Predictors of response to omalizumab and relapse in chronic spontaneous urticaria: a study of 470 patients

Predictors of response to omalizumab and relapse in chronic spontaneous urticaria: an Italian experience in 470 patients

A. V. Marzano[1], G. Genovese[1], G. Casazza[2], M. T. Fierro[3], P. Dapavo[3], N. Crimi[4], S. Ferrucci[1], P. Pepe[5], S. Liberati[5], P. D. Pigatto[6], A. Offidani[7], E. Martina[7], G. Girolomoni[8], M. Rovaris[8], C. Foti[9], L. Stingeni[10], A. Cristaudo[11], G. W. Canonica[12], E. Nettis[13], R. Asero[14]

1. UOC Dermatologia, IRCCS Fondazione Ca' Granda Ospedale Maggiore Policlinico, Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di Milano, Milan, Italy.
2. Dipartimento di Scienze Biomediche e Cliniche "L. Sacco", Università degli Studi di Milano, Milan, Italy.
3. Department of Medical Sciences, Section of Dermatology, University of Turin, Turin, Italy.
4. Department of Clinical and Experimental Medicine-Respiratory Medicine & Allergy, University of Catania, Catania, Italy.
5. Dermatology Unit, Surgical, Medical and Dental Department of Morphological Sciences Related to Transplant, Oncology and Regenerative Medicine, University of Modena and Reggio Emilia, Modena, Italy.
6. Clinical Dermatology, Department of Biomedical, Surgical and Dental Sciences, IRCCS Galeazzi Orthopaedic Institute, University of Milan, Milan, Italy.
7. Dermatology Unit, Department of Clinical and Molecular Sciences, Polytechnic Marche University, Ancona, Italy.
8. Department of Medicine, Section of Dermatology, University of Verona, Verona, Italy.
9. Department of Biomedical Science and Human Oncology, Section of Dermatology, University of Bari, Bari, Italy.
10. Section of Clinical, Allergological and Venereological Dermatology, Department of Medicine, University of Perugia, Perugia, Italy.
11. Service of Occupational and Environmental Allergic Dermatology, San Gallicano Dermatology Institute for Research and Care, Rome, Italy.
12. Department of Internal Medicine, Respiratory Disease Clinic, IRCCS Humanitas Clinical and Research Center, Humanitas University, Milan, Italy
13. Department of Emergency and Organ Transplantation, School of Allergology and Clinical Immunology, University of Bari Aldo Moro, Bari, Italy.
14. Ambulatorio di Allergologia, Clinica San Carlo, Paderno Dugnano, Milan, Italy.

Running head: predictors of response to omalizumab and relapse in CSU

Keywords: chronic spontaneous urticaria; omalizumab; IgE; D-dimer; UAS7

Corresponding author: Angelo Valerio Marzano, MD

Unità Operativa di Dermatologia, IRCCS Fondazione Cà Granda Ospedale Maggiore Policlinico, Via Pace, 9, 20122 - Milano

E-mail: angelo.marzano@unimi.it

Phone number: +390255036289

Fax number: +390255035236

Word count: 2481 words

Figures: 1

Tables: 5

Funding/support: none

Conflict of interest: all authors declare no conflicts of interest

ABSTRACT

Background Chronic spontaneous urticaria (CSU) is defined as spontaneous occurrence of wheals and/or angioedema for ≥ 6 weeks. Omalizumab is a monoclonal anti-IgE antibody effective in refractory CSU but its mechanism of action and markers predictive of response remain not completely defined.

Objectives To correlate baseline levels of two proposed biomarkers, total IgE (bIgE) and D-dimer (bD-dimer), and clinical parameters to omalizumab response and to relapses after drug withdrawal.

Methods In this retrospective Italian multicenter study, clinical data were collected in 470 CSU patients, and bIgE and bD-dimer were measured in 340 and 342 patients, respectively. Disease activity was determined by Urticaria Activity Score 7 (UAS7) at week 1 and 12 after omalizumab starting. Relapses were evaluated during a 2-month and 3-month interval after a first and a second course of treatment, respectively.

Results bIgE correlated to a good response to omalizumab since levels were significantly higher in responders than non-responders ($P = 0.0002$). Conversely, bD-dimer did not correlate to response. There was no correlation between both bIgE and D-dimer and either first or second relapse. Disease duration was significantly longer in patients who experienced either first or second relapse ($P < 0.0001$ and $P = 0.0105$, respectively), whilst baseline UAS7 correlated only to first relapse ($P = 0.0023$).

