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IgE and D-dimer baseline levels are higher in responders than non-responders to omalizumab in chronic spontaneous urticaria

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Running head: IgE and D-dimer baseline levels in CSU patients treated with omalizumab

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Dear Editor,

Recently, it has been demonstrated that IgE levels may predict the clinical response to omalizumab treatment in chronic spontaneous urticaria (CSU) patients¹. The authors showed that baseline total IgE levels and notably the ratio between their levels at week 4 of treatment and baseline are predictors of response to omalizumab in CSU¹. In another recent study, IgE levels before treatment have been shown to be inversely proportional to CSU relapse time after omalizumab discontinuation². Other potential disease-related blood biomarkers of CSU activity are mean platelet volume, C-reactive protein, IL-6, F1 + 2 and D-dimer³. Since the activation of the coagulation cascade is involved in the pathophysiology of CSU⁴, we have previously studied D-dimer (a routinely available marker of coagulation and fibrinolysis activation) in CSU patients, demonstrating that its levels may parallel and predict the clinical response to omalizumab^{5,6}.

Here, we measured at the same time baseline IgE and D-dimer levels in plasma from patients with CSU before starting omalizumab treatment in order to see whether both biomarkers are higher in patients who will respond to the drug.

Total IgE and D-dimer were measured by immunoenzymatic methods in 25 adults (mean age 40.3 years, range 15-69 years; male/female 11/14) with severe CSU unresponsive to second-generation antihistamines at up to 4 times licensed dose (urticaria activity score over 7 days (UAS 7) > 30; mean disease duration 56.9 months; range 4-540 months). All patients underwent an at least 3-month cycle of omalizumab administered subcutaneously at the dose of 300 mg every 4 weeks. The UAS 7 was measured 12 weeks after the start of omalizumab and this parameter was used to subdivide patients into non-responders (no UAS 7 reduction or exacerbation), partial responders (UAS 7 reduction $\geq 30\%$), and complete responders (UAS 7 of 0).

Because data were positively skewed, they were log-transformed before analysis. The results are reported as anti-log values of means with standard deviation (SD). Student's *t*-test for unpaired values was used to assess statistical significance of differences between groups. Correlations were assessed by linear regression. The significance level was set at $p < 0.05$.

Baseline IgE levels were significantly lower in non-responders (16 ± 24 kUA/L) than in partial responders (115 ± 432 kUA/L; $p=0.017$) and complete responders (148 ± 114 kUA/L; $p=0.004$). Baseline D-dimer levels were also significantly lower in non-responders (162 ± 82 ng/ml) than in partial responders (676 ± 1957 ng/ml; $p=0.017$) and complete responders (619 ± 1599 ng/ml; $p=0.004$). Since no significant differences were evident between partial and complete responders both in IgE and D-dimer, the two groups were merged and simply

classified as responders. Figure 1 shows differences in plasma levels of IgE ($p=0.004$) and D-dimer ($p=0.001$) between responders and non-responders to omalizumab (panels A and B); the two parameters (IgE and D-dimer) were significantly correlated ($r=0.683$, $p=0.001$) in all CSU patients (panel C).

Different aetiopathogenic factors are responsible for symptoms variability in different subsets of CSU patients, and more than one pharmacological mechanism of omalizumab may be involved in clinical responses. Our findings show that, in the same CSU patients responders to omalizumab, the basal levels of two broadly accessible and inexpensive biomarkers like IgE and D-dimer are higher.

In conclusion, both IgE and D-dimer are potentially involved in the mechanism of action of omalizumab in CSU, and may be predictors of the therapeutic effectiveness of this drug. Further studies on larger series of CSU patients are needed to confirm the predictive value of these two biomarkers and to clarify how they are related to different endotypes of the disease.

Figure legend

Figure 1. Panels A and B: baseline plasma levels of total IgE and D-dimer in 20 patients with chronic spontaneous urticaria who were responders to omalizumab after 12 weeks of treatment and in 5 patients who were non-responders to the drug. Small horizontal lines indicate geometric means. Dotted lines indicate the lower and upper limit of the normal range.

Panel C: Correlation between baseline plasma levels of total IgE and D-dimer in responders (open circles) and in non-responders (open triangles) to omalizumab.

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Conflict of interest statement

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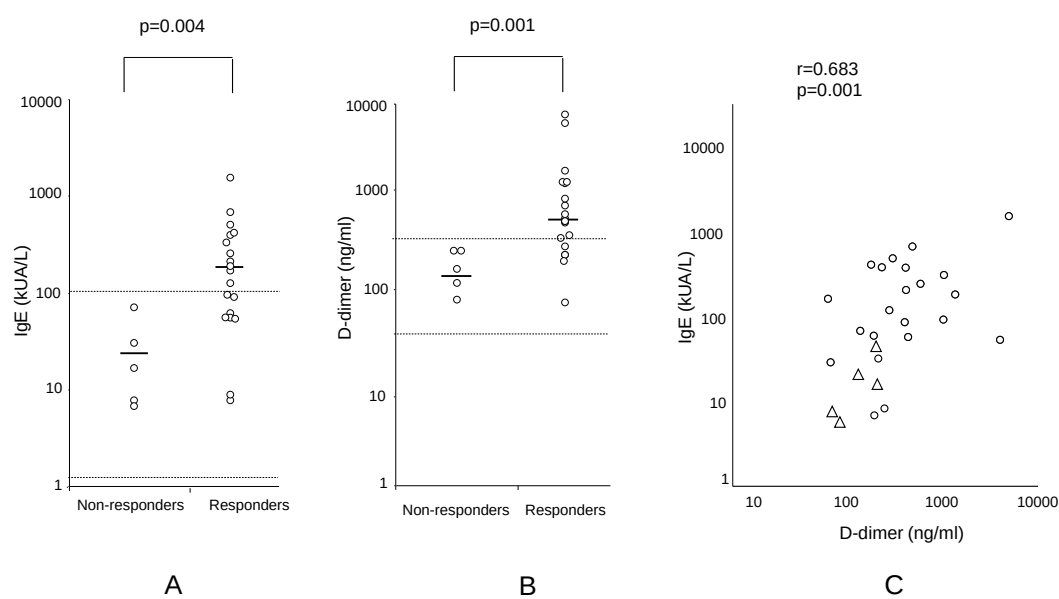


Figure 1