Received: 17 March 2023 | Accepted: 3 August 2023

DOI: 10.1111/jdv.19485

JEADV JOURNAL OF THE EUROPEAN ACADEMY OF DERMATOLOGY & VENEREOLOGY

ORIGINAL ARTICLE

Elevated baseline soluble FcεRI may be linked to early response to omalizumab treatment in chronic spontaneous urticaria

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Abstract

Background: Omalizumab, an anti-IgE monoclonal antibody, is an effective treatment in chronic spontaneous urticaria (CSU). Predictors of fast and good response for omalizumab treatment have not yet been identified and characterized.

Objective: To evaluate whether soluble FcεRI (sFcεRI), a marker of IgE-mediated mast cell activation, predicts the time of response to omalizumab in CSU.

Methods: Sera of 67 CSU patients were obtained before omalizumab treatment and analysed for sFcεRI levels by ELISA (2 ng/mL was used as cut-off for elevated sFcεRI). Treatment response during the first 4 weeks was assessed with the urticaria activity score (UAS7), urticaria control test (UCT) and the rolling UAS7 (rUAS7).

Results: Elevated pre-treatment sFcεRI levels were detected in more than 70% of patients with completely controlled disease (UCT = 16) and well-controlled disease (UCT = 12–15) and were significantly associated with disease control ($\chi^2 = 4.94$, $p < 0.05$). More than half of the patients (14/25) with low levels had poor disease control (UCT < 12). Of the patients who achieved complete and marked UAS7 response, respectively, 75% and 63% had elevated baseline sFcεRI levels. Post-treatment UAS7 scores were lower in patients with elevated sFcεRI levels reaching statistical significance at Week 3 ($p < 0.05$). Patients with elevated baseline sFcεRI levels achieved rUAS7 ≤ 6 and = 0 earlier than those with lower levels (Days 9 vs. 13 and Days 12 vs. 14, respectively).

Conclusion: Elevated sFcεRI serum levels predict early and good response to treatment with omalizumab, which may help to better design treatment options for CSU patients.

INTRODUCTION

Chronic spontaneous urticaria (CSU) is a common and debilitating disease characterized by recurrent episodes of itchy wheals, angioedema or both.[1] These symptoms are due to the activation and degranulation of skin mast cells (MCs).[2] Well known mechanisms of MC activation in CSU include crosslinking of the high-affinity IgE receptor (FcεRI) by IgE or IgG autoantibodies, but other mechanisms may also be relevant. The currently licensed treatment options target either the main MC mediator histamine (second generation H1-antihistamines, the first line of CSU therapy) or IgE-FcεRI mediated MC activation (omalizumab, an anti-IgE monoclonal antibody, the second line of CSU therapy). Many more treatments are currently under investigation, some of which have shown positive outcomes in early trials and will possibly broaden the therapy spectrum in the future.[1,3–11]

Omalizumab has proven to be an effective treatment for CSU patients,[1] and pivotal trials showed response rates up to 50%.[12–14] However, some patients require multiple injections and up-dosing to achieve disease

control, and some patients dot not improve at all during the course of treatment. For example, a meta-analysis of 67 real-life CSU studies showed average complete and partial response rates of 72% and 18%, respectively, suggesting that at least every tenth patient is a nonresponder to omalizumab.[15] Recent studies reported that 8% of patients have aiCSU, characterized by the production of IgG or IgM against FcεRI or IgE.[16] Markers of aiCSU, for example positive autologous serum skin (ASST), positive basophil histamine release assay (BHRA) and low total IgE levels, were associated with slow and/or nonresponse to omalizumab. Non-response and slow response to omalizumab are linked to type IIb autoimmune CSU (aiCSU).[15,16] However, endotypes, phenotypes and biomarkers of fast and good response to omalizumab are poorly investigated. A recent study found that high expression levels of FcεRI on basophils were linked to fast response.[17]

Some evidence exists that low total IgE levels might be an indicator of poor response omalizumab therapy.[18] However, no standard threshold levels have been established and total IgE levels have not shown to provide any indication on the overall effectiveness rate or speed of response.