Conclusions Our study confirms bIgE as a reliable biomarker predicting response to omalizumab in CSU, while it does not support the usefulness of bD-dimer unlike previous findings. CSU duration before omalizumab and baseline UAS7 may be clinical markers of relapse risk.

INTRODUCTION

Chronic spontaneous urticaria (CSU) is defined as the spontaneous occurrence of wheals and/or angioedema for six or more weeks.[1] All over the world, more than 50 million people are affected by CSU, a disease which exerts negative effects on different aspects of the quality of life, such as sleep, school and work performance, daily life activities and social relationships.[2,3] Physiopathology of CSU has not been completely elucidated, but the role of histamine as well as several other proinflammatory cytokines released by skin mast cells and basophils in wheal formation is undisputed. However, different biologic systems, i.e. autoimmunity, coagulation and autoallergy, may contribute in determining CSU symptoms.[4] The autoimmune pathomechanism is based on the presence of circulating histamine-releasing immunoglobulin (Ig) G autoantibodies directed against either the high-affinity IgE receptor (FcεRI) on mast cells and basophils or membrane-bound IgE.[5-8] The coagulation cascade is activated in CSU and involves mainly the so-called extrinsic pathway, which is mediated by the overexpression of tissue factor on activated eosinophils, as seen in the lesional skin of CSU patients.[9] Moreover, thrombin, which is the final enzyme of coagulation cascade, increases vascular permeability and induces mast cell degranulation in experimental models.[10,11] Thus, the activation of coagulation concurs to CSU pathogenesis and correlates to disease severity, as demonstrated by the elevated levels of D-dimer, a biomarker of coagulation activation and fibrinolysis, in the plasma of CSU patients.[12-14] Another mechanism recently identified and classified as "auto-allergic", is mediated by IgE specific for different auto-allergens like thyroperoxidase (TPO),[15] double stranded DNA[16] and interleukin (IL)-24.[17]

Omalizumab is a recombinant DNA-derived humanized monoclonal anti-IgE antibody widely proved to be effective and safe for the treatment of CSU.[18] Albeit its exact mechanism of action is not completely understood, the omalizumab-induced reduction of free IgE levels seems to diminish mast cell and basophil activity, also down-regulating FcεRI in the skin.[19]

Recently, a subdivision of omalizumab responders in early responders and late responders was highlighted,[20] suggesting that this drug may act through distinct mechanisms of action depending on

the rate of response.[20-23] Therefore, the delineation of different categories of responders to omalizumab as well as the investigation of both biological and clinical markers predictive of response to omalizumab could ameliorate the management of CSU patients.

Deza et al.[24] found FcεRI expression levels on basophils before omalizumab treatment to be significantly lower in non-responders than in responders. They also showed that, after starting omalizumab, a significant drop by almost 90% in the basophil FcεRI expression occurred 1 month after the first dose with the reduction being lower in non-responders than in responders. (Deza-Pujol) Moreover, a study of the same authors suggested a possible link between baseline levels of basophil FcεRI expression and time to response to omalizumab in CSU, with higher levels shown in early responders.[25] (Deza-Sanchez)

Ertas *et al*.[27] showed that total IgE levels and their change predict the response to treatment with omalizumab in CSU. Asero *et al*.[28] found that elevated baseline D-dimer plasma levels are associated with a prompt response to omalizumab in patients with severe CSU. The same authors demonstrated that not only IgE but also D-dimer baseline levels are higher in responders than non-responders to omalizumab in CSU.[29] Moreover, increased total IgE seem to be linked to a faster relapse in patients with omalizumab-discontinued CSU.[30]

Here, we retrospectively evaluated baseline levels of both total IgE (bIgE) and D-dimer (bD-dimer) in a large cohort of Italian CSU patients treated with omalizumab, with the primary endpoint of correlating these two biomarkers to the clinical response, stratifying the patients in "early responders", "late responders" and "non-responders", as well as to relapses after drug withdrawal. As secondary endpoints, we investigated for the possible correlation between clinical response/relapses and several parameters, such as age at diagnosis, sex, disease duration, baseline Urticaria Activity Score over 7 days (UAS7) and thyroid autoimmunity.

METHODS

Patients

In this retrospective multicenter study involving 12 different Italian Dermatology and Allergology Units, we evaluated clinical (sex, age at diagnosis, disease duration, disease activity at baseline assessed by means of UAS7) and laboratory (thyroid autoimmunity, notably presence of autoantibodies directed against thyroglobulin or TPO) findings of 470 patients with severe CSU.

