Allergy Asthma Immunol Res. 2023 Jul;15(4):496-511
https://doi.org/10.4168/aair.2023.15.4.496
pISSN 2092-7355·eISSN 2092-7363

Allergy, Asthma & Immunology Research AAIR

Original Article

Check for updates

Efficacy of Second-Line Treatments in Chronic Urticaria Refractory to Standard Dose Antihistamines

Mi-Ae Kim,[1] **Jeong-Hee Choi**,[2] **Yoo-Seob Shin**,[3] **Hae-Sim Park**,[3] **Young-Min Ye**,[3*] **KAAACI Work Group on Urticaria/Angioedema/Anaphylaxis**

[1]Department of Pulmonology, Allergy and Critical Care Medicine, CHA Bundang Medical Center, CHA University, Seongnam, Korea
[2]Department of Pulmonology and Allergy, Hallym University Dongtan Sacred Heart Hospital, Hwaseong, Korea
[3]Department of Allergy and Clinical Immunology, Ajou University School of Medicine, Suwon, Korea

OPEN ACCESS

Received: Nov 3, 2022
Revised: Dec 26, 2022
Accepted: Jan 11, 2023
Published online: Mar 7, 2023

Correspondence to
Young-Min Ye, MD, PhD
Department of Allergy and Clinical Immunology, Ajou University School of Medicine, 164 World cup-ro, Yeongtong-gu, Suwon 16499, Korea.
Tel: +82-31-219-5155
Fax: +82-31-219-5154
Email: ye9007@ajou.ac.kr

ORCID iDs
Mi-Ae Kim
https://orcid.org/0000-0003-1253-6075
Jeong-Hee Choi
https://orcid.org/0000-0002-0599-875X
Yoo-Seob Shin
https://orcid.org/0000-0002-9855-3185
Hae-Sim Park
https://orcid.org/0000-0003-2614-0303

ABSTRACT

Purpose: The prevalence of chronic urticaria (CU) is increasing worldwide, and it imposes a major burden on patients. Few studies have evaluated the efficacy of second-line treatments of CU, particularly for patients being considered for costly third-line treatments such as omalizumab. We compared the efficacy and safety of second-line treatments of CU refractory to standard doses of nonsedating H_1-antihistamines (nsAHs).
Methods: This 4-week, prospective, randomized, open-label trial divided patients into 4 treatment groups: 4-fold updosing of nsAHs, multiple combination of 4 nsAHs, switching to other nsAHs, and adjunctive H_2-receptor antagonist. The clinical outcomes included urticaria control status, symptoms, and rescue medication use.
Results: This study included 109 patients. After 4 weeks of second-line treatment, urticaria was well-controlled, partly controlled, and uncontrolled in 43.1%, 36.7%, and 20.2% of patients, respectively. Complete control of CU was achieved in 20.4% of patients. Among the patients with high-dose nsAHs, the proportion with well-controlled status was higher compared to the patients who received standard doses (51.9% vs. 34.5%, $P = 0.031$). No significant difference was observed in the proportion of well-controlled cases between the updosing and combination treatment groups (57.7% vs. 46.4%, $P = 0.616$). However, increasing the dose of nsAHs 4-fold was associated with a higher rate of complete symptom control compared to multiple combination treatment with 4 nsAHs (40.0% vs. 10.7%, $P = 0.030$). Logistic regression analysis confirmed the higher efficacy of updosing of nsAHs for complete control of CU compared to the other treatment strategies (odds ratio, 0.180; $P = 0.020$).
Conclusions: In patients with CU refractory to standard doses of nsAHs, both updosing of nsAHs 4-fold and multiple combination treatment with 4 nsAHs increased the rate of well-controlled cases without causing significant adverse effects. Updosing of nsAHs is more effective for complete CU control than combination treatment.

Keywords: Chronic urticaria; histamine H1 antagonist, nonsedating; efficacy; safety

Allergy, Asthma & Immunology Research AAIR

Young-Min Ye
https://orcid.org/0000-0002-7517-1715

Disclosure

There are no financial or other issues that might lead to conflicts of interest.

INTRODUCTION

Urticaria is characterized by wheals and/or angioedema. Acute urticaria is common, affecting almost 20% of the general population. Chronic urticaria (CU) persists for > 6 weeks.[1-4] The prevalence of CU is increasing worldwide and is currently estimated at 0.1% in North America and 1.4% in Asia.[5-7] The prevalence of CU varies among regions and is higher in Asia and Latin America than in Europe and North America.[6] Due to its chronic and unpredictable disease course and frequent sleep disturbances, CU negatively impacts the quality of life (QOL), work productivity, and daily activities.[7-9] The health status scores of CU patients were comparable to those of patients with coronary artery disease, while their subjective life satisfaction was lower than that of patients with respiratory allergy.[3] Recent Korean population-based studies have found that CU imposes a major burden on patients due to the chronic disease course and the need for frequent healthcare visits.[7,10-16] Therefore, a major goal of CU treatment is effective and complete symptom control.[3,4]

According to the international EAACI/GA^{2}LEN/EuroDerm/APAAACI guidelines,[3,4] a standard dose of second-generation nonsedating H_1-antihistamines (nsAHs) is recommended as the first-line treatment of CU. However, up to 60% of CU patients do not respond adequately to first-line treatment within 2–4 weeks.[5,17-49] When CU is not controlled with first-line treatment, second-line treatments, such as 4-fold updosing of nsAHs, are considered.[19] The Korean CU guidelines recommend the 4-fold updosing of nsAHs when CU is not adequately controlled by a standard dose of nsAHs.[1,2] However, Korean and international guidelines differ regarding the other second-line treatment options, such as treatment with multiple nsAHs (referred to hereafter as "combination treatment"). International guidelines do not recommend the use of combination treatment because of a lack of evidence of efficacy and differences in pharmacological properties among nsAHs.[3,4] No randomized controlled trial has investigated the efficacy of combination treatment, whereas clinical studies and meta-analyses have provided evidence for the efficacy of nsAH updosing.[5,19-23] However, the updosing of nsAHs is not licensed by the Korean Ministry of Food and Drug Safety and the associated costs are not covered by the Korean National Health Insurance Service. Consequently, Korean clinicians prefer to use combination treatment rather than the updosing of nsAHs. Anecdotal evidence suggests the effectiveness of combination treatment for refractory CU, despite the lack of scientific evidence.[11,24] Therefore, the Korean guidelines conditionally recommend combination treatment given the very low evidence level, whereas updosing (low evidence level) is strongly recommended.[1] Nevertheless, concerns still exist regarding the efficacy and safety of combination treatment.[1,4]

Other second-line treatments for CU, i.e., switching to other nsAHs and adjunctive H_2-receptor antagonist (H2RA) treatment, are relatively ineffective.[4] However, real-world evidence indicates that these treatments are still being prescribed.[10] Moreover, 31.0%–69.9% of CU patients are treated with oral corticosteroids (OCSs) in combination with nsAHs, even though guidelines recommend that systemic steroids only be used for a short period to control exacerbation of CU. However, some clinicians still prefer to use OCSs in combination with nsAHs or switching to other nsAHs, rather than nsAH updosing or combination treatment.[1,4,5,20] This discrepancy between guidelines and clinical practice has resulted in poor control of CU and long-term use of OCS, which may increase the disease burden and lead to serious adverse drug effects.[18]

https://doi.org/10.4168/aair.2023.15.4.496

There is an unmet clinical need regarding the efficacy and safety of second-line treatments of CU, particularly for patients being evaluated for possible costly third-line treatments, such as omalizumab. We compared efficacy and safety in second-line treatments for refractory CU to standard doses of nsAHs (i.e., updosing of nsAHs 4-fold, multiple combination treatment with 4 nsAHs, switching nsAHs, and adjunctive H2RA).

MATERIALS AND METHODS

Study design

This 4-week, prospective, randomized, open-label trial was conducted between August 2017 and August 2019 at 2 allergy clinics in university hospitals. The participants were randomized to 4 second-line treatment groups: 4-fold updosing of nsAHs, multiple combination of 4 nsAHs (high-dose nsAH groups), switching to other nsAHs, and adjunctive H2RA (standard-dose nsAH groups). Randomization was performed according to a balanced block design with a centrally generated randomization code. Blocks of 8 randomization numbers were allocated to each center. Antihistamines used in the trial were all second-generation antihistamines, including once a day of levocetirizine, cetirizine, fexofenadine, ebastine, and loratadine and twice a day of bepotastine, olopatadine, and azelastine. Cimetidine was used as H2RA.