The use of predictors of early and good response of CSU patients to omalizumab treatment would be of great value to identify treatment candidates and improve expectation management in a personalized treatment regimen. Besides, it would provide physicians with tools to decide on the course of treatment such as up-dosing or changing of treatment. These features will greatly improve patient's quality of life as it might help reducing try-and-error-type treatments and shorten the time until disease control is achieved.

Since IgE-FcεRI receptor interaction is thought to be the culprit for CSU symptoms and the target of the mode of action of omalizumab therapy, we aimed to investigate the value of soluble FcεRI (sFcεRI) as a predictor of treatment response, due to its binding to IgE and possible interaction in IgE-mediated MC activation.

Elevated serum sFcεRI levels have been recently used as a biomarker of IgE-associated allergies, proposing 2 ng/mL as the cut-off value for clinically relevant levels.[19–21] The feature of elevated levels was supported by the molecular and cellular findings that are required for its release, such as specific IgE-mediated FcεRI crosslinking on MCs.[22] Once released, sFcεRI can stably bind circulating IgE and interfere with IgE detection tests[21] as well as inhibit IgE-mediated crosslinking in basophils and systemic anaphylaxis upon antigen exposure in murine models.[22] These findings suggest that sFcεRI might function as an 'endogenous omalizumab'.

Based on the inhibitory function of sFcεRI, its release upon IgE activation, the use as marker for allergies and its potential similarities with omalizumab mechanism of action, we aimed to investigate sFcεRI as a predictor of response to omalizumab in CSU.

MATERIALS AND METHODS

Patients

CSU patients ($n = 67$) were investigated at the Urticaria Center of Reference and Excellence (UCARE) at the Department of Dermatology and Allergy, Charité–Universitätsmedizin Berlin.[23] CSU was diagnosed, and disease activity was assessed according to the recent international EAACI/GA^{2}LEN/EuroGuiDerm/APAACI guideline for urticaria.[1] Patient characteristics are given in Tables S1 and Table S2. Patient blood samples and data were obtained as part of their clinical diagnostic workup. Serum was collected in yellow cap BD Vacutainer® SST II Advance tubes. After forming a clot (30 min), tubes were centrifuged at 2000 *g* for 10 min at 25°C and stored at −20°C for short-term and −80°C for long-term storage. All patients provided prior informed consent on the use of left-over serum as well as their clinical data for research purposes. As all analyses were performed retrospectively and anonymously, additional ethics approval was not needed or obtained. All patient's records were handled in an anonymous manner following data protection laws and regulations and local ethics recommendations.

Omalizumab treatment

CSU patients were treated according to the international urticaria guideline, initially with antihistamines in up to fourfold daily doses and subsequently, after failure to respond to treatment, with 300 mg omalizumab injections subcutaneously administered every 4 weeks.[1] The results of response to treatment were previously published.[18,24]

Evaluation of response to treatment

Starting 1 week before treatment, patients were advised to fill out a daily symptom diary. Urticaria activity was assessed using the 7-day urticaria activity score (UAS7). This composite score is a sum score of daily assessed number of wheals (scores 0–3) and itch severity (0–3) of seven consecutive days, resulting in a maximum of 42 points. Treatment response, 4 weeks after the first treatment, was assessed by UAS7 as follows: <30% reduction of UAS7 score (non-responder), 30%–90% reduction (partial responder) and >90% reduction (complete responder).

In terms of speed of response, patient's diaries were evaluated by rolling UAS7 (rUAS7[25]). Using the rUAS7, we analysed if patients reached, at any time point, on 7 consecutive days a UAS7 of 0 or lower than 6, and if so, at which day after treatment initiation.

Disease control was assessed using the four-item urticaria control test (UCT) before and 4 weeks after treatment initiation.[26] Response to treatment was assessed by UCT as follows: UCT score of <12 (poorly controlled disease) and UCT

≥12 (well-controlled disease). The latter group was further separated into UCT = 12–15 (well-controlled disease) and UCT = 16 (complete controlled disease). Clinically relevant improvement was defined as an increase in UCT of at least three points.[27]

sFcεRI assessment

Serum sFcεRI levels were analysed by ELISA (#BMS2101-2, ThermoFisher Scientific, USA) according to manufacturer's protocol as previously described.[21] A highly significant and strong correlation between total and IgE-bound sFcεRI ($r = 0.974$, $p < 0.001$) allowed that only total sFcεRI was used.

