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Patients who have anti-FcεRI nonreactive basophils do not represent patients with severe chronic spontaneous urticaria



A recent article by Oda et al¹ concluded that a low responsiveness of basophils via FcεRI reflects the disease activity in chronic spontaneous urticaria (CSU). Especially in a subgroup analysis of nonresponders (<10% CD203c^{high} basophils by the basophil activation test) and responders (>10% CD203c^{high} basophils), the nonresponders had a significantly higher urticaria activity score 7 (UAS7) and lower urticaria control test (UCT) scores than the responders. We did the same analyses using a total of 30 Japanese patients with CSU including 17 responders and 13 nonresponders (Tables E1 and E2, available in this article's Online Repository at www.jaci-inpractice.org). We found that there was no significant difference in UAS7 between the responders and nonresponders, and that the nonresponders had significantly higher UCT scores than the responders ($P = .0433$, Figure 1, A and B). Rauber et al² showed no significant difference in UCT scores between responders and nonresponders. The means $\pm$ standard deviations for UAS7 were 17.08 ± 12.09 and 25.57 ± 12.10 in Oda et al's and our studies, respectively. Although the mean severities of the patients with CSU in both studies were moderate,³ our patients with CSU tended to have a greater disease severity. Note that the responders in our study included 5 patients with a UAS7 of 42 (Figure 1, A, and Table E2, available in this article's Online Repository at www.jaci-inpractice.org).

Oda et al¹ demonstrated that the duration of disease was significantly shorter among nonresponders than among responders. In our (Figure 1, C) and Rauber et al's studies,² no significant difference in the disease duration was seen between the 2 groups. Oda

et al also showed a significant correlation between the disease duration and the proportion of CD203c^{high} basophils in patients with CSU. In our study, however, no significant correlation between these 2 factors was found (Figure 1, D).

Oda et al¹ compared the proportions of CD203c^{high} basophils among patients with CSU classified into 3 groups based on their UAS7 and healthy controls (HCs). Their classification into 3 groups according to UAS7 (UAS7 0-6, mild; 7-15, moderate; 16-42, severe) is not common. Following Hawe et al's classification,³ we used the following classification: UAS7 0, free; 1-6, well-controlled; 7-15, mild; 16-27, moderate; 28-42, severe (Table E3, available in this article's Online Repository at www.jaci-inpractice.org). Using this classification, we compared the proportions of CD203c^{high} basophils among patients with CSU classified into 4 groups based on UAS7 and HCs. We confirmed their findings that the proportion of CD203c^{high} basophils was significantly lower in the severe group than in the HCs, when stimulated with anti-human IgE antibody (clone E124-2-8D, from Allergen kit [Beckman Coulter, Tokyo, Japan]; $P = .0049$, Figure 1, E). Although Oda et al showed that there was no significant difference between the severe group and the HCs; when stimulated with anti-FcεRI antibody (clone CRA1), the proportion of CD203c^{high} basophils was significantly lower in the severe group than in the HCs in our study ($P = .0311$, Figure 1, F).

Taken together, we agree with their findings, which show that the responsiveness of basophils via FcεRI was significantly lower in the severe group than in the HCs. However, it is difficult to conclude that nonresponders represent patients with severe CSU.