To be part of this observational study, each center was asked to provide data for patients with refractory CSU, defined as having a history of spontaneous urticaria for more than 6 weeks. We included only CSU patients resistant to standard first line treatments, i.e. all patients were refractory to standard dosed and up to four-fold dosed second generation anti-histamine (sgAH) treatment, and all had a baseline UAS7 > 16. Some patients had treatments other than antihistamines before inclusion in this study.

Patients were treated with omalizumab 300 mg every 4 weeks for 24 weeks, and they were instructed to continue their daily treatment with an up to four-fold dosed sgAH for the first four weeks. According to the Italian Drug Agency (AIFA) recommendations,[23] omalizumab was discontinued after 24 weeks (first course) and re-administered in case of relapse of symptoms (UAS7 >16) for other 20 weeks (second course). Patients were assessed for their clinical response at the end of the first week and at week 12 after the start of omalizumab treatment.

All patients agreed with the treatment regimen and signed a written consent form. Control subjects provided written consent to the use of their blood samples in an anonymous form for research purposes. In view of the retrospective nature of the study, only a notification to the Ethical Committee of the principal investigator Center (IRCCS Fondazione Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy) was requested.

Clinical response and relapses

Disease activity was determined by the use of UAS7, which is the weekly sum score of the daily sub score values for number of wheals (no wheals=0 points; 1-20 wheals=1 point; 21 - 50 wheals=2

points; >50 wheals=3 points) and intensity of itch (no itch=0 points; mild itch=1 point; moderate itch=2 points; severe itch=3 points).[31]

An early complete (EC) response was defined as the disappearance of the CSU symptoms (UAS7 of 0) within 1 week from the start of omalizumab treatment. A late complete (LC) response was defined as the disappearance of the CSU symptoms (UAS7 of 0) within 12 weeks from the start of omalizumab treatment. A late partial (LP) response was defined as an at least 30% reduction of UAS7 as compared to baseline evaluated at week 12 while no response (N) was defined as a less than 30% reduction of UAS7 or an exacerbation at week 12.

Two relapses were evaluated: the first one, defined as first relapse, during the 2 months following omalizumab withdrawal after the first course of treatment and the second one, defined as second relapse, during a period of 3 months following omalizumab withdrawal after the second course of treatment (see above). The relapse was considered to be the reappearance of CSU symptoms in complete responders and the increase in UAS7 as compared to the value at the end of omalizumab treatment in partial responders.

Laboratory data

Serum bIgE were measured by chemiluminescent immunoassay (ImmunoCAP; ThermoFisher Scientific, Uppsala, Sweden) and levels of 100 kUA/L or greater were defined as increased based on the reference range of the laboratory of the principal investigator Center.

Sodium citrate-anticoagulated plasma bD-dimer were measured by immunoenzymatic methods (Zymutest D-Dimer; Hyphen BioMed, Neuville-sur-Oise, France) in accordance with the manufacturer's instructions. The intra- and inter-assay coefficients of variation were 10 and 15%, respectively. Levels below 500 ng/mL were regarded as normal.

Statistical analysis

Continuous variables are reported as mean (standard deviation, SD) or median (interquartile range, IQR), as appropriate. Categorical data are reported as counts (percentages). Considering clinical

response and relapses, the Student's two-sample t test or the Mann-Whitney non-parametric test were used for the comparisons of continuous variables between groups, as appropriate. Fisher exact test was used for group comparison of categorical variables. Kolmogorov-Smirnov test was used to assess if bIgE and bD-dimer data were normally distributed Since bIgE and bD-dimer data were skewed, they were log-transformed before performing the analyses. The results are reported as antilog values of means (geometric means) and standard deviations. For comparisons of continuous variables (log-transformed bIgE) among the four categories of clinical responders (EC, LC, LP and N) a general linear model analysis was performed. Finally, considering only the first relapse, a logistic regression analysis was performed in order to provide a joint assessment of the two variables that showed an association with the first relapse. P values for pairwise comparisons between the four responder categories were adjusted using Sidak's adjustment method. P values lower than 0.05, two sided, were considered statistically significant. All the statistical analyses were performed with the statistical software SAS (release 9.4, SAS Institute, Inc., Cary, North Carolina).

RESULTS

Clinical features

Demographic and clinical features of the patients are summarized in Table 1.