Statistical analyses and software

Statistical analyses were performed using Prism 8 (GraphPad Software) or SPSS. Normality tests (D'Agostino and Pearson) failed to confirm normal distribution on sFcεRI levels, so median levels and interquartile range (IQR) were used. In tables, mean and standard error mean (SEM) data are also included. Correlations were calculated by Spearman rank correlation, and correlation coefficients are displayed as '*r*'. Statistical analysis was performed using Mann–Whitney test for two unmatched groups and Kruskal–Wallis plus Dunn's multiple correction for multiple comparisons between three or more groups. Chi-square analysis was performed for comparison of categorical variables. ROC curve analysis with Wilson/Brown method was performed with a confidence interval of 95%. A p value ≤ 0.05 was considered significant.

RESULTS

Elevated baseline sFcεRI is linked to disease control after the first administration of omalizumab

UCT data were available for 64/67 CSU patients treated with omalizumab, and 39 (61%) of them achieved disease control, that is UCT ≥12, within 4 weeks. Among these, 20 and 19 patients achieved well controlled (UCT = 12–15) and completely controlled (UCT = 16) disease, respectively. The remaining 25 patients had poorly controlled disease (UCT < 12) at the end of Week 4 after the first omalizumab treatment (Table 1 and Figure S1).

Pre-treatment sFcεRI levels were significantly higher in patients who achieved controlled disease, that is mean ± SD = 6.5 ± 11.5 ng/mL, as compared to 2.9 ± 3.5 ng/mL in those who did not ($p = 0.03$, Figure 1a and Table S1). Patients with UCT = 12–15 at Week 4 had threefold higher baseline sFcεRI levels (8.8 ± 15.5 ng/mL) as compared to those with UCT < 12 (2.9 ± 3.5 ng/mL; $p = 0.07$). Also, patients with clinically relevant improvement (UCT increase of ≥3) within the first 4 weeks of treatment showed numerically higher baseline sFcεRI levels (6.1 ± 11.2 ng/mL) as compared to patients without (3.5 ± 4.3 ng/mL, $p = 0.36$, Figure 1b and Table S1).

TABLE 1 Number of CSU patients with different response rates presenting low or elevated (>2 ng/mL) baseline sFcεRI levels.

Type of response	Number of patients for baseline sFcεRI (*N*, %)		Total number of patients (*N*)
	>2 ng/mL	<2 ng/mL	
Response as reduction in UAS7			
All patients	39 (62%)	24 (38%)	65
UAS7 < 30%	8 (50%)	8 (50%)	16
UAS7 > 30%	31 (66%)	16 (34%)	47
UAS7 = 30–90%	22 (63%)	13 (37%)	35
UAS7 > 90%	9 (75%)	3 (25%)	12
Response as UCT score			
All patients	39 (61%)	25 (39%)	64
UCT < 12	11 (44%)	14 (56%)	25
UCT ≥ 12	28 (72%)	11 (28%)	39
UCT = 12–15	14 (70%)	6 (30%)	20
UCT = 16	14 (74%)	5 (26%)	19

Abbreviations: UAS7, weekly urticaria activity score; UCT, urticaria control test.

When applying a pre-established cut-off for elevated sFcεRI levels, patients with elevated pre-treatment sFcεRI levels (>2 ng/mL) showed high rates of controlled disease at Week 4 (Figure S2). Of 39 patients with elevated sFcεRI, more than two thirds (28, 72%) achieved UCT ≥12, of which 14/20 (70%) and 14/19 (74%) had UCT = 12–15 and UCT = 16, respectively. In contrast, less than half of patients (11 of 25, 44%) with normal baseline sFcεRI had controlled disease at Week 4, with only six (30%) and 5 (26%) patients achieving UCT = 12–15 and UCT = 16, respectively ($p = 0.06$, Figure 1c and Table 1).

Patients with elevated baseline sFcεRI showed better improvement in UCT scores (+6.3 ± 0.7 points) and higher mean UCT scores (11.7 ± 0.7 points) at Week 4 as compared to patients with normal levels (+5.3 ± 0.9 points and 10.3 ± 0.9 points, respectively; Figure 1d,e), although these differences did not reach significance ($p = 0.39$ and $p = 0.22$, respectively). Elevated sFcεRI levels were significantly associated with overall achieving disease control ($p = 0.03$).

