demonstrated to be more efficient than ciclosporin in clearing symptoms.[5] Omalizumab is licensed for the treatment of CSU, while montelukast and ciclosporin are not.[1,2]

In the pivotal randomized clinical trials ASTERIA I, ASTERIA II, and GLACIAL, omalizumab demonstrated excellent efficacy and safety for the treatment of CSU,

with significant reductions in CSU signs and symptoms compared with placebo.[6-8] Mean changes in weekly Itch Severity Score from baseline to week 12 were significantly greater with omalizumab 300 mg compared to placebo (-67% in ASTERIA I, -71% in ASTERIA II and -62% in GLACIAL).[9,10] Significantly more patients had well controlled CSU (7-day Urticaria Activity Score [UAS7] ≤6) at week 12 following omalizumab 300 mg (52–66% of patients), compared with placebo (11–19% of patients).[6-8] In addition, significantly more patients were itch- and hive-free with a complete response (UAS7=0) at week 12 following omalizumab 300 mg (34–44% of patients) compared with placebo (5–9% of patients).[6-8] Omalizumab also controls angioedema and normalizes angioedema-driven quality of life impairment in patients with CSU.[11]

Whether practical approaches used and outcomes seen with omalizumab in CSU are similar outside of clinical trials, in the real-world setting, is an important consideration for clinicians, and there are still some unanswered questions.

Practical management of urticaria with omalizumab in the real-world setting

Response to omalizumab in the real-world clinical setting in patients with CSU has been shown to be similar to, and in some cases better than that seen in the pivotal randomized controlled trials (**Table 1**).[6-10,12-15]

Real-world evidence has shown that patients with CSU can have a particularly fast response to omalizumab treatment. In one retrospective analysis of patients treated outside of clinical trials, symptom control was rapid, with 57% of patients who achieved a complete response doing so within one week, and 86% within four weeks (**Fig. 2**).[14] These real-world response results with omalizumab in patients with CSU were consistent with published reports from clinical studies.[14]

In chronic urticaria (CU) patients who had previously responded to omalizumab, but who show relapse when they discontinue treatment, real-world evidence has shown that retreatment can be successful. In a further retrospective analysis, of 25 CU (CSU or chronic inducible urticaria [CIndU]) outpatients, most experienced relapse (reappearance of symptoms) after treatment discontinuation within 2–8 weeks, when previously all patients had complete symptom control after their first use of

omalizumab.[16] Following retreatment with omalizumab (150–600 mg/month), all patients reported a rapid and complete response within the first 4 weeks, and usually during the first days of retreatment; no relevant adverse events were reported.[16]

In a retrospective analysis of 110 patients with inadequately-treated CSU at nine hospitals in Spain, use of omalizumab was associated with a complete or significant response in 81.8% of patients; furthermore, 60% of patients were able to discontinue concomitant medications and remain asymptomatic with omalizumab alone.[12] After 1–18 months, 41 patients (37.3%) discontinued omalizumab treatment due to complete response. Of these, 20 patients (47.5%) had omalizumab treatment re-introduced due to CSU symptom relapse. With retreatment, complete response was achieved in 18 patients (90%) within 1 week to 2 months.[12]

Assessment of response to treatment with omalizumab in CSU

It is desirable to objectively monitor treatment of CSU. Different tools may be used to assess treatment response including the UAS7,[3] Angioedema Activity Score (AAS),[17] the Urticaria Control Test (UCT),[18] specific disease quality of life questionnaires (Chronic Urticaria – Quality of Life Questionnaire [CU-Q_2oL] and Angioedema – Quality of Life Questionnaire [AE-QoL]). Many physicians rely on their own experience and clinical judgement to assess disease activity.

The EAACI/GA^{2}LEN/EDF/WAO urticaria guideline recommends that disease activity is assessed in CSU patients using the UAS7.[3] However, only six of 26 randomized controlled trials analyzed in a systemic review of studies with inadequately-treated CSU patients reported using the UAS7.[19] Heterogeneity was also seen in the way that outcomes were presented, with some studies reporting scores as change from baseline, some reporting only the score at study end, and others reporting the percentage of patients who demonstrated an improvement.[19] There is still heterogeneity in the measurement of disease activity in patients with CSU.

A consensus is needed regarding what scoring system and threshold should be used to best define the activity of CSU. Furthermore, there should be consideration of which score represents an important/meaningful burden to the patient. There is currently no consensus on how response to treatment should be described in

patients with CSU. There are also differences in how response is measured and defined in clinical trials versus real-world clinical practice (**Table 1**).