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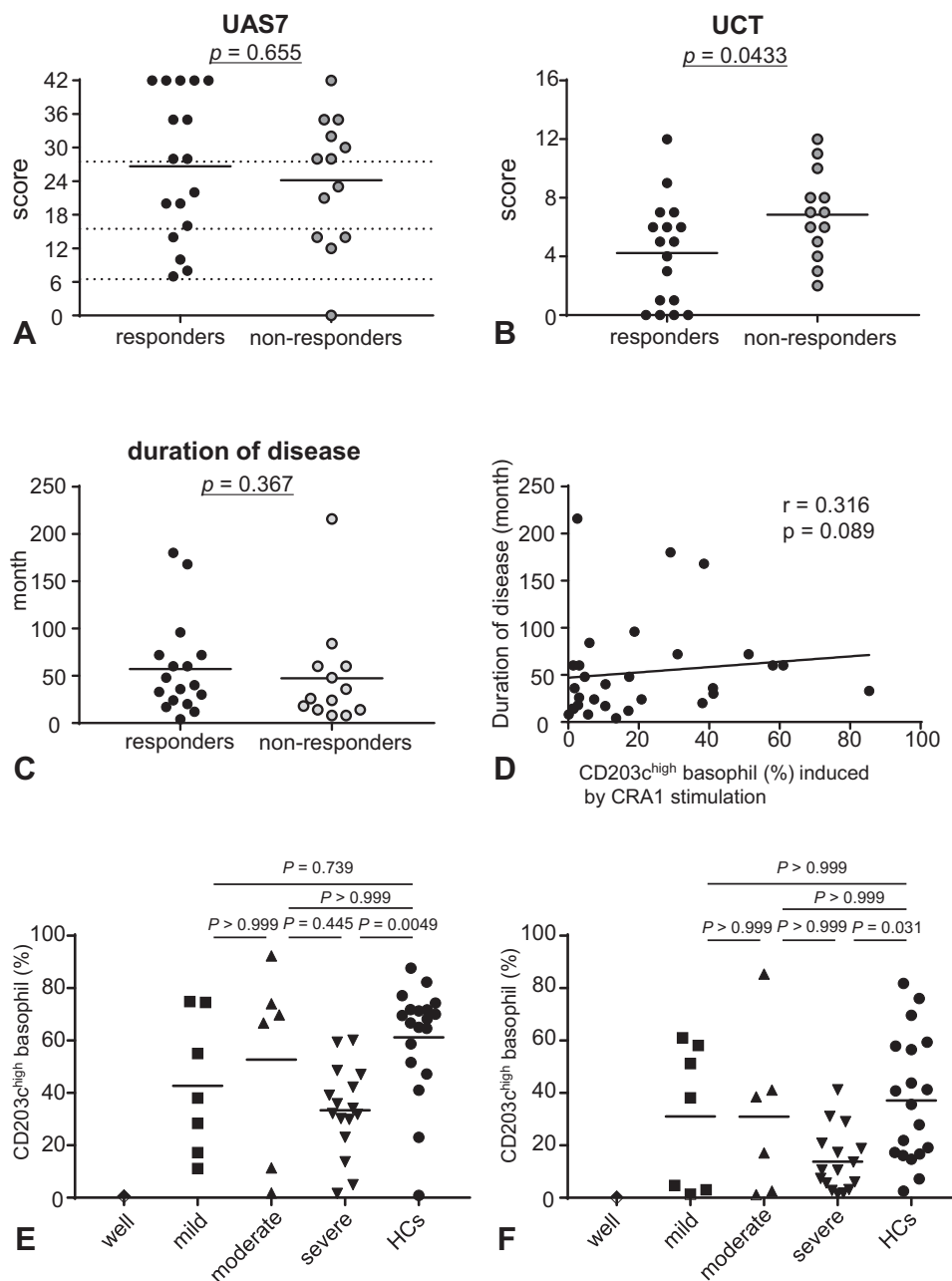


FIGURE 1. Comparison of UAS7 (A), UCT (B), and duration of disease (C) between responders (n = 17 donors) and nonresponders (n = 13 donors), and correlation of disease duration and proportion of CD203^{high} basophils in patients with CSU (D). Statistical analyses were performed using the Mann-Whitney *U* test (A, B, and C), or Spearman's rank correlation coefficient (D). Comparison of the proportion of CD203^{high} basophils among patients with CSU classified into 4 groups based on UAS7 and HCs. E, Anti-human IgE antibody (10 μ g/mL, clone E124-2-8D, from Allergenicity kit, Beckman Coulter) stimulation. F, Anti-human Fc ϵ RI antibody (CRA1; 3 μ g/mL, eBioscience, San Diego, Calif) stimulation. Statistical analyses were performed using the Kruskal-Wallis result with the Dunn test. CSU, Chronic spontaneous urticaria; HCs, healthy controls; mild, mild urticaria; moderate, moderate urticaria; severe, severe urticaria; UAS7, urticaria activity score 7; UCT, urticaria control test; well, well-controlled urticaria.

ONLINE REPOSITORY

TABLE E1. Clinical and laboratory characteristics of patients with chronic spontaneous urticaria

	CSU (n = 30)
Age (y), mean $\pm$ SD	48.0 $\pm$ 16.5
Female, n (%)	19 (63.3%)
Disease duration (mo), median (range)	36 (4-216)
Total IgE (IU/mL), median (range)	257 (1-2129)
UAS7, mean $\pm$ SD	25.57 $\pm$ 12.10
UCT, mean $\pm$ SD	5.37 $\pm$ 3.47
ASST positive rate (n = 27), n (%)	8 (29.6%)
Presence of angioedema at baseline, n (%)	4 (13.3%)
Treatment, n (%)	
H1 antihistamine at the conventional dosage	2 (6.7%)
H1 antihistamine at high dosage	28 (93.3%)
Leukotriene receptor antagonists	26 (86.7%)
Systemic corticosteroids	0 (0%)
Cyclosporine	0 (0%)
History, n (%)	
Asthma	2 (6.7%)
Allergic rhinitis	2 (6.7%)
Atopic dermatitis	5 (16.7%)
Pollinosis	4 (13.3%)

Data are given as mean $\pm$ standard deviation (SD) for age, UAS7, and UCT; n (%) for sex, ASST positive rate, presence of angioedema, treatment, and history; and median (range) for disease duration, and serum total IgE.