During the study period, poor control or worsening of CU was treated with rescue medications, i.e., sedating H_1-antihistamines (10 mg of hydroxyzine or 2 mg of chlorpheniramine) followed by OCSs (10 mg of prednisolone) for 3 consecutive days. The study design is presented in **Fig. 1**.

Patients

We included outpatients aged > 18 years who had persistent urticaria (wheal formation or angioedema for > 6 weeks) and poor disease control despite treatment with at least 2 nsAHs for > 2 weeks. The control status of CU was determined by allergy specialists, as described in the evaluation of treatment efficacy below.[11] Patients with other chronic dermatological diseases or liver enzyme levels > 2-fold higher than the reference ranges were excluded from the study.

At enrollment (visit 1, V1), clinical data were collected including age, sex, height, body weight, medical history (hypertension, diabetes mellitus, thyroid disease, asthma, allergic rhinitis, atopic dermatitis, food allergy, and drug allergy), history of adverse reaction to nsAHs, onset age of CU, disease duration, and response to previous medications. Body mass index (BMI) was calculated as Weight/Height^2. We also recorded laboratory parameters, including the complete blood count (neutrophils, eosinophils, and lymphocytes) and aspartate transaminase (AST), alanine transaminase (ALT), creatinine, and total immunoglobulin E (IgE) levels. The patients were divided into normal and high total IgE level (0–114 and > 114 kU/L, respectively) groups according to previous studies.[25-28] The autologous serum skin test was also performed according to the method described in the EAACI/GA^{2}LEN task force consensus report.[29]

Evaluation of treatment efficacy

The primary endpoint was urticaria control status after 4 weeks of second-line treatment. Urticaria control state was categorized by physicians as well-controlled, partly controlled, or uncontrolled.[11] CU was considered well-controlled if patients on medication had no itchy wheals, partly controlled if the urticarial symptoms were reduced but not fully controlled, and uncontrolled if the urticarial symptoms were not controlled by medications.

https://doi.org/10.4168/aair.2023.15.4.496

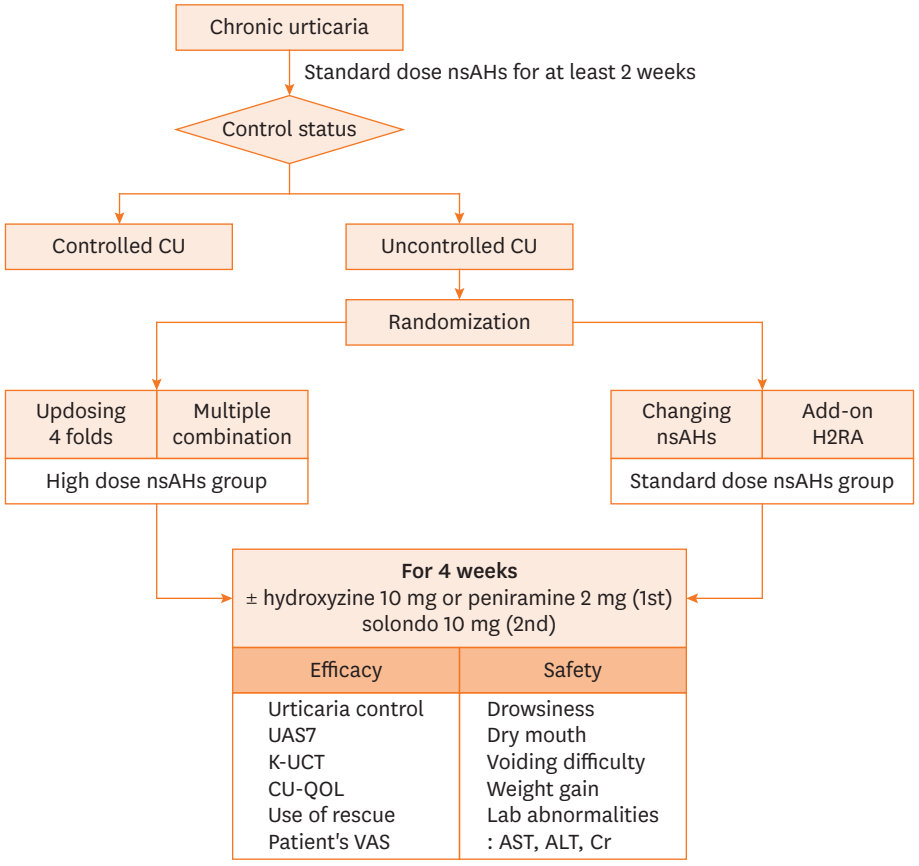

Fig. 1. Study design.
CU, chronic urticaria; nsAH, nonsedating H_1-antihistamine; H2RA, H_2-receptor antagonist; UAS7, urticaria activity score over 7 days, K-UCT, Korean version of the urticaria control test; CU-QOL, chronic urticaria-specific quality of life; VAS, visual analogue scale; AST, aspartate transaminase; ALT, alanine transaminase; Cr, creatinine.

The secondary endpoints were patient-reported outcomes (PROs) including the urticaria activity score over 7 days (UAS7), score on the Korean version of the urticaria control test (K-UCT; originally developed in German), chronic urticaria-specific quality of life (CU-QOL) score, visual analogue scale (VAS) score, and rescue medications used.[8,11,15,24,30] The UAS7 was calculated by summing the itch severity score (0, none; 1, mild; 2, moderate; 3, severe) and wheal score (0, no wheals; 1, 1–19 wheals; 2, 20–50 wheals; 3, > 50 wheals). A UAS7 of 0 indicated complete symptom control. The CU-QOL consists of 17 items distributed over 4 domains: urticarial symptoms, emotional distress, food and environmental distress, and stigma. Rescue medication use was analyzed in terms of frequency, cumulative dose, and the number of participants who used such medications (i.e., H_1-antihistamines or OCS).

Safety profile

Adverse reactions to nsAHs were recorded at V1 and V2, including drowsiness, dry mouth, voiding difficulty, weight gain, and abnormal serum creatinine and liver function tests.

Ethical issues

This study was approved by Ajou and Hallym University Hospital Institutional Review Boards (AJIRB-MED-OBS-17-173 and HDT2017-08-002). All patients provided written informed consent at the time of enrollment.

https://doi.org/10.4168/aair.2023.15.4.496

Statistical analysis

Continuous variables are presented as means ± standard deviations, and categorical variables as numbers (percentages). Clinical characteristics and treatment responses were compared between high- and standard-dose groups using Student's *t*-test for continuous data and the χ^2 test for categorical data. The 4 groups were compared using analysis of variance and the χ^2 test, with *P* values adjusted according to the false discovery rate using R software (version 4.1.0; R Foundation for Statistical Computing, Vienna, Austria). Changes in symptom scores after 4 weeks of second-line treatment were analyzed using generalized estimating equations. Associations were analyzed using Pearson's correlation for continuous data and logistic regression for categorical data. All tests were 2-sided, and $P < 0.05$ was considered significant. Statistical analyses were conducted using SPSS software (version 18.0; IBM Corp., Armonk, NY, USA).

RESULTS

Study participants

In total, 114 patients participated in this study, 11 of whom could not complete it because of adverse reactions (n = 2) or insufficient efficacy (n = 9). Available data were used in the full data analysis, and a total of 109 patients' V2 data were included in the analysis (**Supplementary Fig. S1**). The mean age of the participants was 39.8 ± 12.7 years, and 56.0% were female. The onset age of CU was 37.6 ± 13.5 years, and the mean disease duration was 25.2 months. In total, 26 (23.9%) patients did not respond to standard doses of nsAHs, whereas the remaining 83 (76.1%) exhibited insufficient improvement. **Table 1** presents the CU symptom scores and demographic characteristics of the participants. Most clinical characteristics showed no statistically significant differences among groups, including age, sex, urticaria duration, and laboratory parameters (**Table 1**).

