Lower efficacy of omalizumab in older adults with chronic spontaneous urticaria

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The efficacy of omalizumab based on age

Abstract:

Omalizumab is known to be effective in treating chronic spontaneous urticaria (CSU) with an inadequate response to H1-antihistamine. Although many reports have described pre-treatment biomarkers to predict the efficacy of omalizumab in CSU, there are few reports that examined the relationship between age and the therapeutic effectiveness of omalizumab.

Thus, we aimed to investigate the relationship between response to omalizumab and age. This retrospective study comprised 52 CSU patients receiving three consecutive omalizumab courses during the period from April 2017 to March 2021. Participants were categorized as responders or non/partial responders using the urticaria control test to evaluate clinical variables on week 12. The female rate tended to be higher, and the mean age and the median disease duration tended to be lower with no significant in responders than in non/partial responders. In addition, they exhibited no significant differences regarding serum IgE levels, basophil counts, eosinophil counts, d-dimer and autologous serum skin test (ASST) results reported as predictor in the past between two groups. Interestingly, when patients were categorized as age <65 years or ≥65 years, those in the ≥65 years group had a significantly lower response to omalizumab than those aged <65 years. These findings suggest that physicians should keep in mind that

the age of their CSU patients may be a predictor of the therapeutic efficacy of omalizumab. (220/250)

Key word: chronic spontaneous urticaria, age, omalizumab, <65 years, ≥65 years

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Introduction

Chronic spontaneous urticaria (CSU) is a common condition, characterized by transient wheals and angioedema lasting for more than 6 weeks with unknown etiology or occurring as the result of autoreactivity.[1] A survey in Italy reported that while the prevalence of CSU was highest among patients aged 40–49 years, people over the age of 65 years accounted for approximately 20% of cases.[2] In addition, the prevalence rate peaked at 0-9 and 70-79 years in Korea.[3] Patients with CSU often have a poor quality of life (QOL), with itchy skin and interrupted sleep. Therefore, appropriate and prompt treatment is important to improve QOL. The EAACI/GA^{2}LEN/EDF/WAO urticaria guidelines recommend second-generation H_1- receptor antagonists (antihistamines) as a first-line treatment, with increased antihistamine dose as second-line treatment and add-on omalizumab as third-line treatment.[1] While many studies have demonstrated the efficacy of omalizumab in treating CSU, the numbers of older participants included in the studies are low.[4]

Previous reports have described pre-treatment biomarkers to predict the efficacy of omalizumab in CSU. Poor responders to omalizumab have low baseline total serum IgE [5], low d-dimer levels[5] or a positive autologous serum skin test (ASST).[6] Recently, low blood eosinophil and basophil counts have also been reported to be

associated with poor response to treatment.[7] However, few studies have focused on the relationship between age and the therapeutic effect of omalizumab in CSU patients.[8, 9] Hence, we aimed to investigate the relationship between the therapeutic effect of omalizumab and age or previously reported predictors[5,6,7] in Japanese patients in the real-world setting.

Methods

Fifty-two patients with CSU treated with omalizumab at Kobe University Hospital were included in the study, conducted from April 2017 to March 2021. Omalizumab 300 mg was administered every 4 weeks. Participants were designated as responders (n = 42) or non or partial responders (N/PRs, n = 10). Responders were defined as those who achieved UCT (urticaria control test) scores ≥12 on week 12. N/PRs were defined as those with UCT scores <12 even on week 12 (Table I).[6] All statistical analyses were carried out using GraphPad Prism 8 (GraphPad Software, San Diego, CA).

Results

The female rate tended to be higher, and the mean age and the median disease duration tended to be lower with no significant in responders than in N/PRs (Table I). There were no significant differences in serum IgE levels, basophil counts, eosinophil

counts, d-dimer and ASST between the two groups (Table I). Interestingly, when participants were categorized into age groups <65 years or ≥65 years, Fisher's exact test for the association between age <65 and being a responder was highly significant (p = 0.038) (Table II). In addition, we showed the results of demographic characteristics based on the age (Table EI). Since basophil counts showed tendency to be higher and D-dimer to be lower in <65 group than ≥ 65, we performed logistic regression models to investigate independent associations between age and predictors of the therapeutic efficacy of omalizumab (Table EII). Multivariable logistic regression founded that basophil counts and d-dimer were not significantly associated with age. The ASST result had a small number of participants and multivariable logistic regression could not be analyzed.

Discussion

A previous study reported that omalizumab was safe and effective in older patients with CSU.[9] Nettis et al. reported that no significant differences between the two age groups (<65 years and ≥65 years) were detected in the change from baseline to weeks 4, 12, and 24 in urticaria activity score 7.[8] However, in the current study, while the number of participants was small, older participants showed significantly lower response to omalizumab compared with younger participants. Similarly, a previous

103 study in patients receiving a single omalizumab course or two consecutive courses
104 reported a lower probability of maintaining treatment response among patients aged ≥60
105 years compared with those aged <60 years.[10]

106 The observed age differences in the therapeutic effect of omalizumab may be
107 related to the presence of comorbid disease or organ insufficiency in older adults. The
108 aging process may interfere with pharmacokinetics and pharmacody namics, resulting in
109 different treatment responses.[11] Moreover, autoimmune urticaria has reported to possibly
110 preferentially affect older patients.[12] However, in this study, differences in comorbid
111 disease, organ insufficiency, or ASST were not detected, most likely because of the
112 small number of participants (Table E1). Additionally, the result of multivariable
113 logistic regression that basophil and eosinophil counts tended to be higher in <65 group
114 than ≥ 65 might contribute to the lower efficacy rate in patients more than 65 years of
115 age in this study. Patients who are refractory to antihistamine therapy may use
116 cyclosporine.[1] However, prescribing of cyclosporine may be hampered by adverse drug
117 reactions such as renal and/or liver insufficiency. Thus, treatment in elderly patients
118 with CSU may be complicated.