ASST, Autologous serum skin test; CSU, chronic spontaneous urticaria; UCT, urticaria control test; UAS7, urticaria activity score 7.

TABLE E2. Response characteristics of patients with chronic spontaneous urticaria

No	Age	Sex	Disease duration (mo)	UAS7	UCT	Blood basophil count (per μ L)	Stimulation (proportion of CD203c ^{high} basophil)		ASST
							CRA1	anti-IgE Ab	
1	65	F	8	0	11	52.8	0.15	0.56	n
2	38	M	14	21	8	38.5	1.19	11.4	p
3	61	M	60	14	12	60.9	1.41	11.1	n
4	35	F	14	35	7	31.5	1.51	4.93	n
5	41	F	36	28	7	42.4	1.79	30.2	n
6	31	F	216	23	8	42.4	2.56	1.8	ND
7	47	F	18	35	6	37.2	2.8	13.7	p
8	29	F	26	14	2	10.6	3.07	28.4	p
9	49	F	60	32	6	11.8	3.12	1.59	p
10	37	M	48	12	10	32.2	4.69	17.2	ND
11	41	M	8	42	4	18	5.64	47.9	p
12	33	M	84	28	5	19.4	6.04	23	n
13	82	F	24	30	3	12.4	7.38	34.1	n
14	71	M	17	42	1	54	10.5	29.9	n
15	68	M	40	35	3	8.8	10.6	32.1	n
16	64	F	4	35	5	33.2	13.6	31.8	p
17	24	F	12	20	6	38.5	17.1	69.8	n
18	39	F	48	28	0	10.6	17.3	42.2	p
19	47	F	96	42	0	9	18.8	59.4	n
20	51	M	24	28	7	69.3	20.8	35.9	ND
21	48	F	180	42	0	32.7	29	60.1	p
22	67	M	72	42	0	18.2	31	39.1	n
23	32	F	20	8	9	42.6	38.1	55	n
24	44	F	168	22	6	29.6	38.5	74	n
25	58	M	36	16	6	33.2	41.1	66.7	n
26	60	F	30	42	1	11.4	41.2	48.5	n
27	32	M	72	10	7	2.88	51.2	74.5	n
28	87	F	60	7	5	31.8	58.1	38	n
29	27	F	60	14	4	19.2	61	74.9	n
30	33	F	33	20	12	17.7	85.4	92.3	n

Ab, Antibody; ASST, autologous serum skin test; MFI, mean fluorescence intensity; n, negative; ND, not done; p, positive; PBS, phosphate buffered saline; UCT, urticaria control test; UAS7, urticaria activity score 7.

CD203c expression without stimulation (PBS) is described as MFI. CD203c expression under CRA1 (anti-FcεRI Ab) or anti-IgE Ab stimulation is described as proportion of CD203c^{high} basophils (%).

TABLE E3. Clinical and laboratory characteristics of patients with chronic spontaneous urticaria classified into 4 groups based on disease activity

	Well (UAS7, 1-6) (n = 1)	Mild (UAS7, 7-15) (n = 7)	Moderate (UAS7, 16-27) (n = 6)	Severe (UAS7, 28-42) (n = 16)
Age (y)	65	43.6 ± 20.7	38 ± 10.8	52.7 ± 13.9
Female	1 (100%)	4 (57%)	4 (67%)	10 (63%)
Disease duration (mo)	8	60 (20-72)	34.5 (12-216)	33 (4-180)
Total IgE (IU/mL)	1131	112 (8-1595)	424 (69-2129)	295 (1-1149)
UAS7	0	12 (7-14)	20.5 (16-23)	35 (28-42)
UCT	11	7 (2-12)	7 (6-12)	3.5 (0-7)
ASST positive rate	1 (100%)	1/6 (17%)	1/5 (20%)	6/15 (40%)

Data are given as mean ± standard deviation for age; n (%) for sex and ASST positive rate; and median (range) for disease duration, and serum total IgE, UAS7, and UCT. ASST, Autologous serum skin test; UCT, urticaria control test; UAS7, urticaria activity score 7.

Reply



To the Editor:

Endo et al¹ raised interesting and insightful points regarding our manuscript.² Although these authors performed similar analyses to our study² regarding the relationship between basophil reactivity via FcεRI and clinical features in Japanese patients with chronic spontaneous urticaria (CSU), they showed some similar, as well as different, results.