Outcomes after 4 weeks of second-line treatment

Urticaria was well-controlled, partly controlled, and uncontrolled in 43.1%, 36.7%, and 20.2% of patients after 4 weeks of treatment, respectively (**Fig. 2**). There were significant differences in urticaria control status among all 4 groups ($P = 0.007$; **Fig. 2A**), and between the high- and standard-dose groups; the proportion of well-controlled cases was significantly higher in the high-dose group than in the standard-dose group at V2 (51.9% vs. 34.5%; $P = 0.031$; **Fig. 2B**). However, there was no significant difference in urticaria control status between the nsAH updosing and combination treatment groups (57.7% vs. 46.4%, $P = 0.616$; **Fig. 2A**).

Complete symptom control (i.e., UAS7 = 0 at V2) was achieved in 21 (20.4%) patients after 4 weeks of treatment. The rate of complete urticaria control was higher in the nsAH updosing group than in the combination treatment group ($P = 0.030$; **Fig. 3A**), but there was no significant difference between the high- and standard-dose groups ($P = 0.292$; **Fig. 3B**).

Next, we compared the CU symptom scores and changes therein after 4 weeks of second-line treatment. All treatments significantly improved the CU-related PROs, including the UAS7, K-UCT, CU-QOL, and VAS scores (**Table 2**), and there were no differences in the degree of improvement among the 4 groups (**Supplementary Fig. S2**).

https://doi.org/10.4168/aair.2023.15.4.496

Table 1. Comparison of clinical characteristics by second-line treatments

Variables	Total (n = 109)	High dose of nsAHs		Standard dose of nsAHs		*P* value
		Updosing 4 folds (n = 26)	Multiple combination (n = 28)	Changing nsAHs (n = 28)	Add-on H2RA (n = 27)	
Age (yr)	39.8 ± 12.7	35.8 ± 12.4	41.3 ± 13.2	40.3 ± 12.5	41.6 ± 12.5	0.308
Female	61 (56.0)	9 (34.6)	14 (50.0)	15 (53.6)	10 (37.0)	0.816
BMI (kg/m^2)	23.7 ± 3.5	22.4 ± 3.9	23.3 ± 3.4	24.6 ± 3.4	24.5 ± 2.8	0.054
Hypertension	11 (10.1)	0 (0)	1 (3.6)	6 (21.4)	4 (14.8)	0.031
Diabetes	2 (1.8)	0 (0)	1 (3.6)	0 (0)	1 (3.7)	0.532
Thyroid disease	4 (3.7)	1 (3.8)	2 (7.1)	1 (3.6)	0 (0)	0.346
Previous allergic disease						
Bronchial asthma	2 (1.8)	1 (3.8)	0 (0)	1 (3.6)	0 (0)	0.509
Allergic rhinitis	50 (45.9)	15 (57.7)	7 (25.0)	13 (46.4)	15 (55.6)	0.689
Atopic dermatitis	3 (2.8)	0 (0)	1 (3.6)	1 (3.6)	1 (3.7)	0.442
Food allergy	5 (4.6)	0 (0)	2 (7.1)	1 (3.6)	2 (7.4)	0.316
Drug allergy	5 (4.6)	0 (0)	2 (7.1)	2 (7.1)	1 (3.7)	0.555
Onset age of CU (yr)	37.6 ± 13.5	32.4 ± 13.9	39.9 ± 13.3	37.7 ± 12.8	40.1 ± 13.3	0.132
Duration of CU (mon)	25.2 ± 54.2	39.7 ± 75.0	15.6 ± 24.6	29.8 ± 69.5	16.4 ± 27.3	0.303
Previous treatment response						0.897
No response	26 (23.9)	6 (23.1)	7 (25.0)	6 (21.4)	7 (25.9)	
Insufficient efficacy	83 (76.1)	20 (76.9)	21 (75.0)	22 (78.6)	20 (74.1)	0.897
ASST positivity (n = 82)	30 (27.5)	10 (47.6)	8 (34.8)	6 (27.3)	6 (37.5)	0.385
Total IgE (kU/L)	245.3 ± 374.0	178.9 ± 157.9	190.4 ± 184.9	343.4 ± 592.3	264.4 ± 372.6	0.335
Total IgE group						0.828
Normal (0–114)	55 (50.5)	14 (53.8)	14 (50.0)	13 (46.4)	14 (51.9)	
High (> 114)	54 (49.5)	12 (46.2)	14 (50.0)	15 (53.6)	13 (48.1)	
WBC (%)						
Neutrophil	59.0 ± 8.3	59.3 ± 8.2	58.2 ± 7.8	60.3 ± 8.5	58.5 ± 8.9	0.969
Lymphocyte	30.4 ± 7.9	30.1 ± 9.4	30.5 ± 6.6	29.9 ± 7.6	30.9 ± 8.2	0.969
Eosinophil	2.4 ± 1.8	1.9 ± 1.4	2.8 ± 2.1	2.2 ± 1.5	2.8 ± 2.0	0.198
AST (IU/L)	20.8 ± 6.9	19.1 ± 4.1	22.9 ± 9.7	19.1 ± 5.0	22.2 ± 6.6	0.069
ALT (IU/L)	22.7 ± 13.6	19.2 ± 9.3	23.3 ± 13.3	23.3 ± 15.4	25.0 ± 15.5	0.461
Creatinine (mg/dL)	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.569
CU symptom score						
UAS7 (0–42)	23.3 ± 9.5	22.9 ± 8.3	22.0 ± 10.4	23.0 ± 9.5	25.4 ± 9.7	0.591
K-UCT (0–16)	7.1 ± 3.0	8.2 ± 3.0	7.1 ± 3.0	6.9 ± 2.9	6.3 ± 2.9	0.132
CU-QOL (0–100)	63.3 ± 20.0	69.2 ± 18.4	64.1 ± 22.2	59.3 ± 20.0	60.8 ± 18.5	0.275
Patient's VAS (0–100)	57.1 ± 28.0	51.5 ± 28.0	49.4 ± 27.5	60.8 ± 31.3	66.7 ± 22.3	0.074

Values are presented as number (%) or mean ± standard deviation. *P* values were calculated by linear-by-linear association test in categorical variables and by analysis of variance in continuous variables.

ALT, alanine transaminase; ASST, autologous serum skin test; AST, aspartate transaminase; BMI, body mass index; CU, chronic urticaria; CU-QOL, chronic urticaria-specific quality of life; H2RA, H_2-receptor antagonist; IgE, immunoglobulin E; K-UCT, Korean version of urticaria control test; nsAH, nonsedating H_1-antihistamine; UAS7, urticaria activity score over 7 days; VAS, visual analogue scale; WBC, white blood cell.

Parameters associated with urticaria control status after 4 weeks of second-line treatment

Baseline clinical characteristics were compared according to the therapeutic response after 4 weeks of treatment (**Table 3**). There were significant differences in CU duration, total IgE level, CU symptom scores, and treatment types. Next, logistic regression analysis was performed to identify clinical parameters associated with well-controlled urticaria after 4 weeks of treatment (**Table 4**). No parameters, except the K-UCT score, showed an association with well-controlled status. Additionally, there was no significant difference in the proportion of well-controlled cases between the nsAH updosing and combination treatment groups (odds ratio [OR], 0.636; $P = 0.409$). The initial K-UCT score was significantly associated with successful treatment outcomes, indicating that the lower initial symptom burden was associated with the well-controlled state. The other clinical and laboratory parameters analyzed in previous studies[27] were not associated with the well-controlled state of CU in the present study.