As physicians, how should we define a complete, partial or non-response to treatment in our daily clinical practice? Published studies have defined response based on the UAS7; a good response has been defined as stable UAS7=0, UAS7≤6, ≥90% improvement in UAS7, or simply no itch or hives (by clinical judgement). Based on the UAS7 and clinical assessment, non-response could be defined as no change or increased disease activity compared with the baseline. A partial response could be defined as a mild and unstable reduction of the UAS7 versus baseline (without reaching UAS7≤6).

It is thought that there may be different categories of 'omalizumab responders', with some CSU patients responding to treatment more quickly than others.[20] 'Fast responders' are thought to respond to omalizumab treatment within 4–6 weeks and 'slow responders' more gradually by Weeks 12–16 of treatment. Some of the fast responders show an immediate or early response with 1 week of treatment. An understanding of response patterns to omalizumab could provide clinicians with a better practical approach to the treatment of patients with CSU in the real world setting. For example, the fact that some patients may take longer to respond may mean that there is value in extending treatment with omalizumab in apparent non-responders before considering an alternative. Increased knowledge regarding response patterns could also potentially further our understanding of the treatment mode of action and pathophysiological mechanisms of disease.

Use of omalizumab for the management of CSU in the real-world setting

The licensed dose for omalizumab in CSU is 300 mg in the EU[1] and either 150 or 300 mg in the US,[2] by subcutaneous injection every 4 weeks. Response patterns following omalizumab treatment of CSU patients in the three pivotal phase III clinical trials (ASTERIA I and II, and GLACIAL) were investigated in a retrospective analysis.[20] Patients receiving omalizumab 300 mg demonstrated earlier and more sustained response than patients receiving 75 mg or 150 mg doses or placebo.[20] The 300 mg dose has also been shown to be the only dose that effectively controls angioedema.[7] Some general recommendations can be developed to build an algorithm for the use of omalizumab in clinical practice, but an individualized

approach is also needed. It may be possible to decrease the dose of omalizumab once patients are controlled, to maintain remission. Cases have been shown to maintain complete symptom control for at least 18 months with omalizumab 150 mg after first achieving symptom control with omalizumab 300 mg (for 2 months).[21] Conversely, the dose could be increased in patients with inadequate response to the current dose. For example, a patient with high activity CSU (UAS7>38) who required fexofenadine 180 mg daily and ketotifen 2 mg twice-daily to maintain symptom control while receiving omalizumab 300 mg, was able to discontinue antihistamine therapy after increasing the omalizumab dose to 450 mg. No immediate or delayed side effects were detected during 21 months of treatment.[22]

The pivotal phase III studies of omalizumab in CSU were designed with dosing every 4 weeks, independent of serum immunoglobulin E level or body weight.[6-8] Different studies have tried dosing intervals other than 4 weeks.[21,23] Monitoring disease activity using the UAS7 each week and analyzing its behavior will help to further define dosing intervals. Some patients may tolerate longer dose intervals, but others may require reduced dose intervals if they begin to relapse before 4 weeks.[22] Dosing algorithms have been proposed for omalizumab based on disease activity;[14,24] and efficacy of omalizumab administered using a dosing frequency determined by patients' clinical response has been demonstrated;[13] the key message being that dose intervals could be individualized.

CSU is a chronic disease with an estimated duration of 1–5 years in the majority of cases, but which can persist for up to 50 years in very rare cases.[4] In some patients, multiple episodes, each lasting several years, can occur. CSU will resolve by itself after a period of time and it is important to reassess whether omalizumab treatment is still required.

There is limited evidence for the long-term use of omalizumab and it is not known for how long omalizumab may be administered continuously. Clinical trials currently only provide data for treatment of CSU with omalizumab for up to 6 months; further trials are ongoing to investigate longer treatment, of up to 1 year (XTEND-CIU; NCT02392624), and retreatment effectiveness (OPTIMA; NCT02161562). It is unknown whether longer treatment duration or retreatment will induce earlier

remission, or if early effective treatment will contribute to rapid, complete and permanent disease control.