CSU patients with elevated baseline sFcεRI show better reduction of disease activity

Disease activity 4 weeks after omalizumab treatment as assessed by UAS7 was reduced by at least 30% in 47 (70%) of 63 CSU patients for which UAS7 data were available. Specifically, 12 (19%) patients showed complete UAS7 response, that is >90% reduction, and 35 (56%) patients had partial response, that is a UAS7 reduction of 30%–90% (Table 1).

Mean pre-treatment sFcεRI levels were numerically higher in patients who had >30% reduced disease activity at Week 4 as compared to those who did not, that is 5.8 ± 10.6

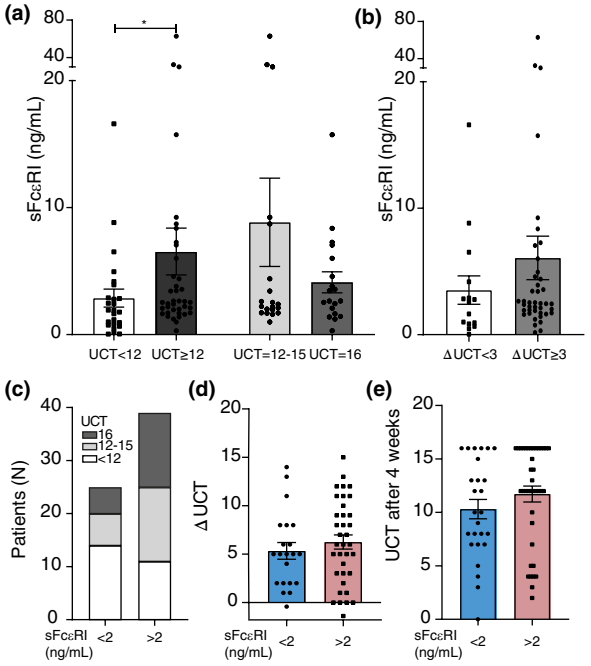

FIGURE 1 Baseline serum sFcεRI is significantly elevated in CSU patients who achieved disease control. Comparison of baseline sFcεRI levels according to UCT (a) and change in UCT 4 weeks after treatment (b). Number of patients for types of disease control with elevated (>2 ng/mL) or normal sFcεRI levels (c). Mean change in UCT (d) and absolute UCT values 4 weeks after treatment (e) in patients with elevated or normal sFcεRI levels. Bars for sFcεRI levels represent the median, and error bars represent IQR. Mann–Whitney and one-way ANOVA tests were performed; where $*p < 0.05$. IQR, interquartile range; UCT, urticaria control test.

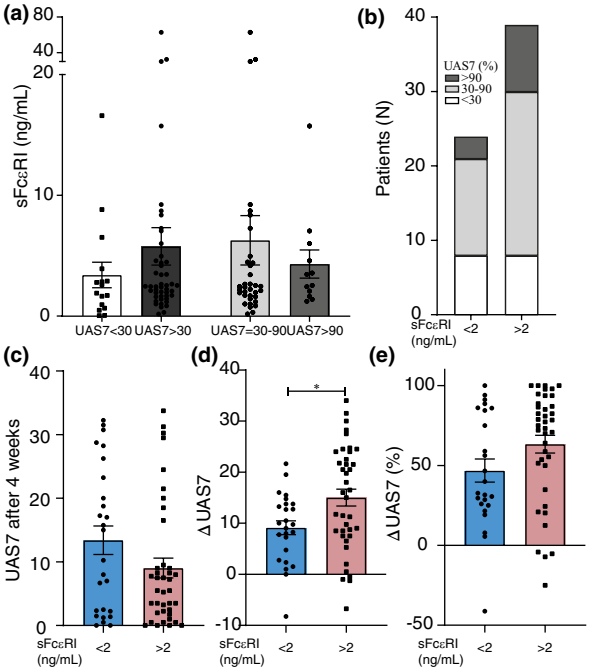

FIGURE 2 Baseline serum sFcεRI is significantly elevated in CSU patients who respond well to treatment. Comparison of baseline sFcεRI levels according to level of UAS7 reduction (a). Number of patients for types of disease control with elevated (>2 ng/mL) or normal sFcεRI levels (b). Mean UAS7 score (c), change in mean UAS7 score in absolute numbers (d) or percentage (e) in patients with elevated or normal serum sFcεRI levels. Bars for sFcεRI levels represent the median, and error bars represent IQR. Mann–Whitney and one-way ANOVA tests were performed; where $*p < 0.05$. IQR, interquartile range; UAS7, weekly urticaria activity score.

