Efficacy of additional treatment for chronic spontaneous urticaria refractory to treatment - A single-center retrospective real-world study

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The H1-receptor antagonist (H1RA) represents the basic treatment for chronic spontaneous urticaria (CSU). However, about 50% of patients remain uncontrolled at the standard dosage of H1RA,[1] and additional treatment options are needed. The Japanese guidelines for diagnosis and treatment of urticaria 2018 recommend that patients with CSU refractory to a standard dose of H1RA, first change/increase/combine it with another H1RA, then add an H2-receptor antagonist (H2RA) or leukotriene receptor antagonist (LTRA), and then add or change to a corticosteroid, omalizumab, or ciclosporin.[2] However, the efficacy of add-on LTRA or H2RA has been reported to vary.[3] Thus, we aimed to compare the efficacy between LTRA or H2RA and omalizumab as additional treatment options in Japanese patients who have insufficient effect for pretreatment. Sixty-two patients with CSU who had a urticaria control test (UCT) score of less than 12 points and were followed at Kobe University Hospital from April 2017 to August 2020 were enrolled. We evaluated their UCT scores four weeks after treatment, and compared changes in UCT scores (ΔUCT) between additional treatment groups of H2RA (lafutidine, n = 10; famotidine, n = 1), LTRA (montelukast, n = 18), or omalizumab (300 mg) (n = 33; UCT scores obtained after a single administration). Their previous treatments and demographic characteristics are shown in Supplemental Table 1 and 2, respectively. There were no participants who had

ciclosporin or a corticosteroid added to their treatment. The one-way ANOVA with Tukey test was used to assess differences among three groups. The statistical analysis was carried out using GraphPad Prism 7 (GraphPad Software, San Diego, CA). ΔUCT was significantly larger in the omalizumab group than in the LTRA group (Fig. 1). Interestingly, there was no significant difference between the H2RA group and the omalizumab group, whereas the ΔUCT tended to be higher in the omalizumab group than in the H2RA group. Furthermore, 27.8% (5/18) in the LTRA group were found to decrease in UCT, indicating that the addition of LTRA worsened disease control in some cases (Supplemental Table 3).

Although there was no difference regarding the efficacy between H2RA (almost lafutidine) and LTRA (montelukast), the addition of LTRA worsened disease control more frequently than did H2RA (Fig. 1 and Supplemental Table 3). A previous study has demonstrated the utility of the addition of lafutidine[4], and it may have a different effect than other H2RAs.

There was no significant difference between H2RA and omalizumab (Fig. 1). Because the UCT was evaluated 4 weeks after treatment, the current results reflect the therapeutic effect at an early treatment response to omalizumab or H2RA. Analysis methods including slow responders to omalizumab may detect significant difference

between two groups. Furthermore, if the number of patients who received H2RA increased, the omalizumab group may have significantly increased ΔUCT than the H2RA group. The limitations of this study are its single-center trial and the limited number of patients.

In conclusion, although our data did not have statistically significant between H2RA and LTRA, we found that that the administration of LTRA exacerbate some cases.

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Conflicts of interest

AF has received fees for speaking from Novartis and Taiho. AF has received funds for sponsored/joint research from Novartis and Taiho. Other authors have no conflicts of interest to declare.

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94 **Figure legends**

95 **Figure 1.** Comparison of treatment efficacy between H2RA, LTRA, and omalizumab in