https://doi.org/10.4168/aair.2023.15.4.496

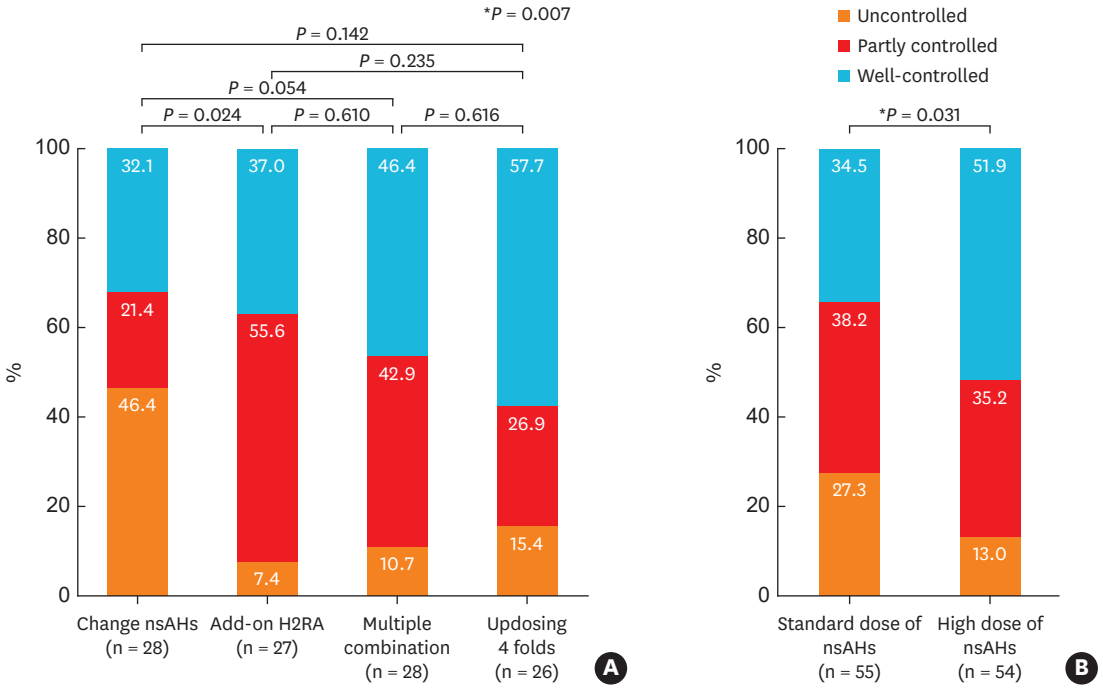

Fig. 2. Urticaria control status, as assessed by physicians after 4 weeks of treatment. Comparisons among the 4 treatment groups: (A) 4-fold updosing of nsAHs, combination treatment with 4 nsAHs, switching to other nsAHs, and adjunctive H2RA and (B) high- and standard-dose nsAH groups are presented. *P* values were calculated by the χ^2 test after adjustment based on the false discovery rate (R 4.1.0; R Foundation for Statistical Computing, Vienna, Austria) to correct bias during multiple comparisons.
nsAH, nonsedating H_1-antihistamine; H2RA, H_2-receptor antagonist.
**P* valuescalculated using the linear-by-linear association test.

The logistic regression analysis according to the nsAH dose groups showed that the serum total IgE level was significantly associated with the well-controlled state when the patients were treated with the standard doses of nsAHs (OR, 0.994; *P* = 0.025; **Supplementary Table S1**). Patients with a high total IgE showed a lower likelihood of well-controlled CU compared to those with a normal total IgE level (OR, 0.202; *P* = 0.011) among those treated with standard doses of nsAHs. Younger age was significantly associated with well-controlled CU (OR, 0.938; *P* = 0.035), whereas low BMI showed a trend toward an association with well-controlled CU (OR, 0.786; *P* = 0.062). However, these associations were not observed in patients treated with high-dose nsAHs (**Supplementary Table S2**). Patients with a high total IgE level had a higher likelihood of well-controlled CU compared to those with a normal total IgE level (OR, 2.919; *P* = 0.058), while age and BMI were not significantly associated with well-controlled CU in these patients. In both nsAH dose groups, outcomes did not differ by treatment regimen.

Logistic regression analysis was performed to identify clinical parameters associated with complete symptom control (UAS7 = 0 at V2; **Table 5**). Unlike the results for well-controlled CU status, a higher rate of complete control was seen in the nsAH updosing group compared to the combination treatment group (OR, 0.180; *P* = 0.020) and patients receiving standard doses of nsAHs (OR, 0.293; *P* = 0.025). CU symptom scores showed significant associations with complete symptom control. Additionally, logistic regression analysis according to the nsAH dose groups revealed no significant associations of clinical parameters with complete urticaria control, except in the nsAH updosing group relative to the other second-line treatments (OR, 0.180, *P* = 0.020, results were not shown).

https://doi.org/10.4168/aair.2023.15.4.496

Table 2. Comparison of CU symptom scores after 4 weeks of second-line treatments

Variables	UAS7 (0–42)			K-UCT (0–16)			CU-QOL (0–100)			Patient's VAS (0–100)		
	Visit 1	Visit 2	*P* value	Visit 1	Visit 2	*P* value	Visit 1	Visit 2	*P* value	Visit 1	Visit 2	*P* value
High dose nsAHs												
Updosing 4 folds (n = 25)	23.2 ± 8.3	10.4 ± 12.6	< 0.001	8.2 ± 3.1	10.0 ± 4.6	0.030	68.2 ± 18.0	78.6 ± 26.5	0.006	53.1 ± 27.3	31.7 ± 30.1	0.002
Multiple combination (n = 28)	22.0 ± 10.4	16.3 ± 11.3	0.012	7.1 ± 3	9.4 ± 3.9	< 0.001	64.1 ± 22.2	74.6 ± 22.7	0.005	49.4 ± 27.5	36.1 ± 30.2	0.020
Standard dose nsAHs												
Changing nsAHs (n = 28)	23.0 ± 9.5	17.0 ± 12.1	0.007	6.9 ± 2.9	9.1 ± 3.8	0.002	59.3 ± 20.0	76.5 ± 18.8	< 0.001	60.8 ± 31.3	38.4 ± 28.2	0.001
Add-on H2RA (n = 27)	25.4 ± 9.7	15.3 ± 12.6	0.001	6.3 ± 2.9	9.3 ± 3.8	0.001	60.8 ± 18.5	75.9 ± 21.5	0.001	66.7 ± 22.3	36.3 ± 28.8	< 0.001

Values are presented as mean ± standard deviation. *P* values were calculated by paired *t*-test between visit 1 and 2.
CU, chronic urticaria; CU-QOL, chronic urticaria-specific quality of life; H2RA, H_2-receptor antagonist; K-UCT, Korean version of urticaria control test; nsAH, nonsedating H_1-antihistamine; UAS7, urticaria activity score over 7 days; VAS, visual analogue scale.

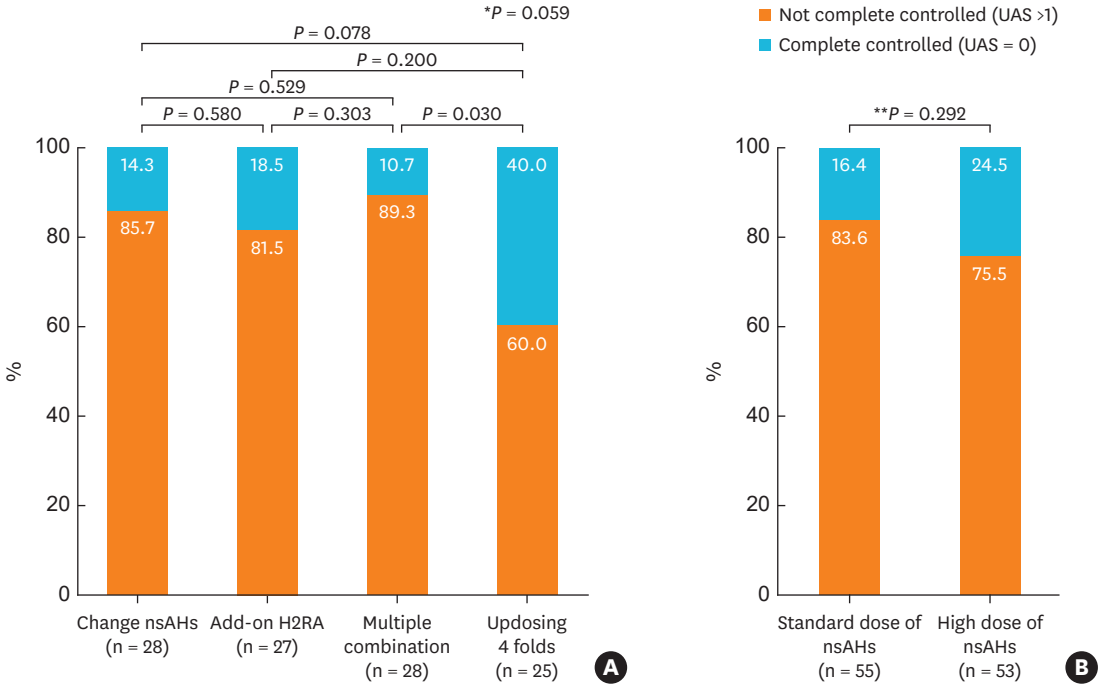

Fig. 3. Proportion of cases achieving complete urticaria control (UAS7 = 0) after 4 weeks of treatment. Comparisons among the 4 treatment groups: (A) 4-fold updosing of nsAHs, combination treatment with 4 nsAHs, switching to other nsAHs, and adjunctive H2RA and (B) high- and standard-dose nsAH groups are presented. *P* values were calculated using the χ^2 test after adjustment based on the false discovery rate (R 4.1.0; R Foundation for Statistical Computing, Vienna, Austria) to correct bias during multiple comparisons.
nsAH, nonsedating H_1-antihistamine; H2RA, H_2-receptor antagonist; UAS, urticaria activity score.
**P* values calculated using the linear-by-linear association test.
***P* values calculated using the χ^2 test.