In a recent retrospective study of eight patients who had achieved a complete response with omalizumab and remained on treatment for longer than a year, the authors concluded that periodic attempts should be made to wean patients off omalizumab because there could be a chance of spontaneous remission.[25] Weaning was not attempted in one patient, and two patients had successful tapering of omalizumab; however, one patient who discontinued omalizumab experienced a small flare after several months, which was well controlled with antihistamines only. In the remaining five patients, a recurrence of symptoms occurred during weaning (after 4–10 weeks) and omalizumab was restarted safely and effectively. In a second retrospective study of seven patients who had received omalizumab for more than 2 years, it was concluded that omalizumab did not appear to alter the natural history of the disease.[23] In three patients, attempts were made to suspend omalizumab treatment; however, all three patients experienced recurrence of symptoms after approximately 6 weeks. Reintroduction of omalizumab was highly efficacious. Further cases have shown effective, well tolerated, long-term treatment with omalizumab for up to 4 years.[22,26] The duration of continuous treatment required with the effective dose of omalizumab is variable in patients with CSU, with studies reporting 1–18 months[12] and 17–112 months.[25]

Analysis of response patterns using data from the three pivotal clinical trials for omalizumab shows that patients who have not responded after 12 weeks may still respond after 24 weeks.[20] In ‘slow responder’ CSU patients, giving fewer than three doses of omalizumab 300 mg may be a missed opportunity to control symptoms.[20] For ‘non-responders’, it is important to revisit their diagnosis at 3 months and determine whether CSU was an accurate diagnosis in the first place.

Omalizumab has an established safety profile, having been approved for the treatment of moderate to severe persistent allergic asthma in more than 90 countries, including the US since 2003 and the EU since 2005.[1,2] There are no long-term safety signals for omalizumab in this setting. As of 31 December 2014, 14,663 patients have received omalizumab through the clinical program, with a cumulative exposure

of 33,408 patient treatment years.[27] In CSU, clinical trials only provide data for 6 months; however, no new safety signals have been identified and on the whole, the short-term safety data are very good with few adverse events. Real-world experience also corroborates this: long-term (>1-year) use of omalizumab has been considered safe in two small retrospective studies and in individual case studies.[22,23,25] Phase III data show a slight increase in sinusitis (4.9% vs 2.1%), viral upper respiratory tract infection (0.5% vs 0%), arthralgia (2.9% vs 0.4%), headache (6.1% vs 2.9%), and cough (2.2% vs 1.2%) with omalizumab 300 mg compared to placebo.[10] Anaphylaxis has been estimated to occur in 0.1–0.2% of patients with allergic asthma;[28,29] however, no cases of anaphylaxis were reported in the phase III trials of omalizumab in CSU. In real-world experience, anaphylaxis has been reported in two patients; however, one patient had recurrent anaphylaxis prior to omalizumab, and in the second patient, symptoms were considered as not consistent with anaphylaxis.[5] A case-control study of patients receiving omalizumab for asthma showed that patients with a history of anaphylaxis to foods, medications, or other causes were at increased risk of anaphylaxis associated with omalizumab, compared to those with no prior history of anaphylaxis.[2]

Omalizumab is administered by subcutaneous injection and is supplied either as a pre-filled syringe or lyophilized formulation for reconstitution.[1,2] Due to previous experience of anaphylaxis in patients with allergic asthma, patients should be observed following administration (first 3 doses for 2 hours and 30 minutes for subsequent doses) and it is suggested that omalizumab should only be administered in a healthcare setting by healthcare providers prepared to manage anaphylaxis, which can be life-threatening.[1,2,30] A survey of clinicians attending the second Global Urticaria Forum confirmed that most clinicians administer omalizumab in a day case/inpatient or clinical setting rather than a home care setting.

Inclusion of a consensus algorithm on the use of omalizumab

The only existing global guideline recommends omalizumab as a third-line add-on treatment for CU;[3] however, local guidelines may vary, with omalizumab included as a fourth-line treatment in the US and Asia.[31,32] Some of these guidelines and consensus documents are a number of years old now and may require updating, and others still retain non-evidence-based, potentially useful treatments in their

algorithms. More recently, the Spanish and German consensus documents recommend omalizumab as the only third-line drug to treat CSU based on its efficacy and safety profile.[33,34]