versus 3.4 ± 4.2 ng/mL ($p = 0.35$, Figure 2a and Table S1). Of the 12 and 35 patients who achieved UAS7 reduction of >90% and 30%–90% at Week 4, 9 (75%) and 22 (63%), respectively, had elevated baseline sFcεRI levels, as compared to only 8 of 16 (50%) without meaningful reduced disease activity (<30% UAS7 reduction, $p = 0.36$, Table 1).

Despite having comparable baseline UAS7 levels, (Figure S2), patients with elevated baseline sFcεRI levels were more likely to achieve disease reduction of 30% or more as compared to patients with normal sFcεRI, that is 31 of 39 (79%) versus 16 of 24 (67%) (Figure 2b). Mean UAS7 after treatment remained numerically higher in patients with normal sFcεRI levels as compared to patients with elevated levels ($p = 0.22$, Figure 2c). Also, patients with elevated baseline sFcεRI showed significantly more UAS7 reduction (−15 ± 1.7 points) at Week 4 as compared to patients with normal levels (−9 ± 1.4, $p = 0.02$, Figure 2d,e).

CSU patients with elevated sFcεRI levels respond earlier than those with normal levels

As early as 1 week after the start of omalizumab treatment, UAS7 values were lower in patients with elevated pre-treatment sFcεRI levels as compared to those with normal sFcεRI, reaching statistical significance at Week 3 ($p = 0.03$, Figure 3a). To evaluate the speed of response, we used the rolling UAS7 (rUAS7), and patients with elevated sFcεRI achieved rUAS7 ≤ 6 4 days earlier and rUAS7 = 0 2 days earlier than those without, on average at Day 9 ± 1 versus 13 ± 2 and Day 12 ± 1 versus 14 ± 2, respectively ($p = 0.08$ and $p = 0.45$, respectively, Figure 3b). Also, mean baseline sFcεRI levels were numerically higher in patients who achieved rUAS7 ≤ 6 at any time point within the 4-week period as compared to those who did not (5.7 ± 10.6 vs. 3.5 ± 4.3, $p = 0.28$, Figure 3c and Table S1).

By Week 4, 48% and 65% of patients with elevated sFcεRI achieved rUAS7 = 0 and ≤6, respectively, as compared to 42% and 50% of patients with normal pre-treatment sFcεRI ($p < 0.001$, Figure 3d,e).

Baseline total IgE levels are not good predictors of response to first omalizumab administration

Baseline serum total IgE and sFcεRI levels were significantly correlated ($r = 0.36$, $p < 0.01$) in CSU patients (Figure S3a), but pre-treatment IgE levels did not show significant differences between responder and non-responders based on UCT, reduction in UAS7, or rUAS7 (Figure S3b–d and Table S2)

