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Serum autoreactivity predicts time to response to omalizumab therapy in chronic spontaneous urticaria

To the Editor:

Omalizumab (anti-IgE) has been shown to be effective in chronic spontaneous urticaria (CSU) in a number of clinical trials.[1] However, in clinical practice, some patients with CSU are fast responders to their first injection of omalizumab, often within days, whereas others are slow responders, with therapy taking weeks to be effective. This letter examines the possible underlying mechanisms.

Sixty-four patients with CSU (46 women) whose symptoms were not controlled with H_1-antihistamines up to 4 times the recommended dose were treated with omalizumab at the Charité Department of Dermatology. Their median age was 47 (range, 23-85 years) years, and the median duration of their CSU was 3 years (range, 4 months to 40 years). Seven patients had received omalizumab in the past but not for at least 6 weeks before enrolment in the study, and their symptoms had returned in full. All analyses were performed according to the Declaration of Helsinki and approval was obtained from the Charité Ethics Committee (EA1/268/13). All patients gave signed informed consent.

Omalizumab 300 mg was injected subcutaneously 3 times at 4-week intervals. *The first day of response* was defined as the first of 7 continuous days when the 7-day urticaria activity score[2] was 6 or less. Venous blood was taken before the first omalizumab treatment and centrifuged at 2500 rpm for 10 minutes.

By the end of week 12, 56 (88%) had responded to omalizumab and 8 (12%) were nonresponders (Fig 1, *A*). Of the 56 responders, 39 patients (70%) responded within 8 days (fast responders) and 18 (32%) within the first day. Seventeen patients (30%) responded between 8 days and 3 months (slow responders). The cutoff time of 8 days between fast and slow responders was chosen because it corresponds with the peak plasma level of omalizumab after its initial injection.[3]

We hypothesized that a slow response to omalizumab occurs in patients with CSU in whom IgG antibodies to unoccupied IgE receptors (FcεRI) activate mast cell mediator release to cause wheal and angioedema formation.[4] This hypothesis is based on the knowledge that omalizumab first complexes soluble IgE then sequesters IgE released from mast cells, thus uncovering membrane FcεRI, which subsequently decays slowly over several weeks.[5]

To test this, the basophil histamine release assay (BHRA) was used. This assay may be used to detect serum autoantibodies directed against either the cell-bound IgE or unoccupied FcεRI. In this study, basophils were stripped of their IgE to assess FcεRI only. The BHRA was done as previously described (see this article's Online Repository at www.jacionline.org).[6] Analysis of the omalizumab responders showed that most BHRA-positive patients responded only after the second injection (Fig 1, *B*), with a median time to response of 29 days, whereas BHRA-negative patients had a median time to response of only 2 days (Fig 1, *C*). Furthermore, only 1 of the 39 fast responders was BHRA positive, whereas 8 of the 17 slow responders were BHRA positive ($P = .0001$; Fisher exact test; Fig 1, *D*).

The hypothesis was also tested using the autologous serum skin test (ASST)[7] in which 50 μL of fresh undiluted autologous serum was injected intradermally into the volar forearm. Similar volumes of 0.9% NaCl saline and 100 μg/mL histamine were used as negative and positive controls. The ASST was taken to be positive when the serum-induced wheal had a diameter at least 1.5 mm greater than the saline-induced wheal at 30 minutes. For clinical reasons, the ASST was performed on 51 patients only. Twelve of the 33 fast responders were ASST positive, whereas 10 of the 13 slow responders showed a positive ASST result ($P = .012$; Fisher exact test; Fig 1, *E* and *F*).

There were no statistical differences between fast and slow omalizumab responders with respect to age, body mass index, or disease activity or duration. Similarly, pretreatment IgE levels, neutralization rates of IgE, and free IgE and omalizumab levels posttreatment were not significantly different between slow and fast responders to omalizumab (Table I).