Serum total IgE levels according to control status

The initial serum total IgE level significantly differed by urticaria control status (well-controlled, partly controlled, and uncontrolled; **Fig. 4A**). No significant difference was observed in serum total IgE according to control status in the high-dose group (well-controlled, 213.8 ± 170.0 kU/L; partly controlled, 142.0 ± 182.7 kU/L; uncontrolled, 185.1 ± 134.6 kU/L; *P* = 0.375; **Fig. 4B**). However, significant differences were observed in total IgE levels according to control status in the standard-dose group (well-controlled, 112.1 ± 99.2 kU/L; partly controlled, 263.2 ± 205.1 kU/L; uncontrolled, 606.3 ± 846.9 kU/L; *P* = 0.011; **Fig. 4C**). The correlation analysis between the initial serum total IgE level and UAS7 scores at V2 showed similar associations (**Fig. 4D-F**), particularly in patients treated with standard doses of nsAHs (**Fig. 4F**; r = 0.334; *P* = 0.013).

https://doi.org/10.4168/aair.2023.15.4.496

Table 3. Comparisons of baseline clinical characteristics according to therapeutic response after 4-week treatment

Variables	Well-controlled (n = 47)	Partly controlled (n = 40)	Uncontrolled (n = 22)	*P* value
Age	38.0 ± 13.3	40.6 ± 11.4	42.1 ± 13.6	0.404
Female	28 (59.6)	21 (52.5)	12 (54.5)	0.613*
BMI (kg/m^2)	23.1 ± 3.6	24.0 ± 3.3	24.5 ± 3.6	0.230
Onset age of CU (yr)	36.7 ± 13.5	38.8 ± 12.0	37.4 ± 16.3	0.787
Duration of CU (mon)	16.1 ± 27.1	19.4 ± 28.6	55.1 ± 104.0	0.013
ASST positivity (n = 81)	15 (38.5)	11 (44.0)	4 (22.2)	0.341*
Total IgE (kU/L)	172.7 ± 152.8	205.6 ± 201.8	472.3 ± 723.6	0.005
Normal (0–114)	25 (53.2)	21 (52.5)	9 (40.9)	0.397*
High (> 114)	22 (46.8)	19 (47.5)	13 (59.1)	
CU symptom score				
UAS7 (0–42)	21.3 ± 8.9	23.3 ± 9.9	27.7 ± 8.8	0.032
K-UCT (0–16)	8.3 ± 2.5	6.6 ± 3.2	5.6 ± 2.9	0.001
CU-QOL (0–100)	67.8 ± 19.8	63.5 ± 19.8	53.3 ± 17.6	0.018
Patient's VAS (0–100)	53.7 ± 26.2	52.7 ± 30.1	72.5 ± 23.3	0.014
Treatment arms				0.007*
Changing nsAH	9 (19.1)	6 (15.0)	13 (59.1)	
Add-on H2RA	10 (21.3)	15 (37.5)	2 (9.1)	
Combined 4 nsAHs	13 (27.7)	12 (30.0)	3 (13.6)	
Updosing 4 folds	15 (31.9)	7 (17.5)	4 (18.2)	
Treatment groups				
High dose nsAHs	28 (59.6)	19 (47.5)	7 (31.8)	0.031*
Standard dose nsAHs	19 (40.4)	21 (52.5)	15 (68.2)	

Values are presented as number (%) or mean ± standard deviation.
ASST, autologous serum skin test; BMI, body mass index; CU, chronic urticaria; CU-QOL, chronic urticaria-specific quality of life; H2RA, H_2-receptor antagonist; IgE, immunoglobulin E; K-UCT, Korean version of urticaria control test; nsAH, nonsedating H_1-antihistamine; UAS7, urticaria activity score over 7 days; VAS, visual analogue scale.
*P value was analyzed by linear-by-linear association test and other P values by analysis of variance.

Table 4. Parameters associated with the well-controlled state after 4 weeks of second-line treatments

Variables (n = 109)	OR	95% CI	*P* value
Age (yr)	0.980	0.951–1.011	0.203
Sex (female)	1.295	0.601–2.789	0.509
BMI (kg/m^2)	0.909	0.808–1.021	0.108
Duration of CU (mon)	0.990	0.981–1.003	0.169
ASST positivity (n = 82)	1.167	0.474–2.869	0.737
Total IgE (kU/mL)	0.999	0.997–1.000	0.106
Total IgE group			
Normal (0–114)	Ref.		
High (> 114)	0.825	0.386–1.763	0.619
CU symptom score at visit 1			
UAS7 (0–42)	0.973	0.923–1.025	0.306
K-UCT (0–16)	1.424	1.128–1.798	0.003
CU-QOL (0–100)	0.992	0.964–1.021	0.602
Patient's VAS (0–100)	1.017	0.997–1.039	0.100
Treatment types			0.139
Updosing 4 folds	Ref.		
Multiple combination	0.636	0.217–1.863	0.409
Standard dose nsAHs	0.387	0.149–1.007	0.052

ASST, autologous serum skin test; BMI, body mass index; CI, confidential interval; CU, chronic urticaria; CU-QOL, chronic urticaria-specific quality of life; IgE, immunoglobulin E; K-UCT, Korean version of urticaria control test; nsAH, nonsedating H_1-antihistamine; OR, odds ratio; UAS7, urticaria activity score over 7 days; VAS, visual analogue scale.

Rescue medication use

Rescue medication use was analyzed in terms of frequencies, cumulative doses, and proportions of patients requiring such medications. There were no significant differences in the use of rescue H_1-antihistamines among the 4 treatment groups (**Table 6**). Comparison of the nsAH dose groups showed a lower frequency of use of sedating H_1-antihistamines in the