With many healthcare professionals gaining experience in treating CSU patients, a practical algorithm on how to use omalizumab would be useful. Such a protocol would include consideration of factors like how to start omalizumab, how long to continue treatment, how to predict response to treatment, how best to monitor response (how should complete or partial response be defined?), when to stop treatment and whether patients can be retreated. Recommendations from existing algorithms and guidelines give advice on how disease activity and control, and impact on patients' quality of life should be monitored, using patient-reported outcome tools such as the UAS7, the UCT, and the Dermatology Life Quality Index (DLQI) or CU-Q_2oL, to determine change from baseline following treatment. A Danish algorithm has been published in 2014 for individualized treatment with omalizumab, dependent on UAS7 score.[24] A proposed algorithm was presented during the Global Urticaria Forum (**Table 2**; courtesy of Prof. Ana Giménez-Arnau) based on the results of 48 patients with CSU refractory to H_1-antihistamines and 36 refractory to ciclosporin (mean UAS7=29), who received treatment with omalizumab at an initial monthly dose of 300 mg.

Based on information ascertained from the pivotal trials of omalizumab, the recommended starting dose for omalizumab is 300 mg. Monitoring disease activity between doses requires evaluation of response (e.g. using the UAS7) week by week. During monitoring, the influence of any exacerbating factor that could modify the response should be considered, e.g. use of non-steroidal anti-inflammatory drugs.

If a complete and stable response is obtained after three doses of omalizumab, decisions regarding subsequent omalizumab treatment can be made, i.e. whether or not to stop treatment, reduce the dose, continue at a dose of 300 mg, or modify the dosing interval. We know from ASTERIA II[7] that 42.7% and 22% of patients treated with omalizumab 150 mg still achieved UAS7 ≤ 6 or UAS7 of 0, respectively. Although it is generally recommended to continue treatment after three doses with omalizumab 300 mg,[20] it may be possible after a further 3 months to attempt dose

reduction or to extend the dosing intervals (**Table 2**; courtesy of Prof. Ana Giménez-Arnau).

In patients with limited improvement after three doses (UAS7 score ranging from UAS7>6 to UAS7=28, some angioedema and a poor UCT score), should omalizumab be stopped or continued at 300 mg? It is generally recommended to continue treatment in partially responding patients after 3 doses with omalizumab 300 mg for at least a further three months. According to data obtained from the ASTERIA I and GLACIAL trials, some patients may be slower to respond but nevertheless will respond eventually.[20]

In patients with no response to omalizumab at any time during dosing intervals after 3 doses, or with partial response after 6 months of treatment at the maximum licensed dose of 300 mg, should omalizumab be stopped, continued at 300 mg or updosed to 450 mg (for 3 months) and then to 600 mg, or should the treatment intervals be shortened? According to guidance from NICE, if there is no response at 300 mg after 4 doses, the drug should be stopped and the patient re-evaluated.[35] Some experts have recommended increasing the dose of omalizumab to 600 mg (**Table 2**; courtesy of Prof. Ana Giménez-Arnau). Professor Giménez-Arnau noted that in her real-life clinic experience, just 16% and 4% of patients, respectively, required 450 mg or 600 mg to achieve complete disease control (personal correspondence, Giménez-Arnau. 2015). Further studies are required to determine whether the dose of omalizumab should be increased beyond 600 mg.

There are, therefore, still many questions to be answered before a consensus algorithm can be determined for omalizumab; however, these are useful insights as to how omalizumab is currently used in clinical practice.

Potential biomarkers for CSU treatment effectiveness

The ability to predict changes in disease activity in response to therapy would be very useful in the development of any proposed treatment algorithms for use in clinical practice. For example, if there were biomarkers that could predict the extent and course of changes in urticaria disease activity in response to treatment, this would represent a major advancement in providing a predictor that could ‘notify’ patients of what to expect. This applies to all treatments used for CSU (H_1-antihistamines,

ciclosporin, leukotriene receptor antagonists and omalizumab). Currently, there are insufficient data on which (and how) biomarkers may predict the outcome of any of these treatments. Nevertheless, different research teams are actively investigating this possibility. In patients treated with ciclosporin, a positive serum basophil histamine release assay (BHRA) indicated that they were more likely to respond to ciclosporin treatment compared with those who were BHRA negative.[36] More recently, lack of basophil CD203c-upregulating activity in the serum of patients with CU has been found to correlate with clinical response to omalizumab in a retrospective study of 41 patients with antihistamine-refractory chronic urticaria.[37] CD203c-upregulating activity was present in 18 of the 41 patients, and of these 18 patients, only 9 (50%) had clinical improvement with omalizumab. In contrast, of 23 patients without CD203c-upregulating activity, 20 (87%) had a clinical response to omalizumab (p=0.02; **Fig. 3**). If this is confirmed in future prospective studies, it may be a clinically useful biomarker of response to treatment. Overall, while there is currently no established biomarker for predicting CSU disease activity or response to treatment, many studies have found some correlation between potential biomarkers and disease outcomes.