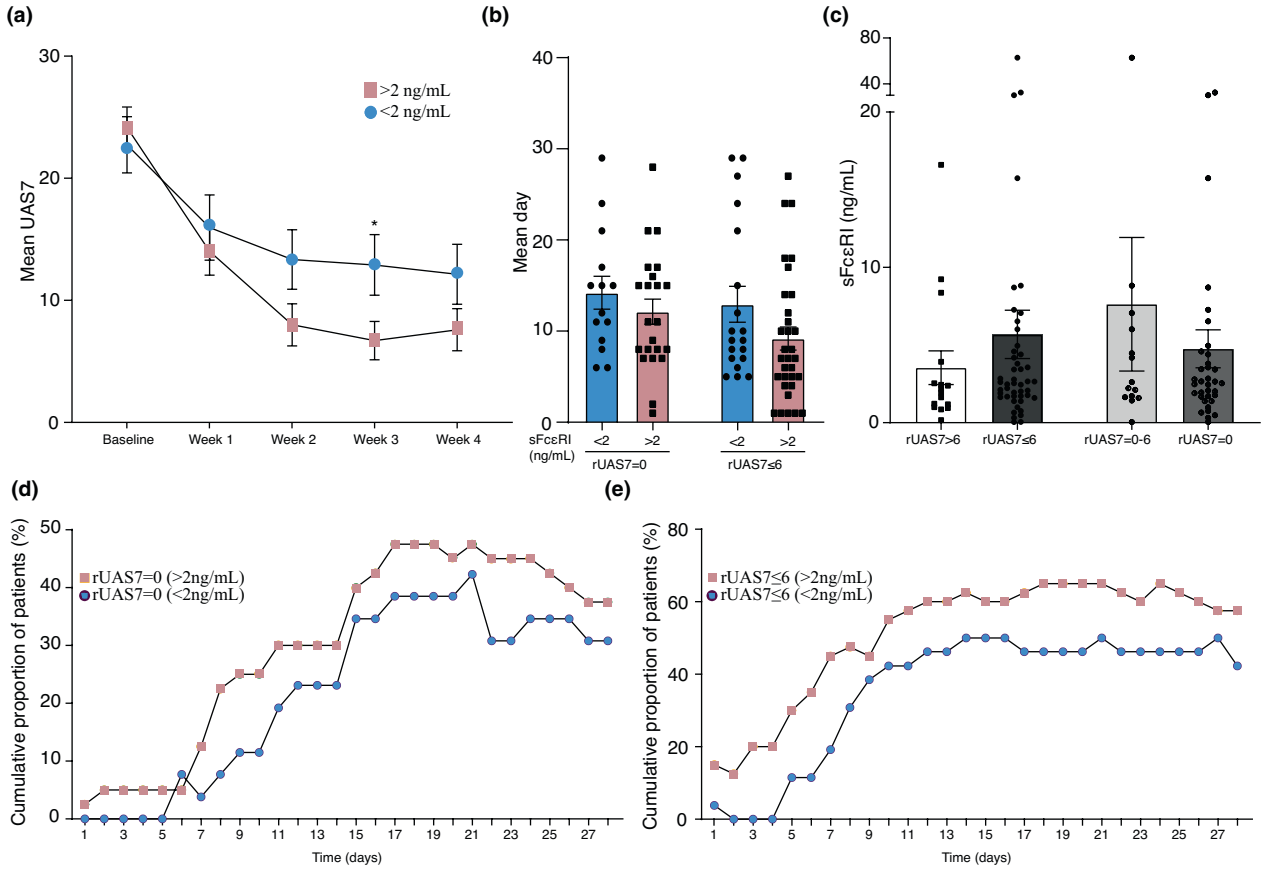

FIGURE 3 Elevated serum sFcεRI is associated with early response to omalizumab treatment. Comparison of elevated (>2 ng/mL) vs normal serum sFcεRI and response to treatment assessed by mean UAS7 at baseline and Weeks 1–4 after treatment (a). Comparison of time as days to respond between patients with elevated and normal sFcεRI levels assessed by rUAS7 = 0 and ≤6 (b). Comparison of baseline sFcεRI levels according to rUAS7 within 4 weeks after treatment (c). Cumulative proportion of patients achieving rUAS7 = 0 (d) or ≤6 (e) in patients elevated or normal sFcεRI levels. Bars for sFcεRI levels represent the median, and error bars represent IQR. Circles and squares (d,e) represent the mean. Mann–Whitney and one-way ANOVA test were performed; where $*p < 0.05$; IQR, interquartile range; rUAS7, rolling UAS7; UAS7, weekly urticaria activity score.

within the first 4 weeks of treatment. However, there was a trend towards higher baseline IgE levels in responders.

sFcεRI of >2 ng/mL is a suitable cut-off for the prediction of response to omalizumab treatment

ROC analyses showed that sFcεRI of >2 ng/mL was well suited to predict well-controlled disease (UCT ≥12) at Week 4 with 72% sensitivity and 56% specificity (Figure 4a). Highest sensitivity and specificity, up to 81% and 56%, respectively, were achieved with sFcεRI levels between 1.7 and 2.0 ng/mL. The optimal cut-off to differentiate between responders and non-responders assessed by UCT was 1.9 ng/mL, similarly as for other response assessments (Figure 4 and Figure S4).

