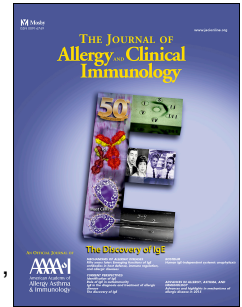


Accepted Manuscript

Elevated IgE levels are linked to faster relapse in omalizumab-discontinued chronic spontaneous urticaria patients

Ragip Ertas, M.D., Kemal Ozyurt, M.D., Emin Ozlu, M.D., Yilmaz Ulas, M.D., Atil Avci, M.D., Mustafa Atasoy, MD., Tomasz Hawro, M.D., Marcus Maurer, M.D.



PII: S0091-6749(17)31351-9

DOI: [10.1016/j.jaci.2017.08.007](https://doi.org/10.1016/j.jaci.2017.08.007)

Reference: YMAI 12979

To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 13 February 2017

Revised Date: 4 August 2017

Accepted Date: 17 August 2017

Please cite this article as: Ertas R, Ozyurt K, Ozlu E, Ulas Y, Avci A, Atasoy M, Hawro T, Maurer M, Elevated IgE levels are linked to faster relapse in omalizumab-discontinued chronic spontaneous urticaria patients, *Journal of Allergy and Clinical Immunology* (2017), doi: 10.1016/j.jaci.2017.08.007.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Elevated IgE levels are linked to faster relapse in omalizumab-discontinued chronic spontaneous urticaria patients

Ragip Ertas^a, M.D., Kemal Ozyurt^a, M.D., Emin Ozlu^a, M.D., Yilmaz Ulas^a, M.D., Atil Avci^a, M.D., Mustafa Atasoy^a, MD. Tomasz Hawro^b, M.D. and Marcus Maurer^b, M.D.

^aSaglik Bilimleri University, Kayseri Education and Research Hospital Dermatology Clinic, Turkey

^bDept. of Dermatology and Allergy, Charité - Universitätsmedizin Berlin, Germany

Corresponding author:
Marcus Maurer, MD
Charité - Universitätsmedizin Berlin
Department of Dermatology and Allergy
Charitéplatz 1
Berlin, 10117 GERMANY
Email; marcus.maurer@charite.de; beate.schinkel@charite.de

Keywords: Chronic spontaneous urticarial; IgE; Relapse; Omalizumab

26 Capsule Summary

27 Total IgE levels predict the time to relapse after omalizumab discontinuation. Complete
28 responders with elevated baseline IgE levels show shorter time to relapse after discontinuation
29 of omalizumab as compared to patients with normal IgE levels.

30

31

32

33

To the Editor:

Omalizumab is effective in chronic spontaneous urticaria (CSU), but little is known about what predicts the response.¹ Recently, Palacios et al and Gericke et al reported that CSU patients with basophil-activating serum activity are less likely to show complete and fast response to omalizumab, respectively.^{2,3} Clinically, most CSU patients, who stop omalizumab treatment, relapse within a few months after the last application, and re-treatment with omalizumab generally results in rapid remission. It is currently unclear, which patient features, if any, are linked to relapse or the time to relapse after stopping omalizumab.

This prospective observational study assessed 93 CSU patients during 2014-2016 for relapse and time to relapse after stopping omalizumab. Patients had an average disease duration of 48 (2-330) months, and total IgE serum level of 81 (7-1540) IU/ml and, clinical findings were independent of the patients atopic status. Patients and physicians, independently, used a visual analog scale (VAS) to rate the overall severity of urticaria signs and symptoms during the previous month. The VAS is a 10-cm scale, where 0 and 10 corresponds to no urticaria signs and symptoms of maximum severity, respectively. At baseline, CSU activity was high as assessed by UAS (Urticaria activity score)(6,3-6), physicianVAS (9,4-10), and patientVAS (9,5-10). Complete responders (CR) showed complete remission (UAS:0, VAS:0) after 12 weeks of omalizumab treatment, and antihistamines and omalizumab were discontinued, as called for by the Turkish reimbursement rules. Most CSU patients benefited from omalizumab treatment: 12 weeks after the start of treatment, 44 patients (47%) showed complete response, and 36 (39%) showed partial response. Thirteen patients (14%) were non-responders (NR). The female: male ratio was highest in NR, lower in partial responders and lowest in CR ($\chi^2=6.86$, $p=0.032$) (Table 1).