The patients were predominantly females (n=310; 66%). The median age at the time of diagnosis was 49 years (IQR 37-61 years). The median CSU duration, assessed as the time from CSU diagnosis to omalizumab initiation in months, was of 20 months (IQR 9-48 months). Positivity for anti-thyroglobulin or anti-TPO autoantibodies was observed in 121 out of 438 patients (27.6%); in 32 patients, laboratory data were not available. A positive clinical response was recorded in 425 patients (90.4%), whereas non-responders were 45 (9.6%). Stratifying patients based on grade and rapidity of response, it was observed that EC response was achieved by 211 patients (44.9%), LC response by 119 patients (25.3%) and LP response by 95 patients (20.2%). First relapse was observed in 236 out of 392 patients (non-responders, cases lost to follow up and patients under treatment when data had

been collected were excluded), with a relapse rate of 60.2%. Second relapse was observed in 116 out of 175 patients, with a relapse rate of 66.3%. Complete responders who had not experienced the first relapse were not further followed up for a possible relapse.

As shown in Table 2, sex, age at the diagnosis, disease duration and thyroid autoimmunity did not significantly differ between responders and non-responders. Similarly, the risk for developing the first and second relapse was not associated with thyroid autoimmunity, sex and age (Table 3). Interestingly, disease duration was significantly longer in patients who experienced either first (median duration 24 versus 13 months, $P < 0.0001$) or second relapse (median duration 25 versus 18 months, $P = 0.0105$) after omalizumab withdrawal. Furthermore, baseline UAS7 significantly correlated with the risk for developing the first ($P = 0.0023$) but not the second relapse.

Table 4 shows the results of the logistic analyses performed for the assessment of the joint association of disease duration and UAS7 with the first relapse.

Laboratory data

bIgE were determined in 340 patients and bD-dimer in 342 patients of our cohort; both were measured in 272 cases. Interestingly, bIgE were associated with the clinical response to omalizumab as levels were significantly higher in responders (mean value: 132 kUA/L) than in non-responders (mean value: 42 kUA/L) ($P = < 0.0001$). Among responders, there was no significant difference in terms of clinical response among the three categories, namely EC, LC and LP; indeed, as shown in Figure 1 and Table 5, all three categories of responders showed a statistical significance when compared with non-responders ($P = 0.0002$ for EC; $P = 0.0182$ for LC; $P = 0.0005$ for LP). On the other hand, there was no association between bIgE and either first or second relapse (Table 3).

Of note, bD-dimer was not associated with the clinical response to omalizumab since bD-dimer mean values were similar in responders and non-responders (Table 2). As in the case of bIgE, there was no association between bD-dimer and either first or second relapse (Table 3).

DISCUSSION

This retrospective multicenter study on a cohort of 470 patients with CSU reflects the Italian real-life experience in the management of the disease with omalizumab and confirms the efficacy of this agent for sgAH–refractory CSU. In fact, in line with most studies present in the literature,[32-35] complete responders to omalizumab were approximately 70% of the patients, with around 65% who responded early, namely within the first week after omalizumab starting, and around 35% who responded more lately, namely at the clinical evaluation at week 12 after omalizumab administration.

Although late responders to omalizumab are regarded as patients who respond after 12 weeks of treatment,[21] we made our clinical evaluation at week 12 since AIFA recommendations for CSU establish that omalizumab has to be discontinued at week 12 in case of non-response, which may lead to possibly missing some patients responding more lately.

Moreover, we evaluated relapses during the 2 months following omalizumab discontinuation after the first course of treatment (defined as first relapse) and during a period of 3 months following omalizumab discontinuation after the second course of treatment (defined as second relapse). In fact, according to the AIFA recommendations for CSU,[23] omalizumab was withdrawn after 24 weeks and re-administered in case of relapse of symptoms for other 20 weeks. Of note, the first relapse occurred in approximately 60% of responders. The second relapse was recorded in approximately 66% of those who responded to the second course of treatment.

The most noteworthy finding of our study is that patients with higher bIgE responded well to the treatment, confirming the findings of previous studies[27,29,36,37] and validating in a larger series of CSU patients bIgE as a reliable biomarker predictive of clinical response to omalizumab. A very recent multicenter retrospective study confirmed that elevated total IgE levels are associated with complete response to omalizumab.[38] These authors found also that normal and particularly low normal total IgE levels were prevalent in non-responders and only rarely detectable in complete responders, possibly representing a marker of lack of response to the drug. On the other hand, they failed to identify a cutoff for total IgE levels for non-responders, thus concluding that total IgE levels cannot be regarded as a stand-alone predictor of response to omalizumab.[38]

bIgE were also reported to correlate to the rapidity of relapse upon omalizumab discontinuation,[30] proposing bIgE as a biomarker potentially helping also to predict fast CSU relapse and to identify patients in whom the treatment has not to be stopped, but we were unable to confirm this finding in the present study, although, notably, we found that disease duration was significantly linked to odds of both first and second relapse. Moreover, baseline UAS7 significantly correlated to the first but not to the second relapse. The latter finding is at least partially in line with the recent study of Ferrer *et al.*,[39] who showed that high baseline UAS7 and slow decrease of CSU symptoms after omalizumab starting indicate a higher probability of rapid relapse upon drug withdrawal.