119 In contrast to previous reports,[5,6,7] there were no difference in serum total IgE,
120 basophil counts, eosinophil counts, d-dimer or ASST between responders and N/PRs in

121 our study. These conflicting data might be because of the definition of treatment
122 response, ethnic differences, or the small number of participants.

123 In conclusion, our study found a significantly lower response to omalizumab in
124 patients aged ≥65 years than in those aged <65 years. This suggests that physicians
125 should keep in mind that the age of their CSU patients may be a predictor of the
126 therapeutic efficacy of omalizumab.

127

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132

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135 The other authors have no conflicts of interest to declare.

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Table I. Demographic characteristics based on the therapeutic effect of omalizumab

	Responders (n = 42)	Non or partial responders (n =10)	*P* value
Age, years	46.1 ± 16.9	57.1 ± 22.1	0.09
Female, n (%)	71% (30/42)	40% (4/10)	0.07
Disease duration, years	4.2 (0.8-35)	8.0 (2.0-24)	0.08
UCT	5.6 ± 2.9	5.6 ± 2.4	0.94
UAS7	22.6 ± 8.6	17.7 ± 10.6	0.20
Serum total IgE (IU/ml)	141.4 (3–4392)	45.3 (4.5–860)	0.23
Basophil counts (/μl)	34.4 (0-192)	26.9 (0–92)	0.63
Eosinophil counts (/μl)	142.0 (0-768)	125.0 (55-413)	0.81
D-dimer (μg/ml)	0.5 (0.5-12.2)	0.5 (0.5-1.1)	0.92
ASST positive rate, n (%)	4/25 (16.0%)	1/6 (16.6%)	0.99

Data are given as the mean ± SD for age, UCT and UAS7; median (range) for disease duration, serum total IgE, basophil counts, eosinophil counts, and D-dimer; n (%) for female and ASST positive rate.

Statistical differences between two groups were analyzed by unpaired *t*-test for age, UCT, and UAS7, Fisher's exact test for female and ASST positive rate, and Mann-Whitney *U*-test for disease duration, serum total IgE, basophil counts, eosinophil counts and D-dimer.

ASST, autologous serum skin test, UCT, urticaria control test; UAS7, 7-day urticaria activity score

Table II. The therapeutic effect of omalizumab based on age group

Age	Responders	Non or partial responders	*P* value
< 65	83% (35/42)	50% (5/10)	0.038
≥ 65	17% (7/42)	50% (5/10)	

Statistical analyses were performed using Fisher's exact test.

Table EI. Demographic characteristics based on the age

	< 65 (n=40)	≥ 65 (n=12)	*P* value
Age, years	40.6 ± 13.2	73.6 ± 4.6	< 0.001
Female, n (%)	67% (27/40)	58% (7/12)	0.73
Disease duration, years	4.7 (0.8-30)	5.5 (1.6-33.3)	0.50
UCT	5.4 ± 2.8	6.3 ± 2.8	0.35
UAS7	22.3 ± 8.7	19.7 ± 10.9	0.49
ASST positive rate, n (%)	17% (4/24)	14% (1/7)	>0.99
Serum total IgE (IU/ml)	151.7 (3-4392)	106.0 (7.4-351)	0.30
Basophil counts (/μl)	45.5 (0-192)	9.0 (0-92)	0.055
Eosinophil counts (/μl)	144.0 (0-768)	88.5 (0-459)	0.16
D-dimer (μg/ml)	0.5 (0.5-10.9)	0.8 (0.5-12.2)	0.08
Comorbid disease	Metabolic disease (n=10) Respiratory disease (n=2) Gastrointestinal disease (n=5) Cardiovascular disease (n=5) Malignant tumor (n=4) Neurological disease (n=3) Autoimmune diseases (n=3)	Metabolic disease (n=4) Respiratory disease (n=2) Gastrointestinal disease (n=4) Cardiovascular disease (n=5) Malignant tumor (n=2) Neurological disease (n=4) Kidney dysfunction (n=1) Autoimmune diseases (n=1)	

Data are given as the mean ± SD for age, UCT and UAS7; n (%) for sex; median (range) for disease duration, serum total IgE, basophil counts, eosinophil counts, and D-dimer; n (%) for female and ASST positive rate.

Statistical differences between two groups were analyzed by unpaired *t*-test for age, UCT, and UAS7, Fisher's exact test for female and ASST positive rate, and Mann-Whitney *U*-test for disease duration, serum total IgE, basophil counts, eosinophil counts, and D-dimer.

ASST, autologous serum skin test, UCT, urticaria control test; UAS7, 7-day urticaria activity score

Table EII. Demographic characteristics based on the age: multiple logistic analysis

	< 65 (n=40)	≥ 65 (n=12)	Odds ratio (95%CI)	*P* value
Serum total IgE (IU/ml)	151.7 (3-4392)	106.0 (7.4-351)	1.00 (0.99-1.01)	0.56
Basophil counts (/μl)	45.5 (0-192)	9.0 (0-92)	1.01 (0.99-1.03)	0.12
Eosinophil counts (/μl)	144.0 (0-768)	88.5 (0-459)	1.03 (0.99-1.10)	0.14
D-dimer (μg/ml)	0.5 (0.5-10.9)	0.8 (0.5-12.2)	0.83 (0.52-1.14)	0.33

Data are given as the median (range) for disease duration, serum total IgE, basophil counts, eosinophil counts, and D-dimer

Statistical differences between two groups were analyzed by multiple logistic regression.