First, Endo et al¹ pointed out that our classification into 3 groups according to the urticaria activity score (UAS) 7 is not common. When we reanalyzed our data using Hawe et al's classification,³ the proportion of CD203c^{high} basophils was significantly lower in the severe group than in healthy controls when stimulated with anti-IgE antibody (Ab) (Figure 1, A). A similar tendency was also observed with stimulation of anti-FcεRI Ab (CRA1) (Figure 1, B). Although we adopted 3 groups modified according to Hawe et al³ in our previous study, even if patients with CSU were classified into 5 groups, similar results were observed in our study (Figure 1, A and B).

Second, unlike our previous study using IgE stimulation, Endo et al¹ showed that when patients with CSU were defined as nonresponders when less than 10% of basophils were CD203c^{high} basophils after FcεRI stimulation, nonresponders did not show severe disease activity. In contrast, Rauber et al⁴ categorized patients with CSU into responders and nonresponders on the basis of basophil CD63 upregulation by FcεRI stimulation. Nonresponders were then subdivided into a third subgroup characterized by basopenia (CU-NR_{B0}), which showed the most severity. Therefore, differences in disease severity between nonresponders and responders in our study and Endo et al's study may be due to differences in stimulating antibodies that distinguish the 2 groups. In addition, we enrolled more mild patients (9 of 38) with a UAS7 score of 0-6 in our study compared with Endo et al's study

(1 of 30). Only 1 in 9 mild patients were nonresponders and the majority of mild cases were responders in our study. Therefore, differences in the patients' demographics may have been responsible for the differences between studies.

Third, we found that the duration of disease was significantly shorter in nonresponders than in responders,² whereas Endo et al's study¹ showed no significant difference in disease duration between the 2 groups. In contrast, Huang et al⁵ found that a basophil nonresponder phenotype using histamine release was associated with a shorter disease duration, similar to our results. Furthermore, they considered that the basophil activation test with 0.1 or 0.01 μg/mL anti-IgE stimulation may be an alternative method to basophil histamine release for classifying basophil functional phenotypes in CSU.⁵ Baker et al⁶ also reported that patients with CSU with a basophil nonresponder phenotype classified by histamine release to anti-IgE antibody had a shorter disease duration than did responders. These differences may be due to differences in stimulating antibodies used for classification of the 2 groups and the patients' background.

Finally, basophils in nonresponders with CSU show an increase in maximum histamine release to anti-IgE stimulation when experiencing remission of disease,⁷ suggesting that basophil reactivity may be related to disease severity, even in individual patients.

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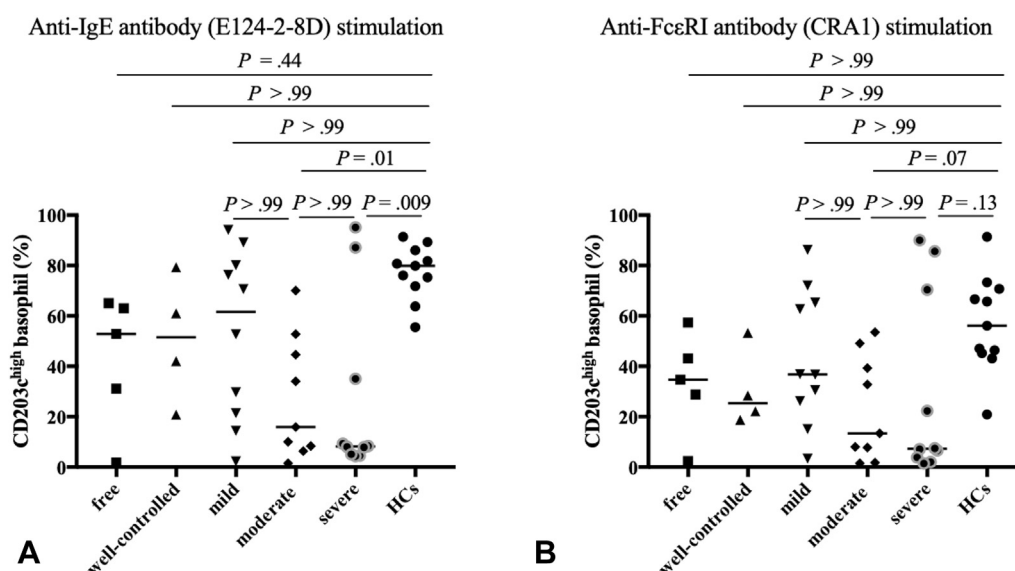


FIGURE 1. Comparison of the proportion of CD203c^{high} basophils between patients with CSU who were classified into 5 groups by the UAS7 score and HCs. **A**, Anti-IgE (E124-2-8D) stimulation. **B**, Anti-FcεRI (CRA1) stimulation. Statistical analyses were performed using the Kruskal-Wallis result with Dunn's test. CSU, Chronic spontaneous urticaria; HCs, healthy controls; UAS, urticaria activity score.

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