After the completion of the 12-week treatment phase, we discontinued omalizumab in the CR and monitored them for relapse for at least 52 weeks. Relapse was defined as the

reappearance of both, hives and pruritus. Only 15 patients showed sustained remission, whereas 29 showed relapse. Total IgE serum levels before omalizumab treatment correlated negatively with the time to relapse after discontinuation of omalizumab in CR ($R_s = -0.456$, $p = 0.019$, $n = 26$). Kaplan-Meier estimates revealed that CR with elevated baseline total IgE levels showed shorter time to relapse after discontinuation of omalizumab than patients with normal IgE levels (log-rank test, $\chi^2 = 5.78$, $p = 0.016$) (Fig 1). Total IgE levels of ≥ 100 IU/ml were defined as elevated levels, based on the reference range of our laboratory.

In contrast, there was no correlation of pre-treatment total IgE levels with time to response to omalizumab ($R_s = -0.084$, $p = 0.612$, $n = 39$), and no difference in the time to response to omalizumab treatment between patients with elevated and normal IgE levels. Time to response and time to relapse after discontinuation of omalizumab therapy did not correlate with each other ($r = -0.239$, $p = 0.232$).

In the current study, most CR patients show relapse after discontinuation of omalizumab within several weeks. We demonstrate for the first time that increased serum levels of total IgE are linked to faster relapse of CSU after discontinuation of omalizumab.

In this study, NR were more frequently female (18%) than male (7%). The reasons for this difference are currently unknown. Asero previously proposed that most female but not male patients have autoimmune CSU as assessed by autologous serum skin testing.⁴

Serum levels of total IgE are held not to be relevant for the probability of CSU patients to respond to omalizumab or the time it takes for them to do so.⁵ The present study confirms this. Importantly, our study shows that serum levels of total IgE do correlate with time to relapse of CSU after stopping omalizumab treatment. The higher the IgE levels, the less time it takes for CSU symptoms to return after omalizumab is discontinued. Specifically, the time to relapse was significantly shorter in CSU patients with high IgE (> 100 IU/ml) as compared to normal IgE. Measuring IgE before omalizumab therapy may, therefore, help to predict and

avoid quick relapse in patients who have to or want to check the need to continue their omalizumab treatment by stopping it.

Why are high IgE levels linked to faster CSU relapse after discontinuation of omalizumab?

The underlying mechanisms are currently unclear but probably involve factors that modulate the speed by which IgE levels recover and return to relevant levels such as the production of IgE and the half-life of omalizumab.⁶ Serum IgE levels are critically determined by the rate of IgE production and its clearance,⁷ and they have a greater dependence on the former than the latter.⁸ IgE clearance from the blood is short (up to a few days) and of low variability.⁹ Patients with high IgE levels and high rates of IgE production can be expected to reach relevant IgE levels more quickly, following omalizumab discontinuation, than those with normal IgE levels.¹⁰

Our study has several strengths and limitations. With our recent observation that CSU patients with basophil-activating serum activity respond slower to omalizumab, it would have been interesting to perform the autologous serum skin test and a basophil activation assay in all patients before, during and after omalizumab treatment.⁵

Our study confirms that CSU patients show different patterns of response to omalizumab, quick versus slow remission, complete versus partial versus no remission. It also provides novel insights on what may be responsible for these different response patterns (patient gender) and what is probably not responsible (e.g. duration of disease, age of patient). Most importantly, our findings demonstrate that CSU patients also show different patterns of response to stopping their omalizumab treatment, i.e. fast relapse or slow relapse or no relapse. The fact that high IgE levels are linked to fast CSU relapse after cessation of omalizumab treatment supports the notion that the signs and symptoms, at least in patients with elevated IgE, are driven by the activation of mast cells by IgE rather than by other mechanisms. Further large-scale studies are needed to elucidate the role of IgE in CSU.