Summary

Omalizumab has demonstrated excellent efficacy in phase III randomized controlled trials and in the real-life clinical setting for the treatment of CSU patients with inadequate response to H_1-antihistamines, and is well tolerated with an established safety profile. Some key questions remain regarding the optimal management of CSU with omalizumab in real-life clinical practice and further investigation of the real-world evidence is required before enough data are available to reach a consensus.

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Table 1 Response to omalizumab in real life versus randomized controlled trials in patients with CSU

Randomized controlled trials	**Dose**	**Responders**	**Response definition**	**Duration of treatment**
X-CUISITE[38]	75–375 mg	70%	UAS7W=0	24w
MYSTIQUE[39]	300 mg	40%	UAS7 -90%	4w
	300 mg	36%	UAS7=0	4w
ASTERIA I + II[7,8,10]	300 mg	59%	UAS7≤6	12w
	150 mg	41%	UAS7≤6	12w
GLACIAL[6]	300 mg	52%	UAS7≤6	12w
X-ACT[11]	300 mg	50%	UAS7=0	28w
Real-world Evidence	**Dose**	**Responders**	**Response definition**	**Duration of treatment**
Metz, 2014[14]	150–300 mg	83%	UAS7 -90% + no antihistamines	NS
Rottem, 2014[15]	300 mg	77%	Clinical judgement	NS
	150 mg	36%	Clinical judgement	NS
Sussman, 2014[13]	150 mg	69%	UAS7=0	Various
Labrador-Horillo, 2013[12]	150–300 mg	82%	Clinical judgement	NS

NS, not specified; UAS7, 7-day Urticaria Activity Score;

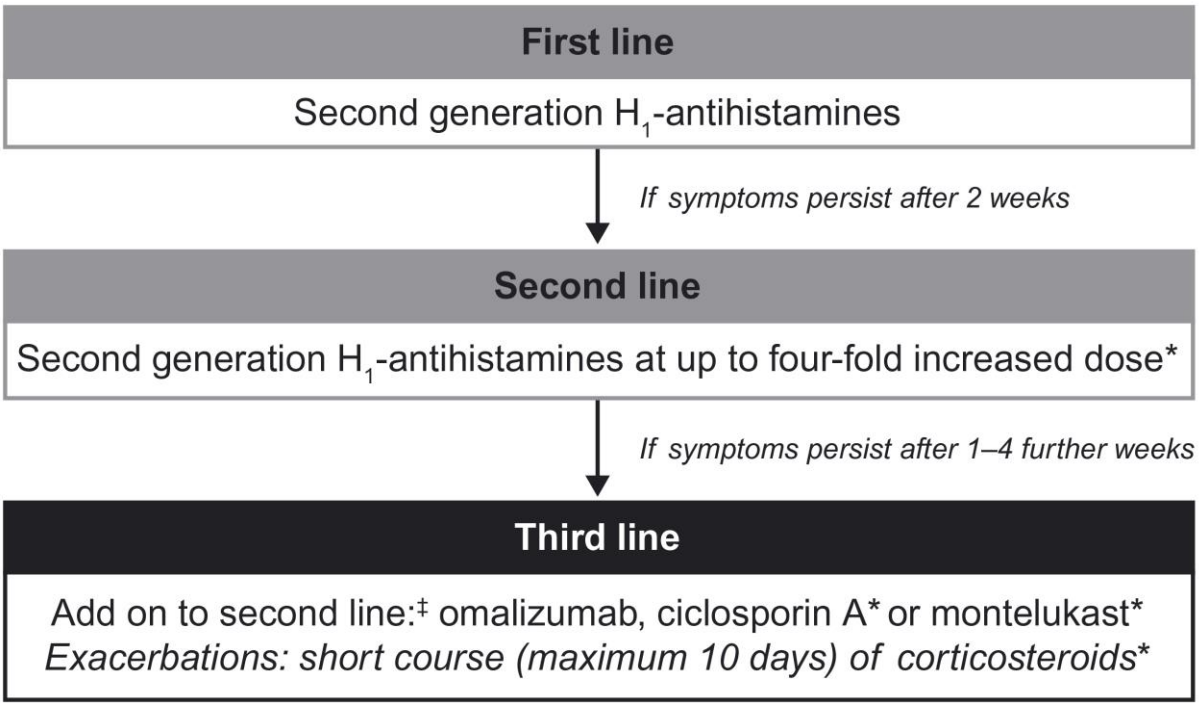
UAS7W, 7-day Urticaria Activity Score: Wheal component; w, weeks.