DISCUSSION

Here, we report the first indicator of fast and good response to omalizumab treatment in CSU patients, sFcεRI. The most relevant finding of our study is that elevated sFcεRI serum levels (>2 ng/mL) before treatment are associated with good and fast response to omalizumab after the first application, with respect to disease activity and control.

The rates of response within 4 weeks in our cohort (61% with UCT ≥12 and 70% with >30% reduction in UAS7) are in line with previous studies, which showed that omalizumab is an effective therapy for most but not all CSU patients.[25,28,29] The response to omalizumab treatment can occur after several months in late responders, or never, in non-responders.[30–32]

Several previous studies aimed to identify biomarkers that predict response to omalizumab treatment in CSU patients. These studies largely focused on overall response following patients for several months and repeated injections. Clinical scores like UAS7, as well as markers of inflammation,[33] basophil count or activation tests[34–37] or ASST[25] were predictive in single studies but failed to predict treatment response in meta-analyses.[38,39] The only biomarker with predictor potential confirmed by meta-analysis was total IgE, which is linked to omalizumab

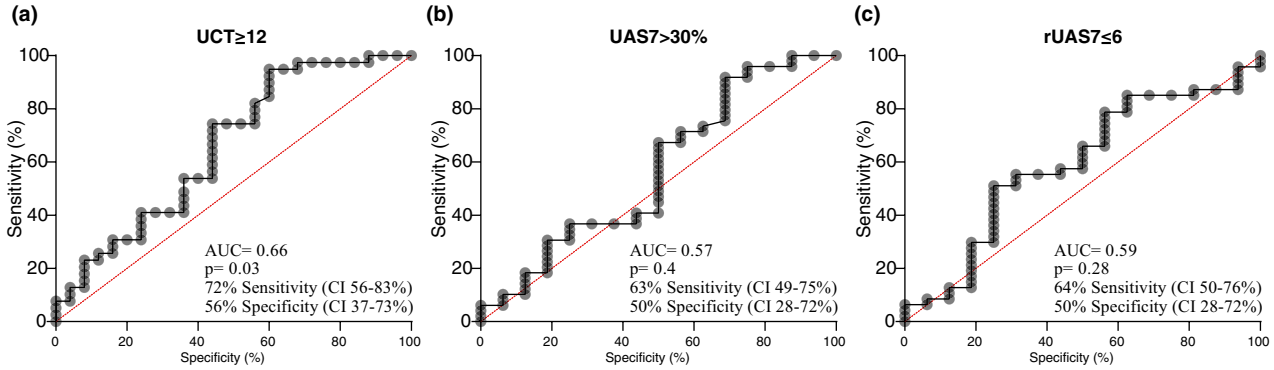

FIGURE 4 ROC analysis of 2 ng/mL as cut-off as predictor of response to treatment. ROC curve analysis for serum sFcεRI using 2 ng/mL as cut-off to predict response evaluated as UCT ≥12 (a), reduction of UAS7 > 30% (b) and rUAS7 ≤ 6 (c). ROC curve analysis with Wilson/Brown method was performed with a confidence interval of 95%. AUC, area under the curve; CI, confidence interval; ROC, Receiver operating characteristic; rUAS7, rolling UAS7; UAS7, weekly urticaria activity score; UCT, urticaria control test.

treatment outcomes in both asthma and chronic urticaria.[40,41] In CSU, elevated total IgE levels predict an overall good response, whereas very low levels before treatment start are usually associated with poor response, even after several injections and up-dosing in some cases.[38] However, no clear cut-off could be established so far, and some patients with low total IgE show good response to omalizumab treatment.[42]

In our study, total IgE levels did not show a good prediction of response within the first 4 weeks after omalizumab treatment. In contrast, elevated pre-treatment sFcεRI levels were significantly associated with higher reduction rates in disease activity and the achievement of better disease control within this time frame. However, some patients with elevated sFcεRI levels did not show response after 4 weeks of treatment (13% of patients for reduction of UAS7 and 17% for UCT). By using the rolling UAS7 score,[25] a novel analysis that provides a more detailed view on the onset of response, we confirmed that a faster and sustained response was achieved by patients with elevated pre-treatment sFcεRI levels. Overall, these patients experienced improvement 2 or 4 days earlier than patients with normal sFcεRI levels.