When comparing BHRA with ASST, it must be realized that BHRA is more specific in that it was designed to identify serum IgG antibodies to FcεRI. However, it is time consuming and may not be available in all clinics. In contrast, the ASST is easy to perform clinically but is less specific, because it will also detect IgG antibodies against mast cell–bound IgE, and may contain other histamine-releasing factors that can lead to a positive ASST response.[7] Even so, there was a significant relationship between BHRA and ASST results (Spearman $\rho = 0.448$, $P < .01$). All BHRA-positive patients were ASST positive. BHRA-positive and ASST-positive omalizumab responders are 4.5 and 5.5 times more likely to have a slow response to treatment compared with BHRA-negative and ASST-negative responders; the relative risks with 95% confidence limits were 4.54 for BHRA (2.42-8.53, z test $P < .001$) and for ASST 5.50 (1.37-22.11, z test $P < .05$).

The strength of this study is the highly significant correlation between the length of time to the onset of activity of omalizumab and BHRA, strongly suggesting that a positive BHRA may predict a slow response to omalizumab. Limitations of the study

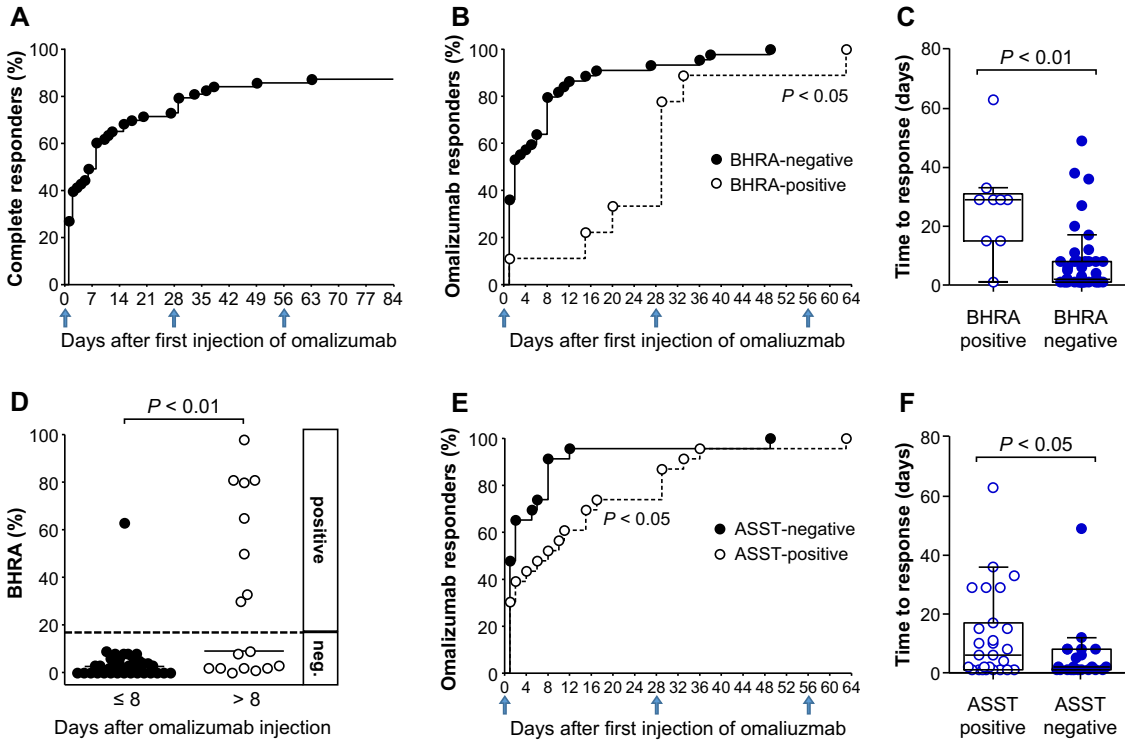

FIG 1. Characteristics of the response to omalizumab treatment in patients with CSU. **A,** The percentage of responders (UAS7 ≤ 6) plotted against the day of response. The blue arrows indicate the days of omalizumab injections. **B-F,** ASST-positive and BHRA-positive omalizumab responders show slower onset of effects. *B* and *E*, Kaplan-Meier curves showing the proportion of patients with positive and negative BHRA (*B*) and positive and negative ASST (*E*) achieving response to therapy over time. *C* and *F*, Box-whiskers plots presenting median, interquartile range, maximum and minimum as well as individual dots of day to therapy response in patients with positive and negative BHRA (*C*) and ASST (*F*). *D*, Release of histamine in cell supernatants expressed as percentage of total histamine from donor cells in fast (≤8 days) and slow (<8 days) responders to omalizumab. The *black solid vertical lines* indicate median values, and the *dotted horizontal line* indicates cutoff for positive values of BHRA. As