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The clinical response to omalizumab in chronic spontaneous urticaria patients is linked to and predicted by IgE levels and their change

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Abstract

Background: Omalizumab is an effective and well-tolerated treatment for chronic spontaneous urticaria (CSU). Markers and predictors of response are largely unknown, but needed to optimize omalizumab treatment. Omalizumab targets IgE, and IgE levels may be linked to the effects of treatment. We evaluated whether response rates to treatment with omalizumab in patients with CSU are linked to their baseline IgE levels, their IgE levels after omalizumab treatment, and the ratio of on treatment IgE and baseline IgE levels.

Methods: Chronic spontaneous urticaria (CSU) patients (n = 113) were treated with omalizumab 300 mg/4 weeks for 12 weeks, when their treatment responses, that is, no, partial, or complete response, were assessed by use of the urticaria activity score, physician and patient visual analog scale, and treatment effectiveness score. Total IgE levels were measured before treatment (bIgE) with omalizumab and 4 weeks thereafter (w4IgE).

Results: Nonresponders to omalizumab had significantly lower bIgE levels (17.9, 17.0-55.0 IU/mL) than partial responders (82.0, 46.2-126.5 IU/mL, $P = .008$) and complete responders (73.7, 19.45-153.8 IU/mL, $P = .032$). Nonresponders also had lower w4IgE levels and lower ratios of w4IgE/bIgE levels than partial and complete responders ($P < .001$). Nonresponse to omalizumab was best predicted by patients' w4IgE/bIgE ratios, significantly better than by bIgE levels ($P = .016$).

Conclusions: In CSU, total IgE levels and their change predict the response to treatment with omalizumab. The assessment of pre- and post-treatment IgE levels and their ratio may help to improve the management of CSU in patients who require omalizumab treatment.

KEYWORDS

baseline IgE, chronic spontaneous urticaria, omalizumab, post-treatment IgE, response

Abbreviations: ASST, autologous serum skin test; AUC, area under the curve; bIgE, baseline total IgE levels; CSU, chronic spontaneous urticaria; IgE, immunoglobulin E; IQR, interquartile range; ROC, receiver operating characteristic; SD, standard deviation; sgAH, second-generation H1 antihistamines; TES, treatment effectiveness score; UAS, urticaria activity score; VAS, visual analog scale; w4IgE, total IgE levels after 4 weeks.

1 | INTRODUCTION

Chronic spontaneous urticaria (CSU), formerly also referred to as chronic idiopathic urticaria (CIU), is defined as the spontaneous occurrence of wheals and/or angioedema for six or more weeks.[1]

Currently, more than 50 million people suffer from CSU, especially its negative effects on quality of life and sleep, school and work performance, as well as daily life activities and social relationships.[2-4]

Omalizumab, a humanized monoclonal anti-IgE antibody, is an effective and well-tolerated treatment for patients with CSU,[5] for which the European Medicines Agency and the US Food and Drug Administration granted marketing authorization in 2014.[6,7]

Defining and better characterizing the response to omalizumab as well as predictors and markers of response to omalizumab will improve the management of patients with CSU. As of now, many questions are still open regarding omalizumab treatment including what predicts the response. Recently, Deza and coworkers reported that CSU patients with a positive autologous serum test (ASST) are less likely to respond to omalizumab than those with a negative ASST.[8] In line with this, Palacios et al[9] had previously reported that CSU patients, who exhibit basophil-activating serum activity, are less likely to show complete response to omalizumab. In addition, Gericke et al[10] showed that CSU patients with basophil-activating serum activity experience slower responses to omalizumab treatment than those without. However, ASST responses and basophil-activating serum activity are not routinely assessed in most CSU patients and the latter test is not widely available.

Omalizumab exerts its effects in CSU by lowering free IgE levels, reducing mast cell and basophil activation, and downregulating the high-affinity IgE receptor, FceRI, in the skin.[11] IgE is held to importantly contribute to the pathogenesis of CSU for many reasons. For example, (i) CSU patients exhibit increased levels of IgE,[12] (ii) some CSU patients exhibit mast cell-activating autoantibodies against FceRI, and FceRI expression is regulated by IgE,[13-15] (iii) many CSU patients express IgE to autoantigens, and this IgE can activate mast cells to release histamine.[16-18] Because of this, clinical responses to omalizumab may be importantly linked to the levels of IgE in patients with CSU and to how omalizumab binds IgE in these patients.

Omalizumab treatment results in a fast reduction in free IgE, whereas total IgE levels increase, two- to 11-fold, as assessed by conventional IgE measurement methods.[19,20] This increase in total IgE levels is explained by the fact that total serum IgE in omalizumab-treated patients consists of free IgE, that is, IgE that is not bound by omalizumab, and IgE/omalizumab complexes that have a longer half-life than free IgE. Conventional IgE assays measure both free and omalizumab-complexed IgE.[19-22]

Here, we hypothesized that CSU patients, who do not respond to omalizumab, have IgE levels that are lower and show less increase after start of treatment as compared to CSU patients who respond to omalizumab. To test this hypothesis, we measured total IgE levels of CSU patients before and after the initiation of omalizumab therapy and then compared those patients who responded to those who did not for differences in their baseline IgE levels, their IgE levels at week four of treatment, as well as their week 4/baseline ratios of total IgE.