In previous studies, a serum sFcεRI level above 2 ng/mL was shown to be associated with clinically relevant IgE sensitization and presence of symptoms.[21,43] In this study, we confirmed that the use of 2 ng/mL as cut-off for serum sFcεRI levels for CSU patients is suitable and predicts disease control with high specificity.

Previous studies have elucidated that the release of sFcεRI is linked to IgE-mediated MC activation.[22] Although this study did not aim to further characterize the biology of sFcεRI, in CSU it can be speculated that elevated sFcεRI is linked to IgE-mediated MC activation, that is autoallergic mechanisms, in these patients. This would explain why patients with elevated serum sFcεRI respond fast and well to an anti-IgE therapy. However, elevated serum sFcεRI could also be present because of other bystander allergic diseases, rather than CSU, and merely reflect an atopic predisposition, rather than a true pathophysiologically important factor for CSU.

Limitations of the study are the retrospective study design and the limited patient numbers of a preselected patient cohort of a tertiary centre. It is possible that some patients would have become responders after subsequent treatment cycles or remain without sufficient disease control, even after a long treatment period. Among our non-responders within the first 4 weeks, 38% and 54% presented elevated total IgE levels (for UAS7 and UCT, respectively) indicating that some of them might become responders over time.[39] However, this study demonstrated an interesting potential marker for managing treatment expectations and, once novel treatment options become available, maybe even for treatment decisions. Its predictive properties may be increased by combining sFcεRI with other markers of fast and good response, which remain to be identified and characterized, since most likely no single biomarker is sufficient to identify the complex pathophysiology behind symptoms. Our findings call for further prospective studies with more diverse and larger cohorts of CSU patients, with omalizumab and non-IgE targeted treatments.

In summary, we showed that patients with elevated sFcεRI levels respond earlier and better than those with levels below 2 ng/mL upon omalizumab treatment initiation. This information might help physicians to identify patients who can be expected to show fast benefit from this therapy.

AUTHOR CONTRIBUTIONS

SMR performed experiments, analysed data and prepared the manuscript. PK and JS analysed data. ZS, TO, KW and MMe contributed to patient recruitment and data collection. SMR, MMa and SA contributed to the preparation of the manuscript.

ACKNOWLEDGEMENTS

We thank all colleagues from the study team and the laboratory team involved in patient recruitment and Beate Schinzel, for her help with submission. Open Access funding enabled and organized by Projekt DEAL.

FUNDING INFORMATION

SMR was supported by an EFIS-IL Fellowship. PK and SMR were supported by a GA²LEN fellowship. This project benefitted from the support of the GA²LEN network of urticaria centres of references and excellence (UCAREs; www.ga2len-ucare.com).

CONFLICT OF INTEREST STATEMENT

SMR, TO, KW, MMe and JS have no conflicts of interest. PK was a speaker and/or consultant for Novartis, Roche and ValenzaBio. ZS is or recently was a speaker and/or advisor for Sanofi, Novartis, Nutricia and AImmune. MMa is or recently was a speaker and/or advisor for and/or has received research funding from Allakos, Amgen, Aralez, ArgenX, AstraZeneca, Celldex, Centogene, CSL Behring, FAES, Genentech, GIInnovation, GSK, Innate Pharma, Kyowa Kirin, Leo Pharma, Lilly, Menarini, Moxie, Novartis, Pfizer, Roche, Sanofi/Regeneron, Third Harmonic Bio, UCB and Uriach. SA is or recently was a speaker and/or advisor for and/or has received research funding from AstraZeneca, Allakos, Biocryst, CSL Behring, Sanofi, Takeda, ThermoFisher, Moxie and Novartis.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Moñino-Romero S, Kolkhir P, Ohanyan T, Szépfalusi Z, Weller K, Metz M, et al. Elevated baseline soluble FcεRI may be linked to early response to omalizumab treatment in chronic spontaneous urticaria. J Eur Acad Dermatol Venereol. 2024;38:167–174. https://doi.org/10.1111/jdv.19485