https://doi.org/10.4168/aair.2023.15.4.496

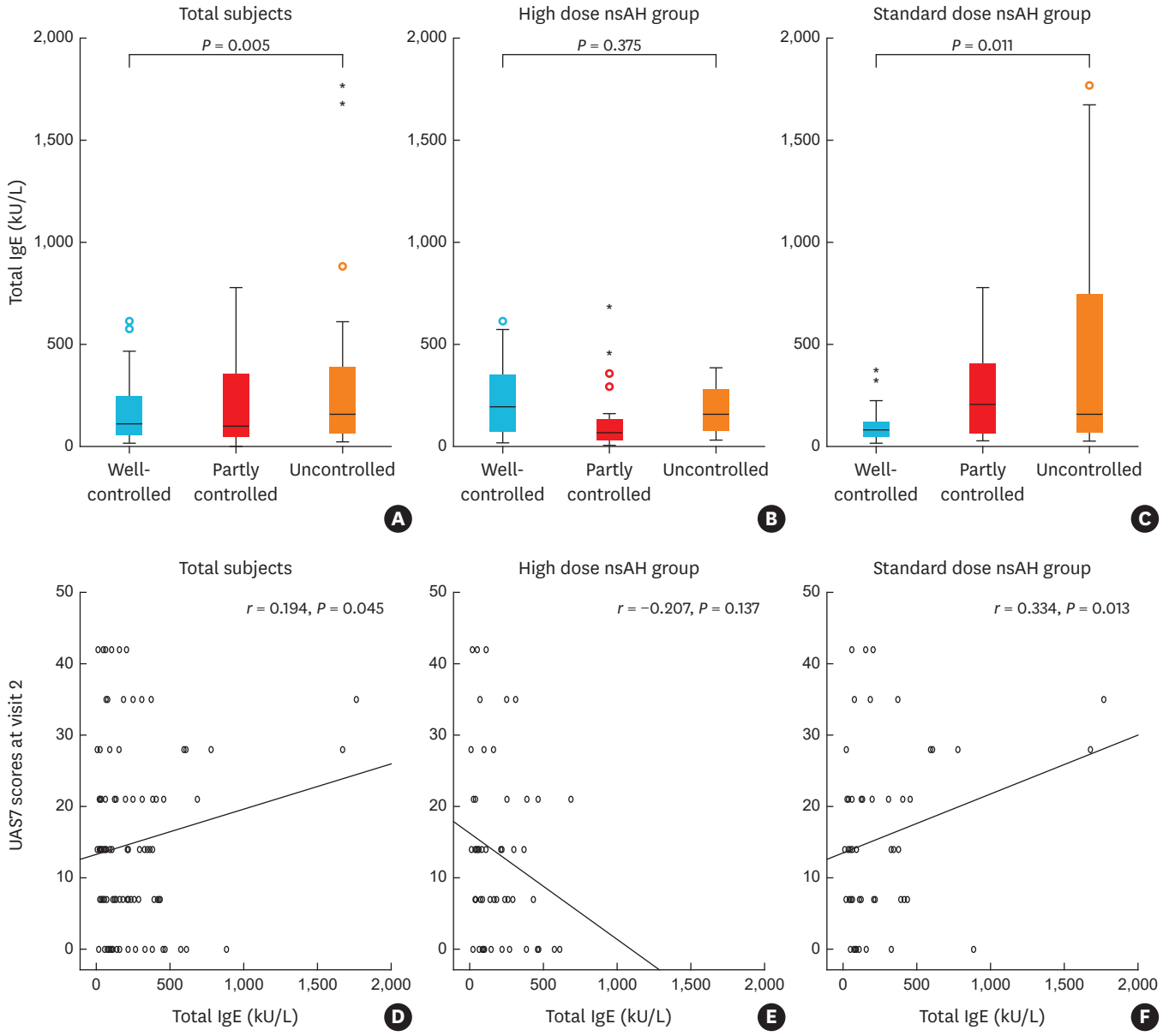

Fig. 4. Comparison of serum total IgE level between well-controlled and partly/uncontrolled chronic urticaria cases after 4 weeks of second-line treatment in all patients (A), the high-dose nsAH group (B), and the standard-dose nsAH group (C). Correlation between serum total IgE level and UAS7 score at visit 2 in all patients (D), the high-dose nsAH group (E), and the standard-dose nsAH group (F).
IgE, immunoglobulin E; nsAH, nonsedating H_1-antihistamine; UAS7, urticaria activity score over 7 days.

high- than low-dose group (0.69 ± 0.87 vs. 1.27 ± 2.35; P = 0.086; **Supplementary Fig. S3A**). However, no significant differences were observed in cumulative dose between the high- and low-dose groups (60.9 ± 104.7 vs. 74.6 ± 96.0; P = 0.480; **Supplementary Fig. S3B**). There were no significant differences in the proportion of patients using sedating H_1-antihistamines as rescue medications between the high- and standard-dose nsAH groups (50.0% vs. 56.6%, respectively; P = 0.502).

The rate of use of rescue OCSs did not show a significant difference among the 4 treatment groups (**Table 6**). No significant difference was observed between the high- and standard-dose groups in OCS use rate (34.0% vs. 32.1%; P = 0.836). Similar results were obtained in

https://doi.org/10.4168/aair.2023.15.4.496

Table 5. Parameters associated with the complete control state (UAS7 = 0)

Variables (n = 108)	OR	95% CI	*P* value
Age (yr)	0.978	0.941–1.016	0.247
Sex (female)	1.863	0.691–5.026	0.219
BMI (kg/m^2)	1.003	0.877–1.148	0.959
Duration of CU (mon)	1.001	0.993–1.009	0.857
ASST positivity (n = 81)	2.304	0.778–6.824	0.132
Total IgE (kU/mL)	1.000	0.999–1.001	0.964
Total IgE group			
Normal (0–114)	Ref.		
High (> 114)	1.000	0.392–2.551	1.000
CU symptom score at visit 1			
UAS7 (0–42)	0.974	0.925–1.026	0.329
K-UCT (0–16)	1.299	1.087–1.553	0.004
CU-QOL (0–100)	1.031	1.002–1.061	0.036
Patient's VAS (0–100)	0.983	0.967–1.000	0.050
Treatment types			0.025
Updosing 4 folds	Ref.		
Multiple combination	0.180	0.043–0.760	0.020
Standard dose nsAHs	0.293	0.100–0.858	0.025

ASST, autologous serum skin test; BMI, body mass index; CI, confidential interval; CU, chronic urticaria; CU-QOL, chronic urticaria-specific quality of life; IgE, immunoglobulin E; K-UCT, Korean version of urticaria control test; nsAH, nonsedating H_1-antihistamine; OR, odds ratio; UAS7, urticaria activity score over 7 days, VAS, visual analogue scale.

Table 6. Use of rescue medications during the study period by the 4 study groups

Variables	High dose nsAHs		Standard dose nsAHs		*P* value
	Updosing 4 folds (n = 26)	Multiple combination (n = 28)	Changing nsAHs (n = 28)	Add-on H2RA (n = 27)	
Rescue H_1-antihistamine					
Frequency	0.69 ± 0.93	0.68 ± 0.82	1.61 ± 3.01	0.93 ± 1.33	0.177
Cumulative dose	63.46 ± 91.87	58.57 ± 116.96	73.21 ± 90.64	75.93 ± 102.97	0.911
No. of subjects	13 (54.2)	12 (46.2)	17 (60.7)	13 (52.0)	0.759
Rescue OCS					
Frequency	0.42 ± 0.90	0.79 ± 1.75	0.79 ± 1.73	0.33 ± 0.56	0.471
Cumulative dose	16.54 ± 39.08	21.07 ± 39.28	22.50 ± 34.06	21.85 ± 40.67	0.941
No. of subjects	7 (29.2)	10 (38.5)	9 (32.1)	8 (32.0)	0.912

Values are presented as number (%) or mean ± standard deviation.
H2RA, H_2-receptor antagonist; nsAHs, nonsedating H_1-antihistamines; OCS, oral corticosteroid.

the comparison of high- and standard-dose groups in terms of the frequency of OCS use (0.61 ± 1.40 vs. 0.56 ± 1.30; *P* = 0.855) and cumulative OCS dose (18.89 ± 38.88 vs. 22.18 ± 37.10; *P* = 0.652).

Safety profile

After 4 weeks of second-line treatment, 18 (16.7%) patients experienced adverse events, including drowsiness (27.6%), dry mouth (20.7%), dyspepsia (13.8%), weight gain (13.8%), and frequent urination (10.3%). There were no significant differences in the frequency of adverse events among all 4 treatment groups (11.5%, 18.5%, 14.3%, and 22.2% in the updosing, combination treatment, switching treatment, and adjunctive H2RA groups, respectively; *P* = 0.396) or between the 2 dose groups (15.1% and 18.2% in the high- and standard-dose groups, respectively; *P* = 0.667). Additionally, no patients exhibited laboratory abnormalities, including in the AST, ALT, or creatinine level, after 4 weeks of second-line treatment.

https://doi.org/10.4168/aair.2023.15.4.496

DISCUSSION

In this randomized, open-label trial, we compared the efficacy of second-line treatments for CU refractory to standard doses of nsAHs. The second-line treatments included high-dose (4-fold updosing of nsAHs and combination treatments of 4 nsAHs) and standard-dose (switching to other nsAHs and adjunctive H2RA) nsAHs. After 4 weeks of second-line treatment, 43.1% of patients achieved well-controlled status, while in the remaining patients, the disease was partly controlled (36.7%) or uncontrolled (20.2%). In the high-dose group, the proportion of well-controlled cases was higher compared to the standard-dose group (51.9% vs. 34.5%, $P = 0.031$). High doses of nsAHs were well-tolerated, and no significant differences were observed in adverse events or laboratory abnormalities after 4 weeks of treatment relative to baseline. A previous meta-analysis showed that the updosing of nsAHs significantly improved the control of pruritus in CU patients, but not the wheal number. However, definitive conclusions could not be drawn because the meta-analysis had certain limitations, such as significant heterogeneity among the included studies.[19] However, another study reported good CU control outcomes with long-term updosing of nsAHs and multiple combination treatment.[31] Our data support the efficacy of high-dose nsAHs for controlling CU: treatment with high-dose nsAHs for 1 month was associated with well-controlled CU in almost half of the patients, with no significant adverse reactions. One-third of CU patients treated with standard doses of nsAHs also achieved well-controlled CU status. These findings suggest that the considering time point for the use of omalizumab should be reconsidered. Current international guidelines recommend the use of omalizumab if CU is uncontrolled after 2–4 weeks of nsAH treatment. In patients refractory to standard doses of nsAHs, CU may be controlled with 1 month of nsAH treatment, particularly when higher doses are used. Similar efficacy was observed between our nsAH updosing and multiple combination treatment groups in terms of CU control, whereas a higher rate of complete control was observed in the updosing group than in the combination treatment group; there were no significant differences in adverse events.