negative control, the buffy coat cells responded to a mixture of healthy sera with less than 5%. As a positive control we used anti-IgE, resulting in 45% release. Statistical analyses were performed using Kaplan-Meier estimator and log-rank statistics (*B* and *E*) or Mann-Whitney *U* test (*C*, *D*, and *F*). *UAS7*, 7-Day urticaria activity score.

TABLE I. CSU responders to omalizumab: Demographic, clinical, and laboratory characteristics

Characteristic	All complete responders (n = 56)	Complete response within 8 d	Complete response after 8 d	*P* value
Age (y)	48 (33-60)	49 (37-58)	42 (31-63)	.544
Sex				
Female	40 (71.4%)	28 (71.8%)	12 (70.6%)	.583
Male	16 (28.6%)	11 (28.2%)	5 (29.4%)	
BMI	27.3 ± 4.8	27.9 ± 4.9	26.1 ± 4.6	.192
UAS7*	24.0 ± 9.7	23.0 ± 9.3	26.5 ± 4.6	.215
Disease duration*	36 (16-102)	40 (18-103)	24 (14-85)	.240
ASST+*	23 of 46 (50.0%)	12 of 33 (36.4%)	11 of 13 (84.6%)	**<.01**
BHRA+*	9 of 55 (16.4%)	1 of 38 (2.6%)	8 of 17 (47.1%)	**<.001**
Anti-FcεRI+*	5 of 44 (11.4%)	4 of 30 (13.3%)	1 of 14 (7.1%)	.485
Anti-IgE+*	1 of 44 (2.3%)	1 of 30 (3.3%)	0 of 14 (0.0%)	.682
Total IgE*	205.4 ± 229.6	239.2 ± 250.6	130.0 ± 155.0	.104
Free IgE after omalizumab†	31.8 ± 47.7	31.2 ± 39.6	33.2 ± 64.7	.893
% IgE neutralization†	94.7 ± 13.4	96.7 ± 2.2	90.0 ± 24.5	.106
Omalizumab (μg/mL)†	16.2 ± 7.8	16.6 ± 7.2	15.2 ± 9.2	.557

Data are given as n (%) for sex, ASST, and BHRA; median (IQR) for age and duration of disease (in months); or mean ± SD for BMI, UAS7, total IgE, free IgE after omalizumab, % neutralization, omalizumab. Statistical differences between responder groups in age, ASST+, BHRA+, anti-FcεRI+, and anti-IgE+ were analyzed using χ^2 or Fisher exact test when appropriate. Statistical differences between responder groups in BMI, UAS7, and total IgE were analyzed using unpaired *t* test. *P* values in boldface indicate statistical significance.

BMI, Body mass index; *IQR*, interquartile range; *UAS7*, 7-day urticaria activity score.

*Before start of omalizumab treatment.

†Four weeks after start of omalizumab treatment. Note that not all the patients were tested for ASST and/or BHRA, because of various reasons including time constraints, availability of personnel to do the serum preparations, and injections and patient consent.