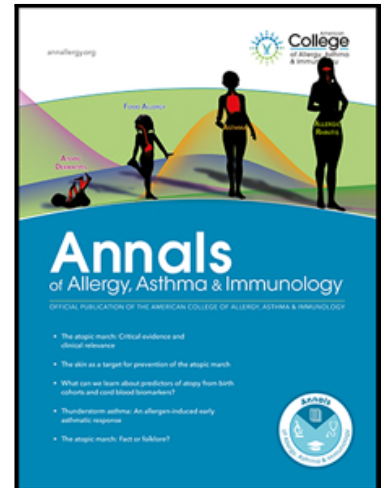


Characteristics of patients with chronic spontaneous urticaria showing early and complete responses to omalizumab

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Characteristics of patients with chronic spontaneous urticaria showing early and complete responses to omalizumab

Running head: Biomarkers of early complete responders

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Key words: chronic spontaneous urticaria, anti-IgE, omalizumab, basophil, CD63, FcεRI

ABBREVIATION

ASST: autologous serum skin test

BHRA: basophil histamine release assay

CSU: chronic spontaneous urticaria

CU-BAT: chronic urticaria basophil activation test

ISS7: weekly itch severity score

LTC4: leukotriene C4

UAS7: weekly urticaria activity score

Chronic spontaneous urticaria (CSU) affects large numbers of people, impacting quality of life and daily activities.¹ Omalizumab, a recombinant humanized anti-IgE monoclonal antibody, has shown its efficacy in treating CSU which might be through its ability on the reduction of the level of free IgE and subsequently reduction of the expression of high-affinity receptor for the Fc region of IgE (FcεRI) on mast cells and basophils.² In previous studies, more than half of the patients with CSU experienced rapid reductions of CSU severity within one week after the first dose of omalizumab.³⁻⁵ However, the characteristics of these rapid omalizumab responders is not well elucidated. In order to better figure out these rapid omalizumab responders, we performed a study in tertiary referral medical center in Northern Taiwan (IRB number: 201707023MIFB) to recruit patients with CSU from December 2017 to February 2019.

These patients should have a diagnosis of CSU for at least 3 months, a weekly urticaria activity score (UAS7)⁶ ≥ 16 and a weekly itch severity score (ISS7) ≥ 8 prior at baseline. Nineteen patients (four males and fifteen females, average age: 44.6 years, range: 23-62) were enrolled and received three subcutaneous injections, spaced 4 weeks apart, of 300 mg of omalizumab (at Week 0, Week 4,

and Week 8) and were then followed up for 2 months (from Week 12 to Week 20). The thyroid auto-antibodies were detected in 2 of the patients (10.5%). Baseline IgE levels were elevated in 12 of the patients (63.2%), with an average value of 357.1 IU/ml. Treatment responses to omalizumab were good. Nine (47.8%) and six (31.6%) patients achieved $UAS7 \leq 6$ and $UAS=0$ at Week 1, respectively. The highest numbers of patients achieving $UAS7 \leq 6$ and $UAS=0$ were observed at week 12 (15 patients, 78.9%) and week 8 (11 patients, 57.8%), respectively. These patients could be separated into three subgroups based on their treatment responses: early complete responders ($UAS7=0$ from Week 1 through Week 12, $n=5$), late complete responders ($UAS7=0$ after the second injection through Week 12, $n=4$), and fluctuant responders (those who ever had $UAS7 \leq 6$, $n=8$)/non-responders (those who never had $UAS7 \leq 6$, $n=2$).

We evaluated the expressions of FcεRI and CD63 on patients' basophils using flow cytometry. In brief, basophils are gated with a high expression of CD193 (BD Biosciences, New Jersey, U.S.A., No. 558208) in leukocytes. At the baseline, all patients had similar levels of basophil FcεRI (BioLegend, San Diego, U.S.A., No. 334609). The mean expressions of FcεRI reduced dramatically at 1 week after the first omalizumab injection. The early complete responders had the lowest expression levels of basophil FcεRI after treatment, which reached statistical significance at Week 3 (P value = 0.006). The mean expressions of CD63 (BD Biosciences, New Jersey, U.S.A., No. 557288) did not show similar patterns as FcεRI. We also performed the evaluations but failed to find significant

changes of FcεRI and CD63 expressions within 24 hours of omalizumab injections. However, notably, despite the mean expression levels of basophil CD63 were similar among the patients, the early complete responders had lower percentage of CD63^{high} (MFI > 3x10³) basophils and higher percentage of CD63^{low} (MFI < 1x10³) basophils comparing with others at the baseline (Figure 1, *P* value = 0.012 and 0.031, respectively). It possibly meant that these early complete responders might have a less activated state of their basophils comparing with others.

Next, in order to examine changes in certain serum factors, such as anti-IgE and anti- FcεRI antibodies, and their contributions to the effectiveness of omalizumab, we used a modified chronic urticaria basophil activation test (modified CU-BAT) to check the influence of patients' sera on leukotriene C4 (LTC4, Aviva Systems Biology, San Diego, U.S.A., No. OKEH02049) released from Ku812 cells (a human leukemic basophil cell line, purchased from Food Industry Research and Development Institute, Taiwan, R.O.C.). The levels of LTC4 released by Ku812 cells remained stationary when being treated with the patients' sera before and after omalizumab treatment. Notably, sera of the early complete responders had significant lower ability to cause Ku812 cells releasing LTC4 (Figure 1, *P* value = 0.017). This probably meant that sera of the early complete responders might have fewer or absence of certain serum factors which may activate Ku812 cells.

One previous study has shown that basophil CD63 expression was significantly higher in patient with CSU, especially in those of positive autologous serum skin test (ASST).⁷ CSU patients with

positive results of ASST, or basophil histamine release assay (BHRA), or CU-BAT show slower responses to omalizumab in previous studies.^{8,9} Sera of these patients may have certain serum factors, such as IgG anti-IgE or anti-FcεRI antibodies, which cause higher activation status of basophils and larger amount of mediators released. All these data support our findings about the characteristics of early complete responders. We also examined serum levels of IgE, D-dimer, C-reactive protein, tryptase, substance P, and interleukin-17 before and after omalizumab treatment. Levels of all these biomarkers were unremarkable to characterize our CSU patients.

Our study had some limitations. The number of patients was too small and the treatment duration was too short, which might weaken the strength of the findings.

In conclusion, we found the characteristics of early complete omalizumab responders in CSU. These patients show lowest basophil FcεRI expressions after omalizumab treatment. They have less activated basophils and less serum releasability on Ku812 cells at the baseline. These findings may help identifying patients who may benefit most from omalizumab.

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FIGURE LEGEND

Figure 1. Characteristics of early omalizumab complete responders at the baseline. The early complete responders had fewer CD63^{high} (MFI > 3x10³) basophils and more CD63^{low} (MFI < 1x10³) basophils. Sera of early complete responders had significant lower releasability in modified CU-BAT. All comparisons were performed with Kruskal-Wallis test.