In addition to the nsAH dose, a higher baseline total IgE level was significantly associated with CU control status after 4 weeks of nsAH treatment, particularly for CU patients treated with standard doses of nsAHs. In these patients, the baseline total IgE level was negatively associated with well-controlled CU status. Additionally, patients with a high total IgE level had a lower likelihood of well-controlled CU status during standard-dose nsAH treatment, whereas control was improved with high doses of nsAHs. Therefore, patients with a high baseline total IgE level may be poorly responsive to standard doses of nsAHs; for such patients, a high dose of nsAHs should be considered. Recent studies have proposed 2 pathogenic mechanisms for chronic spontaneous urticaria (CSU): type I and type IIb autoimmune mechanisms. A higher serum total IgE level is characteristic of type I autoimmune CSU, and a good response to nsAHs or omalizumab. By contrast, type IIb CSU is similar to autoimmune diseases.[32] Our findings also suggest that, in CU patients with a higher total IgE level, the disease may be better controlled with high rather than standard nsAH doses.

Similar to the total IgE level, BMI was negatively associated with urticaria control in the standard-dose group, suggesting that obese CU patients are less likely to respond to the standard doses of nsAHs. We hypothesized that these results may be due to the effect of BMI on the effective medication dose: nsAH levels may be lower in obese CU patients than in CU patients with a normal or low BMI, which could explain the differences in treatment efficacy according to BMI seen with standard-dose treatment. The lack of difference in treatment

efficacy according to BMI at high nsAH doses could be explained by such doses being sufficient regardless of BMI. In a previous study, BMI showed an inconsistent association with responsiveness to nsAHs.[27] However, limited information was available regarding the nonresponse to nsAHs, and the exact nsAH dose was not known in most cases. In our study, BMI was negatively associated with treatment outcomes when standard doses of nsAHs were used. In addition to the total IgE level and BMI, an initial worse symptom score was associated with a poor response to nsAH treatment, similar to previous studies.[27]

Taken together, these findings suggest that high doses of nsAHs are associated with better CU control compared to standard doses, while no significant differences were observed between the nsAH updosing 4-fold and multiple combination treatment groups. CU patients with a higher total IgE level (> 114 kU/L), older age, or higher BMI may be less responsive to standard doses of nsAHs. Such patients should be considered for high-dose treatment, i.e., nsAH updosing or combination treatment.

Most recent randomized controlled trials of CU treatments have focused on third-line treatments, particularly omalizumab.[33] Omalizumab is effective for the treatment of CU cases refractory to previous treatments, although it is prohibitively expensive. By contrast, few clinical trials have evaluated second-line treatments for CU patients refractory to the standard doses of nsAHs. To the best of our knowledge, this is the first prospective, randomized, head-to-head comparison of various nsAH treatment regimens, particularly 4-fold updosing of nsAHs and combination treatment with 4 nsAHs. There was no significant difference in the proportion of well-controlled CU cases between the updosing and combination treatment groups, while the rate of complete CU control was higher in the former group. Additionally, 51.9% of CU patients refractory to standard-dose nsAHs responded to 4 weeks of treatment with high-dose nsAHs, suggesting that clinicians should consider the use of high-dose nsAHs before omalizumab, which is effective but expensive.

The international EAACI/GA²LEN/EuroDerm/APAAACI guideline does not recommend nsAH combination treatment because of insufficient evidence regarding its efficacy and safety. However, our study supports the effectiveness of combination treatment for CU control in patients refractory to standard doses of nsAHs without safety issues. Additionally, 4-fold updosing of nsAHs is safe and effective. The discriminated point between these 2 treatments is the superiority of complete symptom control (i.e., no urticaria after 4 weeks of treatment) in 4-fold updosing of nsAH than combination treatment. The updated EAACI/GA²LEN/EuroDerm/APAAACI international guideline defined the treatment goal of CU as urticarial remission and complete symptom control (continuous UAS7 = 0).[3] To achieve this goal, 4-fold updosing of nsAHs has been recommended as a preferable second-line treatment. However, considering the reimbursement and licensing problems associated with updosing of nsAHs, combination treatment may be more feasible for achieving well-controlled status. Nevertheless, updosing remains the ideal treatment regimen for CU patients refractory to standard doses of nsAHs.

There were some limitations to the present study, including the small sample size and short study duration. The relatively small number of patients in each group may explain the lack of statistically significant differences among them. Additionally, a 4-week study period is insufficient to evaluate the efficacy of second-line treatments in some patients. Nevertheless, we compared the efficacy and safety of various nsAH treatments in this prospective randomized trial, particularly nsAH updosing and combination treatment. Although the study topic may not be of interest to pharmaceutical companies, it offers interestto clinicians.

https://doi.org/10.4168/aair.2023.15.4.496

Additionally, we analyzed clinical parameters that predicted CU control according to nsAH dose (standard or high).

In conclusion, high-dose nsAHs, via updosing or combination treatment, were effective for controlling CU in patients refractory to standard doses, with no adverse effects. However, updosing was more effective than combination treatment for complete CU control. Additionally, CU patients who are old or obese, or have a high serum total IgE level, would be poorly responsive to standard doses of nsAHs; such patients should be considered for high-dose treatment via updosing or combination treatment.

ACKNOWLEDGMENTS

This study was supported by a grant from the Korean Academy of Asthma, Allergy and Clinical Immunology and a grant from the National Research Foundation of Korea (NRF-2022R1A2C2006607).

SUPPLEMENTARY MATERIALS

Supplementary Table S1

Parameters associated with well-controlled state treated by the standard dose of antihistamines

Click here to view

Supplementary Table S2

Parameters associated with well-controlled state treated by the high dose of antihistamines

Click here to view

Supplementary Fig. S1

Consort flow diagram of the study, including enrollment, allocation, follow-up, and analysis.

Click here to view

Supplementary Fig. S2

Comparison of the degree of improvement in chronic urticaria symptom scores after 4 weeks of treatment among the 4 treatment groups: (A-D) 4-fold updosing of nsAHs, combination treatment with 4 nsAHs, switching to other nsAHs, and adjunctive H2RA; and (E-H) high- and standard-dose nsAH groups. *P* values were calculated using generalized estimating equations.

Click here to view

Supplementary Fig. S3

Comparison of rescue medication use between the high- and standard-dose antihistamine groups: frequency (A) and cumulative doses (B) of rescue H_1-antihistamine.