References

1. Zhao, Z., Ji, C., Yu, W., Meng, L., Hawro, T., Wei, J. F., and Maurer, M.: Omalizumab for the treatment of chronic spontaneous urticaria: a meta-analysis of randomized clinical trials. *J. Allergy Clin. Immunol.* 2016; 137; 1742-1750.
2. 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.
3. Gericke, J., Metz, M., Ohanian, T., Weller, K., Altrichter, S., Skov, P. S., Falkenchrone, S., Brand, J., Kromminga, A., Hawro, T., Church, M. K., and Maurer, M.: Serum autoreactivity predicts time to response to omalizumab therapy in chronic spontaneous urticaria. *J. Allergy Clin. Immunol.* 2017; 139; 1059-1061.
4. Asero R. Sex differences in the pathogenesis of chronic urticaria. *J Allergy Clin Immunol* 2003; 111:425-6.
5. Gericke J, Metz M, Ohanian T, Weller K, Altrichter S, Skov PS, et al. Serum autoreactivity predicts time to response to omalizumab therapy in chronic spontaneous urticaria. *J Allergy Clin Immunol* 2016; in press.
6. Slavin RG, Ferioli C, Tannenbaum SJ, Martin C, Blogg M, Lowe PJ. Asthma symptom re-emergence after omalizumab withdrawal correlates well with increasing IgE and decreasing pharmacokinetic concentrations. *J Allergy Clin Immunol* 2009; 123:107-113.e3.
7. Hayashi N, Tsukamoto Y, Sallas WM, Lowe PJ. A mechanism-based binding model for the population pharmacokinetics and pharmacodynamics of omalizumab. *Br J Clin Pharmacol* 2007; 63:548-61.

- 131 8. Lowe PJ, Tannenbaum S, Gautier A, Jimenez P. Relationship between omalizumab
132 pharmacokinetics, IgE pharmacodynamics and symptoms in patients with severe persistent
133 allergic (IgE-mediated) asthma. *Br J Clin Pharmacol* 2009; 68:61-76.
- 134 9. Fick RB Jr, Fox JA, Jardieu PM. Immunotherapy approach to allergic disease. *Immuno*
135 *pharmacology* 2000; 48:307-10.
- 136 10. Corren J, Shapiro G, Reimann J, Deniz Y, Wong D, Adelman D, et al. Allergen skin tests
137 and free IgE levels during reduction and cessation of omalizumab therapy. *J Allergy Clin*
138 *Immunol* 2008; 121:506-11.

139

Table I. Characteristics of study patients according to levels IgE<100 IU/mL and IgE>100 IU/mL and baseline characteristics of patients according to treatment response

	IgE < 100 IU/mL n=48	IgE > 100 IU/mL n=35	p	CR n =44	PR n= 36	NR n = 13	p
Age in years, mean ± SD	37.71 ± 13,66	33.44 ± 9.85	0.198(b)	35.20 ± 11.76	40.94 ± 11.60	37.31 ± 8.98	0.085(c)
Female, n (%)	34 (70,8)	20 (57,)	0.196(d)	24 (54,5)	28 (77,8)	11 (84,6)	0.032(d)
Male, n (%)	14 (29,2)	15 (42,9)		20 (45,5)	8 (22.2)	2 (15,4)	
Duration of disease in months, median (IQR)	57.5 (13.5-120.0)	48.0 (18-96)	0.545(a)	36 (12-72)	90 (15-132)	72.0 (30.5-180.0)	0.043(e)
Baseline UAS, median (IQR)	6 (4.25-6)	5 (5-6)	0.840(a)	5 (4.25-6)	5.5 (5.0-6.0)	6.0 (4.5-6.0)	0.725
Number of responders in 1st, 2nd and 3th months, (%)	1st :7 (33.3%)	1st :7 (38.9%)	0.679(d)				
	2nd:6 (28.6%)	2nd:3 (16.7%)					
	3th:8 (38.1%)	3th:8 (44.4%)					
Relapse rate	27.1 %	37.1 %	0.329(d)				
Time to relapse in weeks, median (IQR)	10 (5 – 30.5)	4 (1.5 – 7.5)	0.022(a)				

(a)Mann Whitney U test, (b)Student t test, (c)Anova Test, (d)Chi-square test, (e)Kruskal-Wallis test, Dunn-Bonferroni post-test corrected for multiple comparisons was not significant for any of the pairs tested.