In our study, we evaluated bD-dimer with the aim of confirming a possible role of this biomarker in predicting clinical response to omalizumab and tendency to develop disease flare-ups. Our group recently suggested possible effects of omalizumab on the coagulation cascade and fibrin degradation leading to a marked reduction in D-dimer plasma levels in CSU patients treated with this agent.[28,29,40] In keeping with our previous findings, elevated bD-dimer levels were observed in CSU patients responders to omalizumab in a recent French study,[41] which showed also a fast normalisation of this biomarker during omalizumab treatment. However, the latter study did not support the usefulness of D-dimer to monitor long-term disease prognosis in adult CSU, indicating the need of further studies on larger series of patients to clearly establish the link between D-dimer and clinical response to omalizumab.

In this large cohort of Italian patients, we failed to confirm the results of our previous study which had revealed that not only bIgE but also bD-dimer were higher in responders than non-responders to omalizumab in CSU.[29] In fact, bD-dimer did not correlate neither to the clinical response to omalizumab, since they were similar in responders and non-responders, nor to probability to develop relapses. We previously reported that D-dimer baseline levels were higher in responders than nonresponders to omalizumab and suggested that this marker of coagulation activation/fibrinolysis was potentially involved in the mechanism of action of omalizumab in CSU, and might be predictor of the therapeutic effectiveness of this drug.[29,40] The present study on a larger series of patients with

CSU failed to confirm the predictive value of this biomarker, making reasonable to consider D-dimer levels as associated with CSU severity, as previously reported by some of ourselves [9,13,14] (but only in a, albeit big, subset of CSU patients), rather than being a marker of clinical response to omalizumab In conclusion, our study confirms the link between bIgE levelsand response to omalizumab treatment in CSU patients, point-ing out bIgE as a predictor of response to omalizumab, while itdoes not support the usefulness of bD-dimer. Interestingly, thestudy shows also that the duration of the disease before omal-izumab starting and high baseline UAS7 values may be clinicalmarkers of relapse risk. In conclusion, our study confirms the link between bIgE levels and response to omalizumab treatment in CSU patients, pointing out bIgE as a predictor of response to omalizumab, while it does not support the usefulness of bD-dimer. Interestingly, the study shows also that the duration of the disease before omalizumab starting and high baseline UAS7 values may be clinical markers of relapse risk

REFERENCES

1. Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B, Bernstein JA, Bindslev-Jensen C, Brzoza Z, Buense Bedrikow R, Canonica GW, Church MK, Craig T, Danilycheva IV, Dressler C, Ensina LF, Giménez-Arnau A, Godse K, Gonçalo M, Grattan C, Hebert J, Hide M, Kaplan A, Kapp A, Katelaris CH, Kocatürk E, Kulthanan K, Larenas-Linnemann D, Leslie TA, Magerl M, Mathelier-Fusade P, Meshkova RY, Metz M, Nast A, Nettis E, Oude-Elberink H, Rosumeck S, Saini SS, Sánchez-Borges M, Schmid-Grendelmeier P, Staubach P, Sussman G, Toubi E, Vena GA, Vestergaard C, Wedi B, Werner RN, Zhao Z, Maurer M. The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy 2018; **73**:1393-1414.
2. Weller K, Maurer M, Grattan C, et al. ASSURE-CSU: a real-world study of burden of disease in patients with symptomatic chronic spontaneous urticaria. Clin Transl Allergy 2015; **5**:29.
3. Maurer M, Staubach P, Raap U, Richter-Huhn G, Baier-Ebert M, Chapman-Rothe N.

ATTENTUS, a German survey of chronic urticaria patients highlighting the burden of disease, unmet needs and real-life clinical practice. Br J Dermatol 2016; **174**:892-894.