2 | METHODS

2.1 | Patients

In this prospective study, we evaluated the clinical and laboratory findings of 113 patients, whose IgE levels were measured before and during omalizumab treatment; 83 of the patients included in this study were previously investigated for their response to omalizumab treatment and relapse after discontinuation of treatment.[23] Patients were predominantly female (65.5%), had an average disease duration

TABLE 1 Baseline characteristics of CSU patients who showed complete response, partial response, or no response to omalizumab at week 12 of treatment

	All patients (n = 113)	Complete responders (n = 43)	Partial responders (n = 55)	Nonresponders (n = 15)	*P* NR vs PR	*P* NR vs CR	*P* NR vs PR + CR
Age in years, mean (SD)	40.0 (13.0)	38.9 (14.5)	41.0 (12.2)	39.7 (11.9)	NS[a]	NS[a]	NS[e]
Female, n (%)	74 (65.5)	23 (53.5)	39 (70.9)	12 (80)	NS[b]	NS[b]	NS[b]
Angioedema, n (%)	69 (61.1)	24 (55.8)	31 (56.4)	14 (93.3)	<.05[b]	<.05[b]	<.01[b]
IgG anti-TPO, n (%)	30 (26.5)	10 (23.3)	14 (25.5)	6 (40.0)	NS[b]	NS[b]	NS[b]
CSU duration, months, median (IQR)	40 (12-120)	36 (12-65)	60 (12-120)	36 (18-168)	NS[c]	NS[c]	NS[d]
UAS, median (IQR)	6 (5-6)	5 (4-6)	6 (5-6)	6 (5-6)	NS[c]	NS[c]	NS[d]
Physician VAS, median (IQR)	9 (8-10)	8 (7-10)	9 (8-10)	10 (8-10)	NS[c]	<.05[c]	NS[d]
Patient VAS, median (IQR)	9 (8-10)	9 (7-10)	9 (8-10)	9 (8-10)	NS[c]	NS[c]	NS[d]
Physician TES, median (IQR)	2 (1-3)	3 (2-4)	2 (1-3)	1 (0-3)	NS[c]	<.01[c]	<.05[d]
Patient TES, median (IQR)	1 (0-2.5)	2 (0-3)	1 (0-2)	0 (0-2)	NS[c]	NS[c]	NS[d]

SD, standard deviation; IgE, immunoglobulin E; CSU, chronic spontaneous urticaria, IQR interquartile range (lower quartile–upper quartile); UAS, urticaria activity score; VAS, visual analog scale; TES, treatment effectiveness score; NR, nonresponders; PR, partial responders; CR, complete responders; NS, not significant.

[a]ANOVA for parametric variables.

[b]Chi-square test.

[c]Kruskal-Wallis with Dunn post-test for nonparametric variables.

[d]Mann-Whitney *U* test.

[e]Student's *t* test; none of the parameters showed statistical significant differences when comparing PR and CR, except for physician TES ($P = .009$).

of 40 (14-120) months, and frequently (61.1%) had angioedema in addition to their wheals (Table 1).

Diagnosis of CSU was based on patient history and the presence of clinical signs and symptoms. Urticarial vasculitis was ruled out by a skin biopsy in those patients who had wheals that lasted for more than 24 hours. We included only CSU patients resistant to standard first-line treatments; that is, all patients were refractory to standard dosed and up to fourfold dosed sgAH treatment, and all had a UAS of 3 or more. Some patients had treatments other than antihistamines before inclusion in this study. We did not include patients who exclusively had angioedema.

2.2 | Treatment and evaluation of responses to omalizumab

Patients were treated with omalizumab 300 mg every 4 weeks for 12 weeks, and they were instructed to continue their daily treatment with an up to fourfold dosed sgAH for the first 4 weeks. Patients were assessed for their clinical response at the end of week 12 after the start of omalizumab treatment.

At baseline, that is, before the first omalizumab treatment, we assessed demographic features including age, gender, and duration of disease, previous treatments, thyroid autoantibodies, and the presence of angioedema. At baseline and during visits at the end of the 4th week, 8th week, and 12th week of treatment, we determined disease activity by the use of the urticaria activity score (UAS), which is the sum score of the daily subscore values for numbers of wheals (no wheals = 0 points, 1-20 wheals = 1 point, 21-50 wheals = 2 points, >50 wheals = 3 points) and the intensity of itch (no itch = 0 points, mild itch = 1 point, moderate itch = 2 points, severe itch = 3 points).[24,25] In this study, the UAS was used retrospectively, that is, patients were asked during the study visits to estimate their average urticaria activity (wheal numbers and pruritus intensity per day) in the last 4 weeks. At baseline and at each follow-up visit, we also assessed treatment responses by use of a visual analog scale (VAS) and a treatment effectiveness score (TES), used by both patients (patVAS, patTES) and physicians (physVAS, physTES). Visual analog scale (VAS) is a 10-cm scale used to determine the overall severity of symptoms in the previous month, where 0 corresponds to no symptoms and 10 indicates maximum symptoms.[26,27] The TES measures treatment effectiveness on a scale from 0 to 10: The higher the score, the more effective the treatment.[27]

