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Management of chronic inducible urticaria according to the guidelines: A prospective controlled study

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ABSTRACT

Background: The recommended treatment approach in chronic inducible urticarias (CIndU) is the same as that for chronic spontaneous urticaria (CSU). But there is a lack of controlled trials assessing efficacy of available treatment options.

Objective: We aimed to evaluate the efficacy of treatment algorithm recommended by the guidelines and comparison of treatment responses in CIndU vs CSU.

Methods: This prospective parallel group controlled study included 70 CIndU and 66 CSU patients. The same treatment algorithm recommended by the European Academy of Allergology and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organization (EAACI/GA²LEN/EDF/WAO) was implemented to both CSU and CIndU patients. Treatment responses of the groups were evaluated with urticaria control test (UCT) and dermatology life quality questionnaire (DLQI) scores at the 0, 4, 8, 12 and 24th weeks for CIndU and 0, 4, 12 and 24 weeks for CSU.

Results: Fourteen patients (20,9%) with CIndU and 25 (37,9%) with CSU responded to standard doses of H1-AHs which was significantly higher in the CSU group ($p = 0,031$, $p < 0,05$). Patients with CIndU and CSU showed statistically similar responses to 2nd line treatments (combining or updosing AHs) ($p = 0,979$; $p > 0,05$). Twenty-seven (40,3%) of CIndU patients and 21 (31,8%) of CSU patients were diagnosed as AH-resistant urticaria. Omalizumab was administered to 15 CSU patients and 17 CIndU patients. Response rates to omalizumab were similar in both groups. Total response rates increased from 37,9% (n:25) to 68,2% (n:45) with the 2nd line treatments in CSU group while it increased from 20,9% (n:14) to 59,7% (n:40) in CIndU group. When omalizumab was introduced to AH-refractory cases as a 3rd line treatment, total response rates evaluated at the 12th week were 76,1% (n:51) in patients with CIndU and 83,3% (n:55) in CSU. Continuing omalizumab treatment for 24 weeks increased response rates in patients who were unresponsive at week 12.

Conclusion: CIndU seem to be more resistant to standard doses of AHs and higher doses of AHs are required for the control of symptoms. The same guidelines for CSU may be implemented to patients with CIndU.

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1. Introduction

Chronic inducible urticaria (CIndU) is a subgroup of chronic urticaria (CU) which is characterized by wheals and/or angioedema

for longer than 6 weeks reproducibly induced by exposure to specific triggers like cold, heat, sustained local pressure, vibration, sunlight, water, and increased body temperature [1,2]. CIndUs are classified into physical urticarias and other inducible urticarias [1]. While

Abbreviations: AHs, antihistamines; AU, aquagenic urticaria; BSACI, British Society for Allergy and Clinical Immunology; CholU, cholinergic urticaria; CIndU, chronic inducible urticaria; ColdU, cold urticaria; CSU, chronic spontaneous urticaria; CU, chronic urticaria; DLQI, dermatology life quality index; DPU, delayed pressure urticaria; EAACI, European Academy of Allergology and Clinical Immunology; EDF, European Dermatology Forum; fg-AHs, first generation H1 antihistamines; GA²LEN, Global Allergy and Asthma European Network; JTFPP, Joint Task Force on Practice Parameters; LTRA, leukotriene receptor antagonists; QoL, quality of life; SD, symptomatic dermatographism; sg-AHs, second generation H1 antihistamines; SU, solar urticaria; UCT, urticaria control test; UNEV, urticaria network e.V; WAO, World Allergy Organization.

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symptomatic dermographism (SD), heat and cold urticarias (ColdU), delayed pressure urticaria (DPU), solar urticaria (SU), and vibratory angioedema are in the group of physical urticarias, cholinergic urticaria (CholU), contact urticaria, and aquagenic urticaria (AU) are the other types of inducible urticarias [1,3,4]. CIndUs occur alone but may also occur in combination with other types of inducible urticarias or chronic spontaneous urticaria (CSU) [2]. In rare cases two or more triggers may be required to induce urticaria [1]. Diagnosis is made by exclusion of differential diagnosis i.e CSU with patient's history and performing specific skin provocation testing [1,2,5]. Threshold testing of eliciting factors is also recommended which is important for assessing disease activity and treatment response [1,3]. It is also useful to determine the trigger threshold which the patient has to avoid [1,3,6]. There are no specific disease activity tools or quality of life (QoL) instruments for CIndU [2]. Although chronic urticaria QoL questionnaire exists for CSU, there are no specific QoL instruments for SD, ColdU and CholU but these are under development. For now, the Dermatology Life Quality Index (DLQI) can be used for assessing QoL in patients with CIndU [1,2]. If threshold testing is not available, treatment response may be evaluated with Urticaria Control Test (UCT). UCT is a reliable new tool for evaluating disease control in patients with CSU as well as CIndU over the past 4 weeks [2,7].