4. Asero R, Tedeschi A, Marzano AV, Cugno M. Chronic spontaneous urticaria: immune system, blood coagulation, and more. Expert Rev Clin Immunol 2016; **12**:229-31.
5. Grattan CE, Francis DM, Hide M, Greaves MW. Detection of circulating histamine releasing autoantibodies with functional properties of anti-IgE in chronic urticaria. Clin Exp Allergy 1991; **21**:695–704.
6. Hide M, Francis DM, Grattan CE, Hakimi J, Kochan JP, Greaves MW. Autoantibodies against the high-affinity IgE receptor as a cause of histamine release in chronic urticaria. N Engl J Med 1993; **328**:1599–604.
7. Fiebiger E, Maurer D, Holub H, et al. Serum IgG autoantibodies directed against the alpha chain of Fc epsilon RI: a selective marker and pathogenetic factor for a distinct subset of chronic urticaria patients? J Clin Invest 1995; **96**:2606–12.
8. Ferrer M, Kinét JP, Kaplan AP. Comparative studies of functional and binding assays for IgG anti-Fc(epsilon)RIalpha (alpha-subunit) in chronic urticaria. J Allergy Clin Immunol 1998; **101**: 672–6.
9. Cugno M, Marzano AV, Tedeschi A, Fanoni D, Venegoni L, Asero R. Expression of tissue factor by eosinophils in patients with chronic urticaria. Int Arch Allergy Immunol 2009; **148**:170-4.
10. Schaeffer RC, Gong F, Bitrick MS, Smith TL. Thrombin and bradykinin initiate discrete endothelial solute permeability mechanisms. Am J Physiol 1993; **264**: 1798-809.
11. Razin E, Marx G. Thrombin-induced degranulation of cultured bone marrow-derived mast cells. J Immunol 1984; **133**: 3282-5.
12. Asero R, Tedeschi A, Riboldi P, Cugno M. Plasma of patients with chronic urticaria shows signs of thrombin generation, and its intradermal injection causes wheal-and-flare reactions much more frequently than autologous serum. J Allergy Clin Immunol 2006; **117**:1113-7.

13. Asero R, Tedeschi A, Coppola R, et al. Activation of the tissue factor pathway of blood coagulation in patients with chronic urticaria. J Allergy Clin Immunol 2007; **119**:705-10.

14. Asero R, Tedeschi A, Riboldi P, Griffini S, Bonanni E, Cugno M. Severe chronic urticaria is associated with elevated plasma levels of D-dimer. Allergy 2008; **63**:176-80.

15. Altrichter S, Peter HJ, Pisarevskaja D, Metz M, Martus P, Maurer M. IgE mediated autoallergy against thyroid peroxidase--a novel pathomechanism of chronic spontaneous urticaria? PLoS One 2011; **6**:e14794.

16. Hatada Y, Kashiwakura J, Hayama K, et al. Significantly high levels of anti-dsDNA immunoglobulin E in sera and the ability of dsDNA to induce the degranulation of basophils from chronic urticaria patients. Int Arch Allergy Immunol 2013; **161**:154-8.

17. Schmetzer O, Lakin E, Topal FA, et al. IL-24 is a common and specific autoantigen of IgE in patients with chronic spontaneous urticaria. J Allergy Clin Immunol 2017 Dec 5 [Epub ahead of print]

18. 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**:1742-1750.

19. Metz M, Staubach P, Bauer A, et al. Clinical efficacy of omalizumab in chronic spontaneous urticaria is associated with a reduction of FceRI-positive cells in the skin. Theranostics 2017; **7**:1266-1276.

20. Gericke J, Metz M, Ohanyan T, Weller K, Altrichter S, Stahl Skov P, Falkencrone S, Brand J, Kromminga A, Hawro T, Church MK, Maurer M. Serum autoreactivity predicts time to response to omalizumab therapy in chronic spontaneous urticaria. J Allergy Clin Immunol 2017; **139**: 1059-1061

21. 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**:474–481.

22. Kaplan AP, Gimenez-Arnau AM, Saini SS. Mechanisms of action that contribute to efficacy of

omalizumab in chronic spontaneous urticaria. Allergy 2017; **72**:519–533.

23. Asero R, Canonica GW, Cristaudo A, et al. Critical appraisal of the unmet needs in the treatment of chronic spontaneous urticaria with omalizumab: an Italian perspective. Curr Opin Allergy Clin Immunol 2017; **17**:453-459.

24. Deza G, Bertolín-Colilla M, Pujol RM, Curto-Barredo L, Soto D, García M, Hernández P, Gimeno R, Giménez-Arnau AM. Basophil FcεRI Expression in Chronic Spontaneous Urticaria: A Potential Immunological Predictor of Response to Omalizumab Therapy. Acta Derm Venereol. 2017; 97:698-704.

25. Deza G, Bertolín-Colilla M, Sánchez S, Soto D, Pujol RM, Gimeno R, Giménez-Arnau AM.Basophil FcεRI expression is linked to time to omalizumab response in chronic spontaneous urticaria. J Allergy Clin Immunol 2018; **141**:2313-2316.