Based on UAS and physVAS assessments, patients were designated, 12 weeks after the start of omalizumab treatment, as nonresponders (NR), partial responders (PR), or complete responders (CR) based on the following criteria: Nonresponders showed no reduction in UAS or physVAS or had severe exacerbations of their symptoms after omalizumab injections. Partial responders showed reduced disease activity in response to omalizumab treatment, but not complete remission (UAS or physVAS reduction ≥ 1). Complete responders showed complete remission (UAS and physVAS of 0).

2.3 | Measurements of IgE

Total IgE levels were measured by quantitative nephelometric analysis (BN™ II System, Siemens, Germany), a standard, conventional technique widely used in clinical laboratories that detects both free and omalizumab-bound IgE. Measurements were taken before treatment (bIgE) and at the end of the fourth week, before the second omalizumab injection (w4IgE).

Patients with IgE levels that exceeded the upper assessment limit (1100 IU/mL) were excluded from further analyses (n = 17). w4IgE/bIgE ratios were calculated and subjected to ROC analyses to define a cutoff point. ROC analyses were also used to define cutoff points of bIgE and w4IgE. Based on these results, patients were categorized into two groups, group 1 in which IgE levels increased by <2 (n = 19) and group 2 in which IgE ratio increased by ≥2 (n = 77). These two groups were compared for responder rates, stratified by bIgE levels.

2.4 | Statistical analysis

Parametric variables are presented as means and standard deviations, nonparametric variables are presented as medians and interquartile ranges (lower and upper quartiles). The Kolmogorov-Smirnov test and histogram analyses were used to determine whether continuous variables were normally distributed. Levene's test was used for the evaluation of homogeneity of variances. Number of cases and percentages were used for categorical variables. Two independent groups of parametric variables were compared using Student's *t* test. For nonparametric variables, the Mann-Whitney *U* test was administered. ANOVA and Kruskal-Wallis were used for comparing three groups of parametric variables and nonparametric variables, respectively. Post-test corrected for multiple comparisons was used if Kruskal-Wallis test was significant. Categorical data were analyzed by chi-square or Fisher's exact test, where applicable. Friedman test with Wilcoxon signed rank test as a post-test was used to evaluate differences between clinical variables across time (ie, UAS, VAS scores, TES scores, and IgE). Receiver operating characteristic (ROC) curves were generated to assess pretreatment and post-treatment total IgE levels and IgE ratio of post-treatment/pretreatment IgE levels. The area under the curve (AUC) of the ROC value was calculated for the response evaluation of omalizumab treatment. When a significant cutoff value was observed, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and positive and negative likelihood ratios (PLR, NLR) were presented. The calculated proportions of sensitivity, specificity, and negative and positive predictive values were then compared using the two-sample test of proportions. The applied test of proportions was based on the prtesti command in the Stata software version 11 (STATA Corp LP, College Station, TX, USA). EasyROC (ver. 1.3) was used for ROC curve analysis to compare the AUCs (bIgE, w4IgE, and the ratio of w4IgE/bIgE).[28] A *P* value of <.05 was considered to indicate statistical significance.