Management of CIndU mainly aims to achieve complete symptom control and trigger avoidance [1]. But trigger avoidance is not always so simple. If avoidance of stimulus is not possible, the first step of treatment is second generation H1 antihistamines (sg-AHs) to achieve complete symptom control [5,8]. If symptoms persist with standard dosing, the European Academy of Allergology and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organization (EAACI/GA²LEN/EDF/WAO) Guideline recommends using the same treatment algorithm for both CSU and CIndU which is up dosing of the sg-AHs up to 4-fold as a 2nd line treatment [5]. While combining different H1-antihistamines (AHs) at the same time is not recommended by the EAACI/GA²LEN/EDF/WAO guideline, Joint Task Force on Practice Parameters (JTFPP) and British Society for Allergy and Clinical Immunology (BSACI) guideline recommends combining sg-AHs besides up dosing them as the 2nd step of treatment. Although there are some treatment differences in AH-resistant cases between the guidelines, they all include omalizumab treatment as the next step [5,8,9].

Recently the definition, diagnostic testing and management of CIndU; the EAACI/GA²LEN/EDF/UNEV (urticaria network e.V.) consensus recommendations 2016 update and revision has been published [1]. Even though this update gives valuable information on the diagnostic testing; treatment is based on primarily case series or uncontrolled studies instead of high level of evidence studies [1]. The reason for that is the lack of prospective controlled studies on the treatment of CIndU.

In this study, we aimed to evaluate the efficacy of the treatment algorithm recommended by the guidelines and comparison of treatment responses in CIndU vs CSU.

2. Materials and methods

2.1. Patient selection and data collection

This was a prospective, controlled, parallel group study which included 70 CIndU patients whose diagnosis were confirmed by provocation testing and 66 CSU patients over 16 years of age who were referred to our Urticaria Clinic from January 2015 to August 2016. The patients who were on treatment other than standard doses of H1-AHs at the time of referral were excluded from the study, but three patients that were already on treatment with omalizumab were only taken to consideration for demographic

evaluation but excluded from the treatment response evaluation. The study was approved by Okmeydani Training and Research Hospital Institutional Review Board (IRB protocol approval number: 48670771-514.10) and was conducted according to the Declaration of Helsinki. All patients has given informed consent.

Sociodemographic characteristics including sex, age, disease duration, accompanying angioedema and diagnosis of the patients, the treatment that have been used for the last month were evaluated in both groups.

The Turkish version of DLQI [10] and UCT were filled for CIndU patients prospectively. The Turkish validation of UCT has been performed by the author of this study (Kocatürk E) (the results have not been published yet). The forward and backward translation processes and cognitive debriefing of the Turkish version has been done and changes to the original tool has been made according to patients' remarks. These changes have been endorsed by the creator of the original tool (Weller K). UCT has 4 questions and each question has 5 answer options which are scored between 0 and 4 points. Total UCT scores were calculated by summing all 4 individual item scores (0–16 points). While a total score of 16 indicates complete disease control and 0 indicates no control, a score of ≥ 12 indicates well-controlled urticaria and a score of < 12 points indicates poor controlled disease [7].

2.2. Treatment design

Patients on standard doses of H1-AHs at least for 2 weeks duration were included to the study. Treatment modality was determined prospectively according to the UCT scores of CIndU patients. UCT scores were assessed at the 1st visit and patients with UCT scores of ≥ 12 and < 12 were accepted as responders and non-responders, respectively. Patients who had a UCT score of < 12 with standard doses of H1-AHs were treated either with combination of two different sg-AHs (combination group: levocetirizine 5 mg/day plus rupatadine 10 mg/day) or up dosing sg-AHs up to 4-folds (up dosing group: ebastine 40 mg/day). The patients with a UCT score of ≥ 12 continued with the standard doses of sg-AHs. At the 2nd visit (4 weeks after the 1st visit) patients with UCT scores of < 12 in the combination group or up dosing group underwent omalizumab treatment alone without AHs. The DLQI scores were also evaluated at the 1st and 2nd visits. Response to treatment with omalizumab was assessed at the following 4th, 8th, 12th and 24th weeks of the treatment.

In order to compare the treatment responses of CSU and CIndU, UCT scores of CSU patients who underwent combination or up dosing treatment and omalizumab treatment were retrospectively reviewed from patient charts. Side effects and compliance to treatment were noted.