26. Palacios T, Stillman L, Borish L, Lawrence M. Lack of basophil CD203c-upregulating activity as an immunological marker to predict response to treatment with omalizumab in patients with symptomatic chronic urticaria. J Allergy Clin Immunol Pract. 2016; 4:529-30. doi: 10.1016/j.jai.

27. 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; **73**:705-712.

28. Asero R, Marzano AV, Ferrucci S, Cugno M. Elevated baseline D-dimer plasma levels are associated with a prompt response to omalizumab in patients with severe CSU. J Allergy Clin Immunol Pract 2017; **5**:1740-1742.

29. Cugno M, Genovese G, Ferrucci S, Casazza G, Asero R, Marzano AV. IgE and D-dimer baseline levels are higher in responders than non-responders to omalizumab in chronic spontaneous urticaria. Br J Dermatol 2018; **179**:776-777.

30. Ertas R, Ozyurt K, Ozlu E, et al. Increased IgE levels are linked to faster relapse in patients with omalizumab-discontinued chronic spontaneous urticaria. J Allergy Clin Immunol 2017; **140**:1749-1751.

31. 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 2013 revision and update. Allergy 2014; **69**:868-87.

32. Maurer M, Altrichter S, Bieber T, et al. Efficacy and safety of omalizumab in patients with chronic urticaria who exhibit IgE against thyroperoxidase. J Allergy Clin Immunol 2011; **128**:202-209

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

34. 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.

35. 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**:67-75.

36. Nettis E, Cegolon L, Leo ED, et al. Omalizumab chronic spontaneous urticaria: efficacy, safety, predictors of treatment outcome and time to response. Ann Allergy Asthma Immunol 2018 Jun 24 [Epub ahead of print]

37. Straesser MD, Oliver E, Palacios T, Kyin T, Patrie J, Borish L, Saini SS, Lawrence MG. Serum IgE as an immunological marker to predict response to omalizumab treatment in symptomatic chronic urticaria. J Allergy Clin Immunol Pract 2018; 6:1386-1388.

38. Weller K, Ohanyan T, Hawro T, Ellrich A, Sussman G, Koplowitz J, Gimenez-Arnau AM, Peveling-Oberhag A, Staubach P, Metz M, Maurer M. Total IgE levels are linked

to the response of chronic spontaneous urticaria patients to omalizumab. Allergy. 2018 Aug [Epub ahead of print]

39. 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**:1191-1197.e5.

40. Asero R, Marzano AV, Ferrucci S, Cugno M. D-Dimer Plasma Levels Parallel the Clinical Response to Omalizumab in Patients with Severe Chronic Spontaneous Urticaria. Int Arch Allergy Immunol 2017; **172**:40-44.

41. Bérard F, Ferrier le Bouëdec MC, Bouillet L, et al. Omalizumab in chronic spontaneous urticaria patients nonresponsive to H1-antihistamine treatment: Results of the phase IV open-label SUNRISE study. Br J Dermatol 2018 Jun 21. [Epub ahead of print]

TABLES

Table 1. Demographic and clinical features of the patients

	n=470
Females, n (%)	310 (66.0)
Age at diagnosis, years, median (IQR)	49 (37-61)
Disease duration, months, median (IQR)	20 (9-48)
Urticaria Activity score 7, median (IQR)	30 (26-36)
IgE[§], kUA/L, geometric mean (SD)	119.1 (494)
D-dimer[^], ng/ml, geometric mean (SD)	323.8 (856)
Positivity for anti-thyroglobulin or anti-thyroperoxidase autoantibodies[#], n (%)	121 (27.6)
Response, n (%) Early complete Late complete Late partial Non-responders	 211 (44.9) 119 (25.3) 95 (20.2) 45 (9.6)
First relapse *, n (%)	236 (60.2)
Second relapse **, n (%)	116 (66.3)

IQR: interquartile range; SD: standard deviation
[§]IgE values missing for 130 patients
[^]D-dimer values missing for 128 patients
[#]data missing for 32 patients
*data on 392 patients
**data on 175 patients

Table 2. Association between clinical and laboratory parameters to response to omalizumab

	Responders n=425	Non-responders n=45	P value
Females, n (%)	285 (67)	25 (55.6)	0.1372
Age at diagnosis, years, median (IQR)	48 (37-61)	52 (40-63)	0.2382
Disease duration, months, median (IQR)	20 (9-48)	16 (7-36)	0.3838
Urticaria Activity score 7, median (IQR)	30 (26-36)	30 (25-33)	0.3949
IgE[§] kUA/L, geometric mean (SD)	131.6 (507)	42.1 (299)	<0.0001
D-dimer[^], ng/ml, geometric mean (SD)	327.0 (874.1)	292.9 (689.6)	0.5560
Positivity for anti-thyroglobulin or anti-thyroperoxidase autoantibodies[#], n (%)	106 (26.7)	15 (36.6)	0.1995