Click here to view

https://doi.org/10.4168/aair.2023.15.4.496

REFERENCES

1. Song WJ, Choi M, Lee DH, Kwon JW, Kim GW, Kim MH, et al. The KAAACI/KDA evidence-based practice guidelines for chronic spontaneous urticaria in Korean adults and children: part 1. definition, methodology and first-line management. Allergy Asthma Immunol Res 2020;12:563-78.
PUBMED | CROSSREF
2. Choi JH, Lee DH, Song WJ, Choi M, Kwon JW, Kim GW, et al. The KAAACI/KDA evidence-based practice guidelines for chronic spontaneous urticaria in Korean adults and children: part 2. management of H1-antihistamine-refractory chronic urticaria. Allergy Asthma Immunol Res 2020;12:750-70.
PUBMED | CROSSREF
3. Zuberbier T, Abdul Latiff AH, Abuzakouk M, Aquilina S, Asero R, Baker D, et al. The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. Allergy 2022;77:734-66.
PUBMED | CROSSREF
4. Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B, et al. The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy 2018;73:1393-414.
PUBMED | CROSSREF
5. Lee N, Lee JD, Lee HY, Kang DR, Ye YM. Epidemiology of chronic urticaria in Korea using the Korean health insurance database, 2010-2014. Allergy Asthma Immunol Res 2017;9:438-45.
PUBMED | CROSSREF
6. Fricke J, Ávila G, Keller T, Weller K, Lau S, Maurer M, et al. Prevalence of chronic urticaria in children and adults across the globe: systematic review with meta-analysis. Allergy 2020;75:423-32.
PUBMED | CROSSREF
7. Maurer M, Costa C, Gimenez Arnau A, Guillet G, Labrador-Horrillo M, Lapeere H, et al. Antihistamine-resistant chronic spontaneous urticaria remains undertreated: 2-year data from the AWARE study. Clin Exp Allergy 2020;50:1166-75.
PUBMED | CROSSREF
8. Lee MS, Yoon J, Kim J, Shin YS, Park HS, Lee HY, et al. Health-related utility of EQ-5D in Korean adults with chronic urticaria: mapping from urticaria outcome measures. Allergy Asthma Immunol Res 2020;12:599-607.
PUBMED | CROSSREF
9. Gonçalo M, Gimenéz-Arnau A, Al-Ahmad M, Ben-Shoshan M, Bernstein JA, Ensina LF, et al. The global burden of chronic urticaria for the patient and society. Br J Dermatol 2021;184:226-36.
PUBMED | CROSSREF
10. Ye YM, Yoon J, Woo SD, Jang JH, Lee Y, Lee HY, et al. Clustering the clinical course of chronic urticaria using a longitudinal database: effects on chronic urticaria remission. Allergy Asthma Immunol Res 2021;13:390-403.
PUBMED | CROSSREF
11. Ye YM, Park JW, Kim SH, Ban GY, Kim JH, Shin YS, et al. Prognostic factors for chronic spontaneous urticaria: a 6-month prospective observational study. Allergy Asthma Immunol Res 2016;8:115-23.
PUBMED | CROSSREF
12. Kim HA, Hyun MC, Choi BS. Natural history and influencing factors of chronic urticaria in children. Allergy Asthma Immunol Res 2022;14:73-84.
PUBMED | CROSSREF
13. Eun SJ, Lee JY, Kim DY, Yoon HS. Natural course of new-onset urticaria: results of a 10-year follow-up, nationwide, population-based study. Allergol Int 2019;68:52-8.
PUBMED | CROSSREF
14. Choi JH. Medication requirements for disease control predict the prognosis of chronic urticaria. Allergy Asthma Immunol Res 2021;13:357-9.
PUBMED | CROSSREF
15. Choi WS, Lim ES, Ban GY, Kim JH, Shin YS, Park HS, et al. Disease-specific impairment of the quality of life in adult patients with chronic spontaneous urticaria. Korean J Intern Med 2018;33:185-92.
PUBMED | CROSSREF
16. Kim BR, Yang S, Choi JW, Choi CW, Youn SW. Epidemiology and comorbidities of patients with chronic urticaria in Korea: a nationwide population-based study. J Dermatol 2018;45:10-6.
PUBMED | CROSSREF
17. Humphreys F, Hunter JA. The characteristics of urticaria in 390 patients. Br J Dermatol 1998;138:635-8.
PUBMED | CROSSREF

18. Maurer M, Raap U, Staubach P, Richter-Huhn G, Bauer A, Oppel EM, et al. Antihistamine-resistant chronic spontaneous urticaria: 1-year data from the AWARE study. Clin Exp Allergy 2019;49:655-62.
PUBMED | CROSSREF

19. Guillén-Aguinaga S, Jáuregui Presa I, Aguinaga-Ontoso E, Guillén-Grima F, Ferrer M. Updosing nonsedating antihistamines in patients with chronic spontaneous urticaria: a systematic review and meta-analysis. Br J Dermatol 2016;175:1153-65.
PUBMED | CROSSREF

20. Zazzali JL, Broder MS, Chang E, Chiu MW, Hogan DJ. Cost, utilization, and patterns of medication use associated with chronic idiopathic urticaria. Ann Allergy Asthma Immunol 2012;108:98-102.
PUBMED | CROSSREF

21. Staevska M, Popov TA, Kralimarkova T, Lazarova C, Kraeva S, Popova D, et al. The effectiveness of levocetirizine and desloratadine in up to 4 times conventional doses in difficult-to-treat urticaria. J Allergy Clin Immunol 2010;125:676-82.
PUBMED | CROSSREF

22. Weller K, Ziege C, Staubach P, Brockow K, Siebenhaar F, Krause K, et al. H1-antihistamine up-dosing in chronic spontaneous urticaria: patients' perspective of effectiveness and side effects--a retrospective survey study. PLoS One 2011;6:e23931.
PUBMED | CROSSREF

23. Weller K, Church MK, Hawro T, Altrichter S, Labeaga L, Magerl M, et al. Updosing of bilastine is effective in moderate to severe chronic spontaneous urticaria: a real-life study. Allergy 2018;73:2073-5.
PUBMED | CROSSREF

24. Lee JH, Bae YJ, Lee SH, Kim SC, Lee HY, Ban GY, et al. Adaptation and validation of the Korean version of the urticaria control test and its correlation with salivary cortisone. Allergy Asthma Immunol Res 2019;11:55-67.
PUBMED | CROSSREF

25. Altrichter S, Fok JS, Jiao Q, Kolkhir P, Pyatilova P, Romero SM, et al. Total IgE as a marker for chronic spontaneous urticaria. Allergy Asthma Immunol Res 2021;13:206-18.
PUBMED | CROSSREF

26. Kolkhir P, Kovalkova E, Chernov A, Danilycheva I, Krause K, Sauer M, et al. Autoimmune chronic spontaneous urticaria detection with IgG anti-TPO and total IgE. J Allergy Clin Immunol Pract 2021;9:4138-4146.e8.
PUBMED | CROSSREF

27. Fok JS, Kolkhir P, Church MK, Maurer M. Predictors of treatment response in chronic spontaneous urticaria. Allergy 2021;76:2965-81.
PUBMED | CROSSREF

28. Weller K, Ohanyan T, Hawro T, Ellrich A, Sussman G, Koplowitz J, et al. Total IgE levels are linked to the response of chronic spontaneous urticaria patients to omalizumab. Allergy 2018;73:2406-8.
PUBMED | CROSSREF

29. Konstantinou GN, Asero R, Maurer M, Sabroe RA, Schmid-Grendelmeier P, Grattan CE. EAACI/GA^{2}LEN task force consensus report: the autologous serum skin test in urticaria. Allergy 2009;64:1256-68.
PUBMED | CROSSREF

30. Ye YM, Park JW, Kim SH, Choi JH, Hur GY, Lee HY, et al. Clinical evaluation of the computerized chronic urticaria-specific quality of life questionnaire in Korean patients with chronic urticaria. Clin Exp Dermatol 2012;37:722-8.
PUBMED | CROSSREF

31. Zhang L, Wu J, Qi Y, Zhu H, Yao X, Li M, et al. Long-term combinations and updosing of second-generation H_1-antihistamines show efficacy and safety in the treatment of chronic spontaneous urticaria: a multicenter real-life pilot study. J Allergy Clin Immunol Pract 2020;8:1733-1736.e11.
PUBMED | CROSSREF

32. Kolkhir P, Muñoz M, Asero R, Ferrer M, Kocatürk E, Metz M, et al. Autoimmune chronic spontaneous urticaria. J Allergy Clin Immunol 2022;149:1819-31.
PUBMED | CROSSREF

33. Agache I, Rocha C, Pereira A, Song Y, Alonso-Coello P, Solà I, et al. Efficacy and safety of treatment with omalizumab for chronic spontaneous urticaria: a systematic review for the EAACI biologicals guidelines. Allergy 2021;76:59-70.
PUBMED | CROSSREF