Table 2 Protocol for the use of omalizumab in CSU in real-life clinical practice *(as presented by Prof. Ana Giménez-Arnau).*

Key questions	**Current answers**
What is the recommended starting dose?	300 mg monthly
How can we monitor clinical efficacy?	With valid "Patient Reported Outcome" tools as UAS7 and UCT
How long should treatment be maintained?	Until the disease is gone. Until there is complete control of symptoms and stable disease without treatment.
Continuous treatment or intermittent treatment?	Continuous treatment is recommended
How safe is it in long-term treatment?	Omalizumab has an established safety profile from its use in allergic asthma; there are no long-term safety signals in this setting. In the pivotal phase III trials in CSU, no new safety signals were identified.
Can we predict who will be a fast responder?	Not yet
When can we stop treatment?	We can always stop the treatment if necessary
How should we stop treatment?	Elongate treatment intervals
Can we retreat the patient following treatment discontinuation?	Yes we can retreat the patient
When should we decide that the patient is a non-responder?	If there is no response with omalizumab 300 mg after 6 months, we can decide to increase the dose to 450 or 600 mg, as this is useful in some cases. Patients who have no response with omalizumab 600 mg after three months could be considered non-responders.
Will it be useful for inducible urticaria (CIndU)?	Although at present omalizumab is unlicensed for the treatment of CIndU, in some cases it is useful
How effective is it for controlling angioedema?	It is effective

CIndU, chronic inducible urticaria; UCT, Urticaria Control Test; UAS7, 7-day Urticaria Activity Score

Figure 1 EAACI/GA^{2}LEN/EDF/WAO guideline-recommended treatment algorithm for urticaria.[3]



**Not licensed for the treatment of urticaria.*

†The order of third-line treatments does not reflect preference.

EAACI, European Academy of Allergy and Clinical Immunology; EDF, European Dermatology Forum; GA^{2}LEN, Global Allergy and Asthma European Network; WAO, World Allergy Organization.

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Figure 2 Retrospective analysis of omalizumab treatment in CSU patients[14]

CSU, chronic spontaneous urticaria.