2.3. Statistical analysis

Statistical analysis was performed with NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA). Differences in measured parameters (quantitative variables) between the groups were analysed with nonparametric Mann–Whitney *U* test or Kruskal–Wallis tests such as age, disease duration, mean scores of DLQI of subtypes of CIndUs at the referral. Means and mean changes in DLQI scores and UCT scores of CIndU and CSU groups were analysed with Mann–Whitney *U* test. Friedman Test and Wilcoxon test were used to compare the changes with skew distribution. The levels of significance values for differences in the median UCT and DLQI scores were calculated by Wilcoxon test. The comparison of the qualitative variables such as gender, accompanying angioedema, adverse effects and compliances as well as the comparison of response rates of treatment steps of CIndU and CSU were analysed with Pearson's chi-square test, Fisher's Exact test

and Yates' Continuity Correction. All data were reported as mean value $\pm$ standard deviation, median (25th–75th percentile), minimum, maximum, frequency and percentages. Statistical significance was achieved at $p < 0,05$ and $p < 0,01$. All analyses were performed by using nonparametric methods.

3. Results

3.1. Patients

Seventy patients with CIndU (46 female and 24 male) and 66 patients (46 female and 20 male) with CSU were included in the study. All demographic data are summarized in Table 1. Mean DLQI scores of subtypes of CIndU were compared at the time of referral and significant differences were observed between the subtypes ($p = 0,043$; $p < 0,05$, Kruskal Wallis Test). Mean scores of the DLQI were highest in patients with CholU ($14,29 \pm 8,36$), followed by combined CIndUs ($11,00 \pm 6,78$), SD ($8,32 \pm 6,44$) and lowest in patients with ColdU ($3,83 \pm 4,07$). The difference was statistically significant only when the mean DLQI of CholU was compared with ColdU ($p = 0,022$; $p < 0,05$) while other subtype comparisons were not statistically significant ($p > 0,05$, Mann Whitney U Test).

3.2. Responses to first line treatment: evaluation of the response to standard doses of AH

The patients with CIndU were evaluated at the 1st visit by means of response to standard doses of H1-AHs and 3 patients who

were already under treatment with omalizumab at baseline were excluded from the study. A total of 67 CIndU patients and 66 CSU patients were eligible for the analysis. The spectrum of treatments taken by the patients in both groups at 1st visit was shown in Fig. 1.

UCT scores were calculated for each patient by the physician (Table 2). When the responses of subtypes of CIndU were evaluated, 21,3% (n: 10) of the patients with SD, and 50% (n:3) of the ColdU patients showed response to standard doses of H1-AHs. While only one of the seven patients with CholU showed response, none of the patients with combined CIndU showed response to standard doses of H1-AHs. A patient with AU also did not achieve control with standard dose of an H1-AH.

3.3. Evaluation of responses to second line treatment: updosing and combination of two different second generation antihistamines

Fifty three patients (79,1%) with CIndU and 41 patients (62,1%) with CSU who did not achieve disease control (UCT < 12) with standard doses of H1-AHs underwent either combination of two different sg-AHs (levocetirizine 5 mg/day plus rupatadine 10 mg/day) or updosing of sg-AH (up to 4 times) (ebastine 40 mg/day) (n = 28 vs 25 in CIndU, n = 7 vs 34 in CSU). There were no significant differences with regard to treatment responses to updosing of sg-AH between the CSU and CIndU patients ($p = 0,523$; $p > 0,05$, Yates' Continuity Correction Test). Response rates to 2nd line treatments were similar between CIndU and CSU groups ($p = 0,979$; $p > 0,05$, Pearson χ^2 test) (Table 2).