Abbreviations: CR: Complete responder, PR: Partial responder, NR: Non-responder, SD: standard deviation; IgE: immunoglobulin E, IQR: interquartile range, UAS: urticaria activity score.

FIGURE:

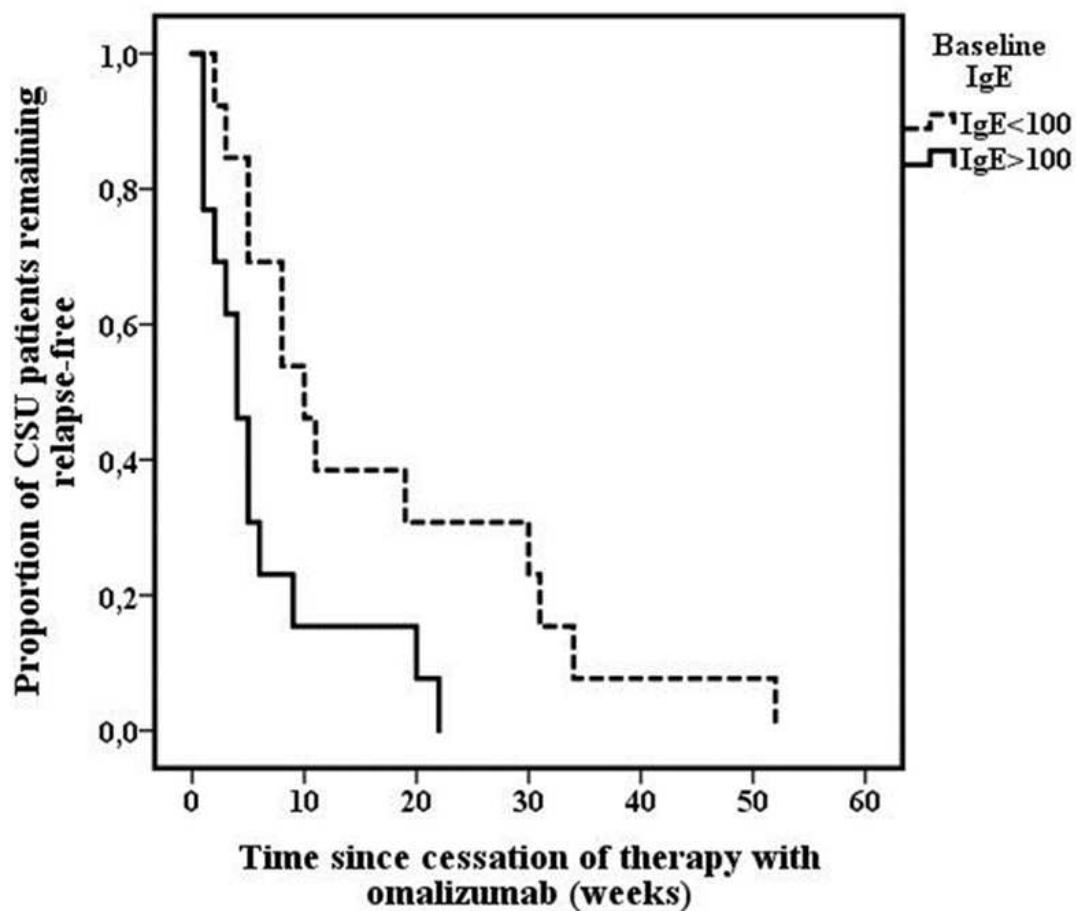


FIG 1. Relapse time in patients with normal (<100 IU/mL) and elevated (>100 IU/mL) IgE levels*

Abbreviations: IgE, immunoglobulin E

*Kaplan-Meier plot. Time to relapse after discontinuation of omalizumab was shorter in complete responders with elevated baseline total IgE as compared to patients with normal IgE levels (log rank test, $\chi^2 = 5.78$, $p = 0.016$, $n = 26$)