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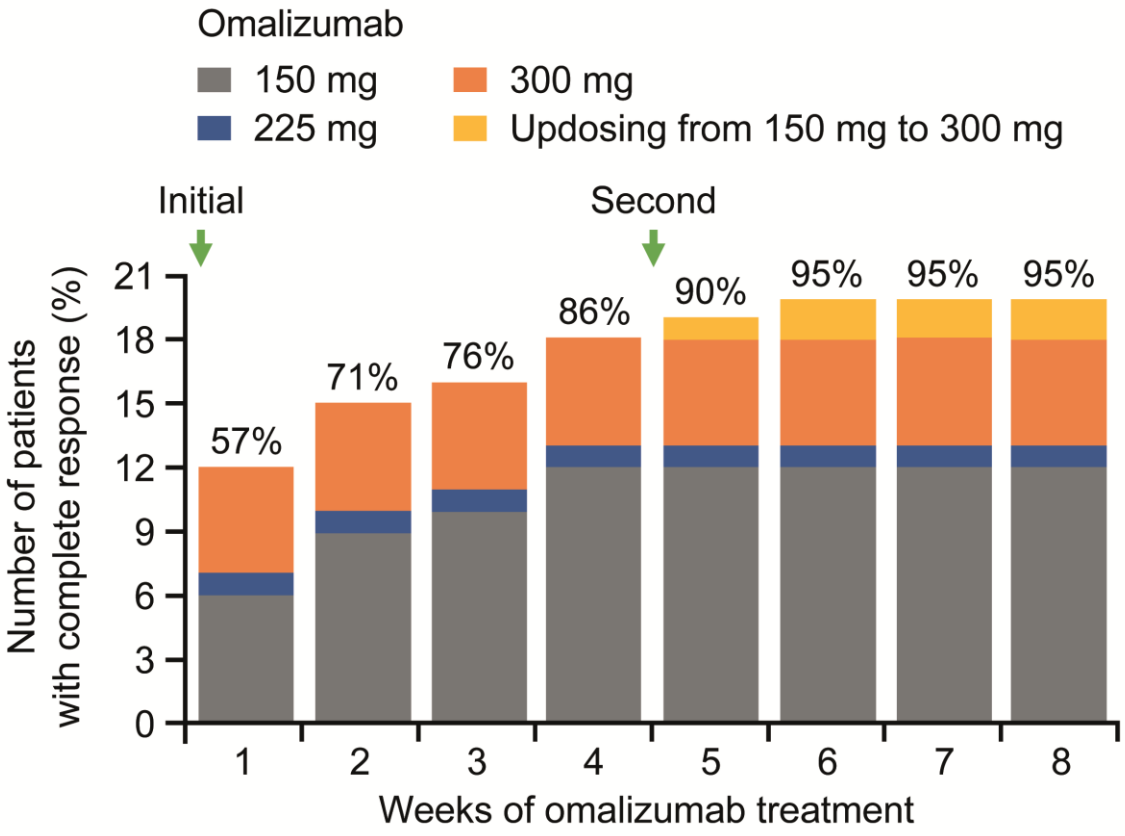
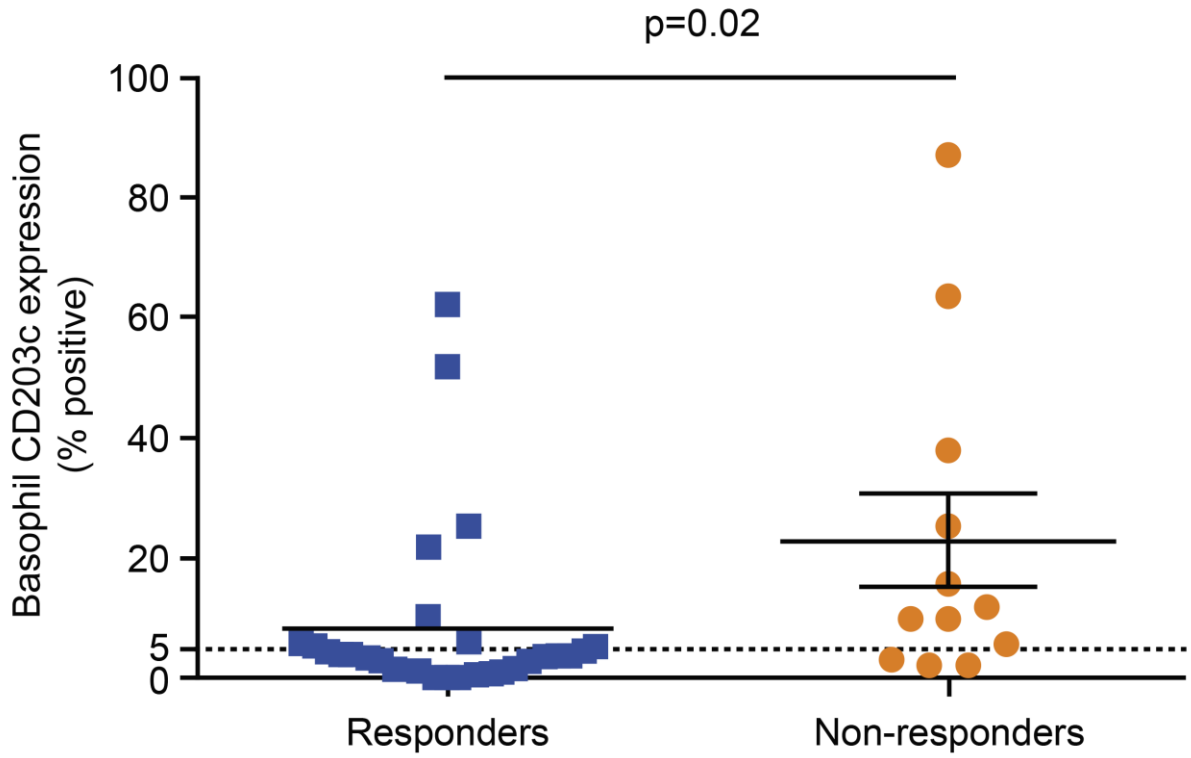


Figure 3 Correlation of basophil CD203c expression in the serum of chronic urticaria patients with clinical response to omalizumab[37]



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