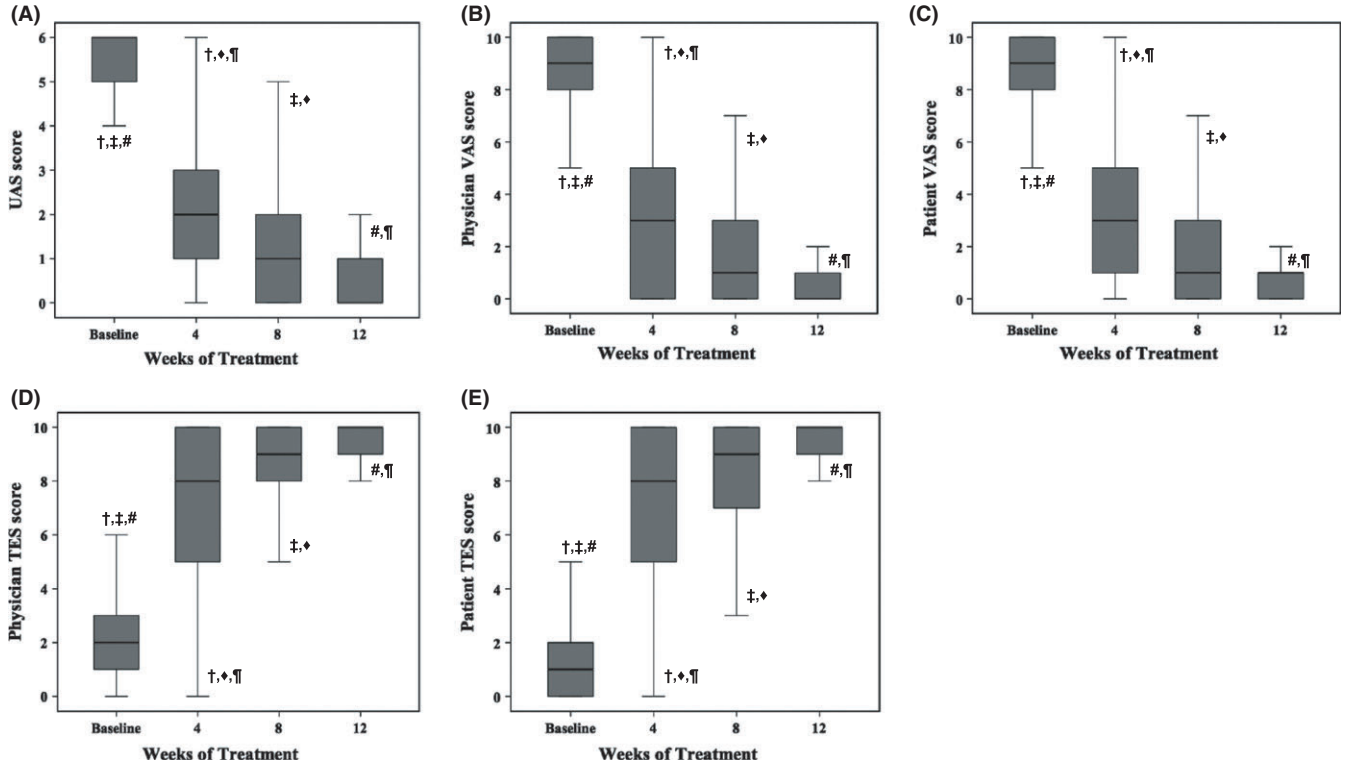

FIGURE 1 Omalizumab significantly reduces chronic spontaneous urticaria (CSU) activity*. Three applications of omalizumab (s.c., 300 mg, every 4 wk) markedly and rapidly reduce disease activity in CSU patients as assessed by urticaria activity score (A) as well as physicians' and patients' VAS (B,C). Use of the TES by physicians (D) and patients shows that omalizumab is effective. *Friedman test with Wilcoxon signed rank test, n = 113. Statistically significant differences with a *P* of <.001 between time points are indicated by †, ‡, #, and ¶ for comparisons of baseline and week 4, baseline and week 8, baseline and week 12, and week 4 and 12, respectively. Statistically significant differences with a *P* of <.05 between time points are indicated by ♦ for comparison of week 4 and 8. UAS, urticaria activity score; VAS, visual analog scale; TES, treatment effectiveness score

3 | RESULTS

3.1 | Most CSU patients benefit from omalizumab treatment

In line with all prior studies and our previous findings from the analyses of a subgroup of the patients investigated here,[23] omalizumab significantly reduced CSU activity as early as 1 month after the initiation of omalizumab treatment (Figure 1). Most CSU patients benefitted from treatment: At the end of week 12 of treatment, 43 patients (38.1%) showed complete response (CR), 55 (48.6%) showed partial response (PR), and fifteen patients (13.3%) showed no response (NR, Table 1). Angioedema and high disease activity were more common in the NR group (Table 1).

TABLE 2 Levels of baseline and week 4 IgE, week 4:baseline IgE ratios, and increases in IgE levels in patients who show complete response, partial response, or no response at week 12 of omalizumab treatment

	All patients (n = 96)	Complete responders (n = 34)	Partial Responders (n = 48)	Nonresponders (n = 14)	P^a NR vs PR	P^a NR vs CR	P^b NR vs PR+CR
bIgE (IU/mL)	66.8 (20.4-127.0)	73.7 (19.5-153.8)	82.0 (46.2-126.5)	17.9 (17.0-55.0)	<.05	<.05	<.055
w4IgE (IU/mL)	257 (108-539.8)	290.5 (121.5-637.5)	298 (205.8-543.5)	17.9 (17.4-86.2)	<.001	<.001	<.001
w4IgE-bIgE (%)	272.7 (120.6-388.5)	285.9 (165.2-384.5)	305.2 (198.5-401.4)	0.28 (0-73.2)	<.001	<.001	<.001
w4IgE:bIgratio	3.7 (2.2-4.9)	3.9 (2.7-4.8)	4.1 (3.0-5.0)	1.0 (1.0-1.7)	<.001	<.001	<.001

bIgE, baseline total IgE; w4IgE, total IgE at the end of week 4 of omalizumab treatment; w4IgE-bIgE, increase in total IgE from baseline to the end of week 4 of omalizumab treatment; w4IgE/bIgE ratio, total IgE at week 4 of omalizumab treatment/total baseline IgE.
All values are medians with interquartile range (lower quartile–upper quartile).
[a]Kruskal-Wallis with Dunn post-test for nonparametric variables was used, [b]Mann-Whitney *U* test. None of these parameters showed statistical significant differences when comparing PR and CR.