96 CSU patients refractory to H1RA.

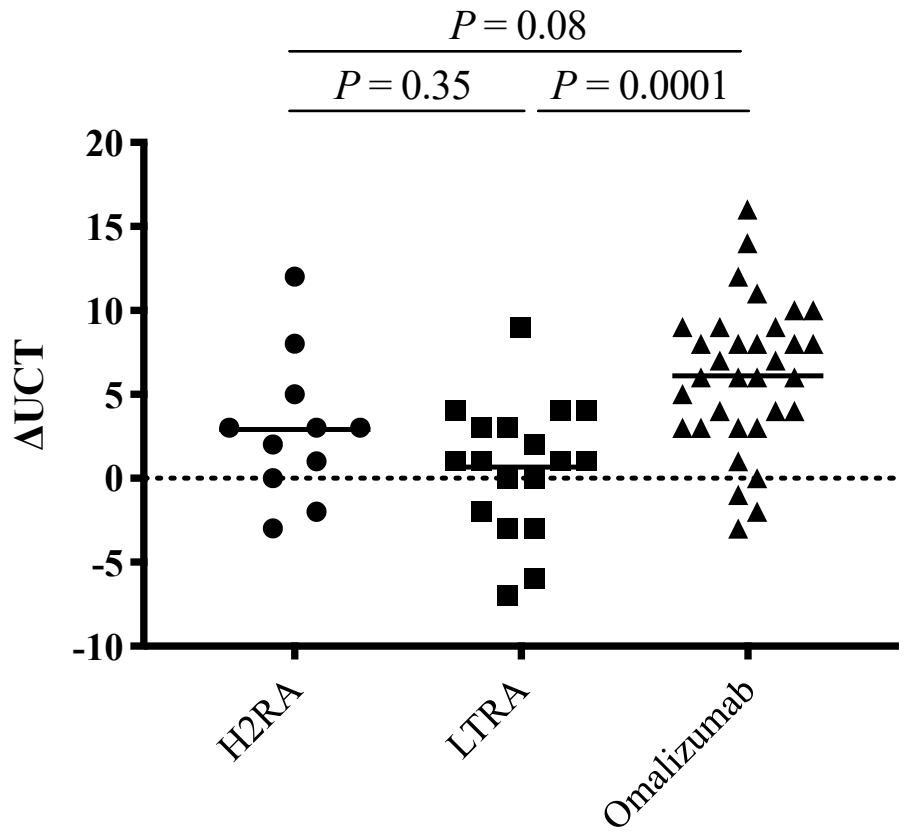
97 Statistical analyses were performed using one-way ANOVA with Tukey test.

98 The bar shows the average value.

99 H2RA, H2-receptor antagonist; LTRA, leukotriene receptor antagonist; CSU, chronic

100 spontaneous urticaria; H1RA, H1-receptor antagonista

Fig. 1



Supplemental Table 1**.** Previous treatment of patients who then added H2RA, LTRA, or omalizumab.

Previous treatment of patients who then added H2RA (Step 2)

Previous treatment	Number
H1RA	n=11

Previous treatment of patients who then added LTRA (Step 2)

Previous treatment	Number
H1RA	n=7
H1RA + H2RA	n=10
H1RA + H2RA + tranexamic acid	n=1

Previous treatment of patients who then added omalizumab (Step 3)

Previous treatment	Number
H1RA	n=4
H1RA + H2RA	n=7
H1RA + H2RA + LTRA	n=9
H1RA + LTRA	n=2
H1RA + LTRA + corticosteroid	n=2
H1RA + H2RA + corticosteroid	n=3
H1RA + corticosteroid	n=2
H1RA + H2RA + LTRA + corticosteroid	n=3
H1RA + H2RA + tranexamic acid + corticosteroid	n=1

H1RA, H1- receptor antagonist; H2RA, H2- receptor antagonist; LTRA, leukotriene receptor antagonist

Supplemental Table 2. Demographic characteristics of patients who then added H2RA/LTRA/Omalizumab.

	H2RA (n=11)	LTRA (n=18)	omalizumab (n=33)
Age, years	44.4 ± 14.4	42.9 ± 14.9	46.3 ± 19.1
Female, n (%)	6 (54.5%)	11 (61.1%)	21 (63.4%)
Disease duration, years	8 (0.67-24)	6.5 (0.25–35)	2.3 (0.25-10)
ASST positive rate, n (%)	1/7 (14.2%)	3/12 (25%)	7/24 (29.2%)
UCT before treatment	6.5 ± 2.7	6.4 ± 2.8	6.1± 2.6

H2RA, H2- receptor antagonista; LTRA, leukotriene receptor antagonist; UCT, urticaria control test

Data are given as the mean ± SD for age, UCT before adding LTRA; n (%) for sex, ASST positive rate; median (range) for disease duration.

Supplemental Table 3. Characteristics of the study population.

Additional treatment	Average of ΔUCT	Worsening rate of ΔUCT
H2RA	3.2 ± 4.4	18.2% (2/11)
LTRA	0.5 ± 4.2	27.8% (5/18)
Omalizumab	6.0 ± 4.3	9.0% (3/33)

Values are shown as means or percentages (numbers).

UCT: Urticaria control test; H2RA, H2- receptor antagonista; LTRA, leukotriene receptor antagonist