IQR: interquartile range; SD: standard deviation
[§]IgE values missing for 130 patients
[^]D-dimer values missing for 128 patients
[#]data missing for 32 patients

Table 3. Association between clinical and laboratory parameters to first and second relapse after omalizumab withdrawal

	First relapse				Second relapse		
	Relapsed n=236	Non-relapsed n=156	P value*		Relapsed n=116	Non-relapsed n=59	P value*
Females, n (%)	152 (64.4)	109 (69.9)	0.2757		76 (65.5)	38 (64.4)	1.000
Age at diagnosis, years, median (IQR)	48 (37-60)	49 (36-62)	0.7274		52 (39-60)	51 (35-62)	0.9522
Disease duration, months, median (IQR)	24 (12-57)	13 (6-36)	<0.0001		25 (14-61)	18 (10-36)	0.0105
Urticaria Activity score 7, median (IQR)	31 (27.5-37)	29.5 (25-35)	0.0023		31.5 (27-37.5)	31 (27-36)	0.5238
IgE[§], kUA/L, geometric mean (SD)	137.0 (473.3)	115.6 (376.3)	0.3147		174.2 (543.5)	116.7 (275.2)	0.0964
D-dimer[^], ng/ml, geometric mean (SD)	340.3 (954.7)	330.3 (823.3)	0.8404		299 (936.9)	383.8 (1012.9)	0.2185
Positivity for anti-thyroglobulin or anti-thyroperoxidase autoantibodies[#], n (%)	62 (27.7)	38 (26.6)	0.9044		33 (29.5)	15 (27.3)	0.8564

IQR: interquartile range; SD: standard deviation

[§]IgE values missing for: First relapse, 58 relapsed and 53 non-relapsed; Second relapse, 23 relapsed and 16 non-relapsed.

[^]D-dimer values missing for: First relapse, 57 relapsed and 57 non-relapsed; Second relapse, 33 relapsed and 14 non-relapsed.

[#]data missing for: First relapse, 12 relapsed and 13 non-relapsed; Second relapse, 4 relapsed and 4 non-relapsed.

* p value for comparison of relapsed *versus* non-relapsed patients

Table 4. Logistic analyses of the joint association of disease duration and Urticaria Activity Score 7 with the first relapse after omalizumab withdrawal

	Univariate analysis			Multivariate analysis		
	OR (95% CI)	P value	c-statistic	OR (95% CI)	P value	c-statistic
Disease duration	1.46 (1.20 - 1.77)	0.0001	0.627	1.44 (1.19 - 1.75)	0.0002	0.65
Urticaria Activity Score 7	4.11 (1.72 - 9.78)	0.0014	0.591	3.84 (1.58 - 9.31)	0.0029	

CI: confidence interval; OR: odds ratio

Disease duration and Urticaria Activity Score 7 were log-transformed. OR refers to the increase of 1-unit in log-scale
c-statistic is a measure of the accuracy of the model on predicting the first relapse

Table 5. Correlation of baseline total IgE levels and clinical response to omalizumab subdivided into four categories: early complete, defined as the disappearance of the chronic spontaneous urticaria (CSU) symptoms within 1 week from the start of omalizumab treatment; late complete, defined as the disappearance of the CSU symptoms within 12 weeks from omalizumab starting; late partial, defined as an at least 30% reduction of Urticaria Activity Score (UAS7) as compared to baseline, evaluated at week 12; no response, defined as a less than 30% reduction of UAS7 or an exacerbation at week 12.

		IgE kUA/L, geometric mean (95% CI)	p value for comparison *versus* non-responders
Response	n		
Early complete	149	143.25 (113.7-180.5)	0.0002
Late complete	90	104.4 (77.6-140.6)	0.0182
Late partial	72	147.4 (105.7-205.4)	0.0005
No response	29	41.9 (24.8-70.73)	–

CI : confidence interval

FIGURE LEGENDS

Figure 1. Correlation between baseline total IgE levels and clinical response to omalizumab subdivided into four categories: early complete (EC), defined as the disappearance of the chronic spontaneous urticaria (CSU) symptoms within 1 week from omalizumab starting; late complete (LC), defined as the disappearance of the CSU symptoms within 12 weeks from the start of omalizumab treatment; late partial (LP), defined as an at least 30% reduction of Urticaria Activity Score (UAS7) as compared to baseline, evaluated at week 12; no response (N), defined as a less than 30% reduction of UAS7 or an exacerbation at week 12.