TABLE 3 Correlations between the baseline IgE level, the week 4 IgE level, and the week 4:baseline IgE ratio of patients with their clinical response to 12 wk of omalizumab treatment

	bIgE		w4IgE		w4IgE:bIgE	
	r	*P*	*r*	*P*	*r*	*P*
Decrease in UAS	−.209	.041	−.300	.003	−.338	.001
Decrease in physician VAS	−.185	NS	−.272	.007	−.357	<.001
Decrease in patient VAS	−.187	NS	−.272	.007	−.299	.003
Increase in physician TES	.099	NS	.125	NS	.253	.013
Increase in patient TES	.179	NS	.183	NS	.198	.053

UAS, urticaria activity score; VAS, visual analog scale; TES, treatment effectiveness score; bIgE, baseline IgE; w4IgE, total IgE levels after 4 wk; IgE, immunoglobulin E; NS, not significant; *r*, Spearman's rho, n = 96.

3.2 | Nonresponders to omalizumab have low baseline total IgE levels

Serum levels of baseline IgE (bIgE) were markedly lower in the NR group (17.9, 17.0-55.0 IU/mL) than in the PR (82.0, 46.2-126.5 IU/mL, $P = .008$) and the CR groups (73.7, 19.5-153.8 IU/mL, $P = .032$, Table 2). Total bIgE levels were weakly correlated with the improvement of CSU at week 12 of treatment as assessed by UAS ($r = -.209$, $P = .041$), but not PhysVAS, PatVAS, PhysTES, or PatTES (Table 3).

3.3 | After 4 weeks of omalizumab treatment, nonresponders have lower total IgE levels than responders

Total IgE levels at week 4 of treatment were also lower in NR (17.9, 17.4-86.2 IU/mL) than in PR and CR (PR: 298.0, 205.8-543.5 IU/mL, $P < .001$; CR: 290.5, 121.5-637.5 IU/mL, $P < .001$, Table 2). Total w4IgE levels were significantly correlated with changes in UAS ($r = -.300$, $P = .003$), PhysVAS ($r = -.272$, $P = .007$), and PatVAS ($r = -.272$, $P = .007$), but not PhysTES or PatTES (Table 3).

3.4 | Increases in IgE levels in response to omalizumab treatment are lower in nonresponders than in responders

Within the first 4 weeks of treatment, total IgE levels increased significantly in PR and CR patients (PR: +305%, $P < .001$; CR: +286%, $P < .001$), but not in NR patients (+0.3%, NS), Table 4). Week 4 over baseline IgE (w4IgE:bIgE) ratios were significantly correlated with the reduction in disease activity as assessed by all measures except for PatTES (Table 3). In other words, the higher the increase in total IgE at week 4, the higher the reduction in disease activity at week 12 of omalizumab treatment.

3.5 | The change in IgE from baseline to week 4 of omalizumab treatment is the best predictor of response

As determined by ROC analyses (area under the curve), the w4IgE:bIgE ratio is the best predictor of response to omalizumab, followed by absolute levels of IgE at week 4 of treatment and baseline levels of IgE (Figure 2, Table 4). In comparison, the w4IgE:bIgE ratio also showed the highest sensitivity, specificity, PPV, NPV, PLR, and the lowest NLR. The cutoffs for w4IgE:bIgE, bIgE, and w4IgE were 1.9, 43 and 51 IU/mL, respectively (Table 4).

3.6 | Increases in total IgE levels by twofold or more within the first 4 weeks of omalizumab treatment increase the likelihood of response

Low baseline IgE, that is, IgE levels below the cutoff, was linked to a 33% risk of nonresponse, as compared to 5% in patients with >43 IU/mL. The assessment of IgE levels in week 4 of treatment and calculation of the w4IgE:bIgE ratio allowed to predict all nonresponders (at week 12 of treatment) in patients with low baseline IgE (Table 5). All IgE-low patients who showed a twofold or higher IgE increase by week 4 of treatment became complete or partial responders. Patients with baseline IgE of >43 IU/mL, in which IgE levels increased by twofold or more within the first

TABLE 4 The ROC analyses of prediction of response to omalizumab based on IgE values

	bIgE (Cutoff=43) (95% CI)	w4IgE (Cutoff =51) (95% CI)	Ratio (w4IgE:bIgE) (Cutoff =1.9) (95% CI)	*P*[a] bIgE vs w4IgE	*P*[a] w4IgE vs Ratio	*P*[a] bIgE vs Ratio
AUC	0.75 (0.59-0.90)	0.87 (0.76-0.99)	0.95 (0.90-0.99)	NS	NS	.016
Sensitivity	0.79 (0.49-0.95)	0.79 (0.49-0.95)	0.93 (0.66-1.00)	NS	.005	.005
Specificity	0.73 (0.62-0.82)	0.90 (0.82-0.96)	0.93 (0.85-0.97)	.002	NS	<.001
PPV	0.33 (0.23-0.74)	0.58 (0.40-0.89)	0.68 (0.49-0.99)	.001	NS	<.001
NPV	0.95 (0.84 -0.97)	0.96 (0.87-0.98)	0.99 (0.92-1.00)	NS	NS	NS

AUC, area under the curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; ROC, receiver operating characteristic; IgE, immunoglobulin E; bIgE, baseline IgE; w4IgE, total IgE levels thereafter 4 wk; NS, not significant, n = 96.

[a]A two-sample test of proportions was used to determine the differences.

4 weeks of treatment, also showed a higher rate of response as compared to those in which the increase was less than twofold (Table 5).

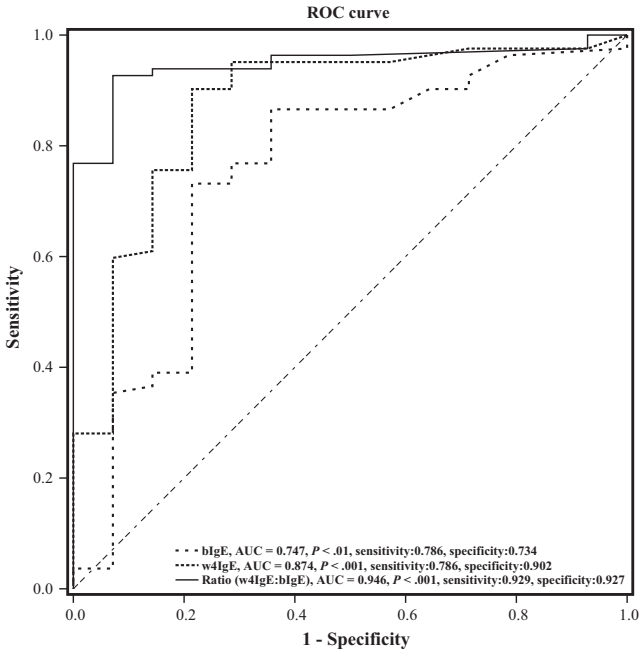

FIGURE 2 In chronic spontaneous urticaria (CSU), baseline IgE, week four IgE, and the increase in IgE during the first 4 wk predict the clinical outcome of 12 wk of omalizumab treatment. ROC, receiver operating characteristic; bIgE, baseline IgE; w4IgE, total IgE levels after 4 wk of omalizumab treatment (n = 96)

4 | DISCUSSION

This study shows, to our knowledge for the first time, that IgE levels of CSU patients and their change can predict the outcome of omalizumab treatment. Our findings strengthen the notion that omalizumab reduces disease activity in CSU patients by acting on IgE. More importantly, our results may point to a novel strategy to improve the management of CSU with omalizumab treatment, by identifying patients who are at risk of nonresponse with the help of a widely available, easy to measure, and inexpensive biomarker, IgE.

Our results confirm and complement earlier studies that demonstrated that omalizumab is effective in CSU.[5] Of note, our study made use of five complementary instruments to assess omalizumab treatment effects, UAS, PatVAS, PhysVAS, PatTES, and PhysVAS, all of which showed that omalizumab markedly and rapidly reduces disease activity in most patients. At the end of week 12, 87% of patients benefitted from treatment, which is very similar to the rates of response of other real-life studies.[29-32]

In this study, patients refractory to other treatment options, with high disease activity or with angioedema, were less likely to respond to omalizumab within the first 12 weeks of treatment. This was also seen in a recent study by Deza and coworkers,[8] although differences in that study were not statistically significant, possibly because of lower patient numbers than in our study. The reasons for this link are not clear. We had recently reported that autoreactive CSU patients, that is, those with a positive autologous serum skin test and/or basophil-activating serum, show a delayed response to omalizumab treatment.[10] Autoreactive CSU patients are also more likely to have high disease activity and angioedema.[33,34] High disease

TABLE 5 Response of CSU patients to omalizumab treatment stratified by baseline IgE levels and week4:baseline IgE ratios

bIgE	n	Response, n (%)		NR (%)	CR + PR (%)		w4IgE:bIgE	n	Response, n (%)		NR (%)	CR + PR (%)	P[a]
≤43 IU/mL	33	NR	11 (33)	11 (33)	22 (66)	→	<2	16	NR	11 (69)	11 (69)	5 (31)	<.001
									PR	3 (19)			
		PR	11 (33)						CR	2 (13)			
							≥2	17	NR	0 (0)	0 (0)	17 (100)	
		CR	11 (33)						PR	8 (47)			
									CR	9 (53)			
>43 IU/mL	63	NR	3 (5)	3 (5)	60 (95)	→	<2	3	NR	2 (67)	2 (67)	1 (33)	<.001
									PR	0 (0)			
		PR	37 (59)						CR	1 (33)			
							≥2	60	NR	1 (2)	1 (2)	59 (98)	
		CR	23 (37)						PR	37 (62)			
									CR	22 (37)			
All patients	96	NR	14 (15)	14 (15)	82 (85)	→	<2	19	NR	13 (68)	13 (68)	6 (32)	<.001
									PR	3 (16)			
		PR	48 (50)						CR	3 (16)			
							≥2	77	NR	1 (1)	1 (1)	76 (99)	
		CR	34 (35)						PR	45 (58)			

bIgE, baseline IgE; IgE, immunoglobulin E; CR, complete responder; PR, partial responder; NR, nonresponder.
[a]Chi-square test, n = 96.

activity and recurrent angioedema may therefore predispose to delayed responses to omalizumab, that is, responses that take longer than 12 weeks to occur, because they are linked to autoreactivity. Indeed, a recent study has shown that responder rates in patients treated with omalizumab for 24 weeks continue to increase, from 59% in week 12%-73% in week 24.[35] Further studies will need to clarify whether high baseline activity, angioedema, and/or autoreactivity are linked to treatment responses that occur after 12 or more weeks of omalizumab treatment.

In contrast to asthma, omalizumab dosing in CSU is independent of IgE levels. We had previously shown that total serum IgE levels, in complete responders to omalizumab, do not correlate with the dose required to suppress symptoms.[32] More recently, Deza et al[8] reported that nonresponders to omalizumab have low baseline IgE levels, a finding that we confirm in the present study. Interestingly, nonresponders in our study also had lower IgE levels after 4 weeks of omalizumab treatment.

The most striking finding of our study is that IgE levels in omalizumab responders increase during the first weeks of treatment, as was to be expected, whereas IgE levels in nonresponders do not. The reasons for this are unclear. One explanation may be that the IgE of nonresponder CSU patients is not bound by omalizumab, as IgE binding and complex formation by omalizumab are held to be the reason for the increase in IgE levels in treated patients. We did not measure free IgE levels in our omalizumab-treated patients, but there is another study that has done so. Metz and coworkers reported that omalizumab treatment, with of variability, resulted in the reduction in free IgE levels in CSU patients by more than 90% within the first days of treatment.[11] Thus, other explanations are more likely, for example, that the size of IgE/omalizumab complexes in nonresponders may be smaller than in responders, resulting in faster clearance of IgE and a lack of increase. The exact mechanisms that underlie this effect should be addressed by future studies.

The available information from omalizumab-treated asthma patients does not help to understand this observation. In one asthma patient, total IgE levels and free IgE levels did not change during omalizumab treatment, but the clinical response was good.[36] Studies that evaluated free IgE levels in omalizumab-treated asthma patients found no correlation with clinical response.[36]

IgE serum levels are easy and inexpensive to assess in clinical practice, for example, before the initiation of omalizumab treatment. Low IgE (<43 IU/mL) comes with a 33% risk for nonresponse to omalizumab within the first 12 weeks of treatment, as compared to 5% in patients with IgE levels of 43 IU/mL and higher. However, the ratio of week 4 IgE to baseline IgE is an even better predictor of nonresponse than baseline IgE ($P = .016$). Based on these two findings, nonresponse to omalizumab within the first 12 weeks of treatment may be best assessed by applying the "2 × 4 rule": When baseline IgE levels fail to double within the first 4 weeks of treatment, nonresponse needs to be expected. The "2 × 4 rule" may be especially helpful in patients with low IgE. One of three patients with low IgE, in our study, failed to respond to omalizumab by week 12 of treatment. When these patients were assessed for their week 4 levels of IgE, all patients with a twofold or more increase in IgE showed response, whereas none of the patients with less than a twofold increase did. We suggest to put the "2 × 4 rule" to the test in future trials and clinical practice.

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CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

All authors contributed to conception and design, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, and final approval of the version to be published.

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REFERENCES

1. 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;132:101-109.
2. Colgecen E, Ozyurt K, Irfan Gul A, Utas S. Evaluation of etiological factors in patients with chronic urticaria. *Acta Dermatovenerol Croat*. 2015;23:36-42.
3. 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.
4. 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.
5. 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.
6. 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(Suppl. 5):25-32.
7. Zuberbier T, Maurer M. Omalizumab for the treatment of chronic urticaria. *Expert Rev Clin Immunol*. 2015;11:171-180.
8. 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.
9. 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;4:529-530.
10. 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;139:1059-1061.
11. Metz M, Staubach P, Bauer A, et al. Clinical efficacy of omalizumab in chronic spontaneous urticaria is associated with a reduction of FcεRI-positive cells in the skin. *Theranostics*. 2017;7:1266-1276.
12. Przybilla B, Ring J, Völk M. Total IgE levels in the serum in dermatologic diseases. *Hautarzt*. 1986;37:77-82.
13. Saini SS, Klion AD, Holland SM, Hamilton RG, Bochner BS, Macglashan DW Jr. The relationship between serum IgE and surface levels of FcepsilonR on human leukocytes in various diseases: correlation of expression with FcepsilonRI on basophils but not on monocytes or eosinophils. *J Allergy Clin Immunol*. 2000;106:514-520.
14. Saini SS, MacGlashan DW, Sterbinsky SA, et al. Down-regulation of human basophil IgE and FcεRIα surface densities and mediator release by anti-IgE-infusions is reversible in vitro and in vivo. *J Immunol*. 1999;162:5624-5630.
15. MacGlashan D, Lichtenstein LM, McKenzie-White J, et al. Upregulation of FcεRI on human basophils by IgE antibody is mediated by interaction of IgE with FcεRI. *J Allergy Clin Immunol*. 1999;104:492-498.
16. Maurer M, Metz M, Magerl M, Siebenhaar F, Staubach P. Autoreactive urticaria and autoimmune urticaria. *Hautarzt*. 2004;55:350-356.
17. Chang TW, Chen C, Lin CJ, Metz M, Church MK, Maurer M. The potential pharmacologic mechanisms of omalizumab in patients with chronic spontaneous urticaria. *J Allergy Clin Immunol*. 2015;135:337-342.
18. Panaszek B, Pawłowicz R, Grzegrzółka J, Obojski A. Autoreactive IgE in chronic spontaneous/idiopathic urticaria and basophil/mastocyte priming phenomenon, as a feature of autoimmune nature of the syndrome. *Arch Immunol Ther Exp (Warsz)*. 2017;65:137-143.
19. Corne J, Djukanovic R, Thomas L, et al. The effect of intravenous administration of a chimeric anti-IgE antibody on serum IgE levels in atopic subjects: efficacy, safety, and pharmacokinetics. *J Clin Invest*. 1997;99:879-887.
20. Bochner B, Saini S. Introduction: anti-IgE. *Clin Rev Allergy Immunol*. 2005;29:1-2.
21. Busse W, Corren J, Lanier BQ, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol*. 2001;108:184-190.
22. Casale TB, Bernstein IL, Busse WW, et al. Use of an anti-IgE humanized monoclonal antibody in ragweed-induced allergic rhinitis. *J Allergy Clin Immunol*. 1997;100:110-121.
23. Ertaş R, Özyurt K, Özlü E, et al. Elevated IgE levels are linked to faster relapse in omalizumab-discontinued chronic spontaneous urticaria patients. *J Allergy Clin Immunol*. 2017; pii: S0091-6749(17)31351-9.
24. 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.
25. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA²LEN/EDF/WAO Guideline for the definition, classification, diagnosis and management of Urticaria. The 2013 revision and update. *Allergy*. 2014;69:868-887.
26. Nettis E, Colanardi MC, Paradiso MT, Ferrannini A. Desloratadine in combination with montelukast in the treatment of chronic urticaria: a randomized, double-blind, placebo-controlled study. *Clin Exp Allergy*. 2004;34:1401-1407.
27. Bagenstose SE, Levin L, Bernstein JA. The addition of zafirlukast to cetirizine improves the treatment of chronic urticaria in patients with positive autologous serum skin test results. *J Allergy Clin Immunol*. 2004;113:134-140.
28. Goksuluk D, Korkmaz S, Zararsiz G, Karaagaoglu AE. easyROC: an interactive web-tool for ROC curve analysis using R language environment. *R J*. 2016;8:213-230.
29. Sussman G, Hébert J, Barron C, et al. Real-life experiences with omalizumab for the treatment of chronic urticaria. *Ann Allergy Asthma Immunol*. 2014;112:170-174.
30. Ferrer M, Gamboa P, Sanz ML, et al. Omalizumab is effective in nonautoimmune urticaria. *J Allergy Clin Immunol*. 2011;127:1300-1302.
31. Ensina LF, Valle SO, Juliani AP, et al. Omalizumab in chronic spontaneous urticaria: a brazilian real-life experience. *Int Arch Allergy Immunol*. 2016;169:121-124.
32. Metz M, Ohanyan T, Church MK, Maurer M. Omalizumab is an effective and rapidly acting therapy in difficult-to-treat chronic urticaria: a retrospective clinical analysis. *J Dermatol Sci*. 2014;3:57-62.
33. Toubi E, Kessel A, Avshovich N, et al. Clinical and laboratory parameters in predicting chronic urticaria duration: a prospective study of 139 patients. *Allergy*. 2004;59:869-873.
34. Sabroe RA, Seed PT, Francis DM, Barr RM, Black AK, Greaves MV. Chronic idiopathic urticaria: comparison of clinical features of patients with and without anti-FcepsilonRI or anti-IgE autoantibodies autoantibodies. *J Am Acad Dermatol*. 1999;40:443-450.
35. Casale TB, Win PH, Bernstein JA, et al. Omalizumab response in patients with chronic idiopathic urticaria: insights from the XTEND-CIU study. *J Am Acad Dermatol*. 2017; pii: S0190-9622(17)32536-7.
36. Korn S, Haasler I, Fliedner F, et al. Monitoring free serum IgE in severe asthma patients treated with omalizumab. *Respir Med*. 2012;106:1494-1500.

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