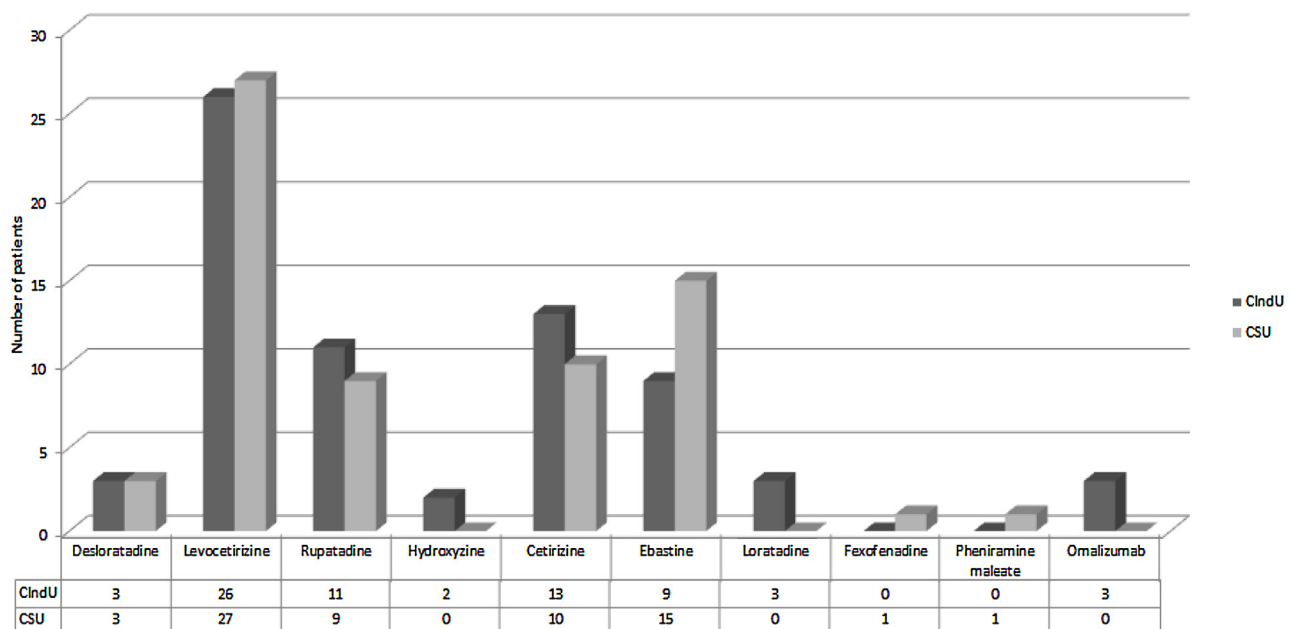
Table 1
Demographic data of patients with CSU and CIndU.

	CSU (n = 66)	CIndU overall (n = 70)	CIndU Subtypes (n = 70)				
			Symptomatic dermatographism (n = 48; % 68,6)	Cholinergic urticaria (n = 7; %10,0)	Cold urticaria (n = 6; %8,6)	Aquagenic urticaria (n = 1; %1,4)	Combined inducible urticaria [†] (n = 8; %11,4)
Age							
Min-Max	17–77 (40,5)	17–58 (38,5)	17–56 (37,5)	17–50 (19)	31–56 (51,5)	43	28–58 (40,5)
(Median)							
mean $\pm$ SD	41,21 $\pm$ 13,51	37,04 $\pm$ 11,78	36,58 $\pm$ 10,82	25,14 $\pm$ 11,94	46,67 $\pm$ 10,86	43,00	42,25 $\pm$ 10,83
Gender n (%)							
Male	20 (30,3)	24 (34,3)	16 (33,3)	5 (71,4)	3 (50)	0 (0)	0 (0)
Female	46 (69,7)	46 (65,7)	32 (66,7)	2 (28,6)	3 (50)	1 (100)	8 (100)
Disease duration (months)							
Min-Max	2–240 (8)	2–240 (24)	3–240 (19)	2–48 (12)	6–240 (18)	72	2–120 (36)
(Median)							
mean $\pm$ SD	21,76 $\pm$ 39,55	38,93 $\pm$ 51,11	36,21 $\pm$ 49,69	22,14 $\pm$ 17,50	56,33 $\pm$ 91,31	72,00	52,75 $\pm$ 44,54
Angioedema n (%)	39 (59,1)	8 (11,4)	4 (8,3)	2 (28,6)	0 (0)	0 (0)	2 (25,0)
DLQI ^{††}	n:66	n: 67	n:47	n:7	n:6	n:1	n:6
at 1st visit							
Min-Max	–	0–24 (8)	0–23 (7)	3–24 (13)	0–9(3)	9	3–21(9,50)
(Median)							
mean $\pm$ SD	–	8,79 $\pm$ 6,79	8,32 $\pm$ 6,44	14,29 $\pm$ 8,36	3,83 $\pm$ 4,07	9	11,00 $\pm$ 6,78
UCT ^{††}	n:66	n: 67	n:47	n:7	n:6	n:1	n:6
at 1st visit							
Min-Max	0–16 (8)	1–16 (8)	2–16 (8)	5–12 (7)	4–14 (10)	3	1–9 (6)
(Median)							
mean $\pm$ SD	9,12 $\pm$ 4,13	8,18 $\pm$ 3,54	8,53 $\pm$ 3,44	7,71 $\pm$ 2,50	9,50 $\pm$ 4,3	3	5,50 $\pm$ 3,62

CIndU, Chronic inducible urticaria CSU, Chronic spontaneous urticaria SD, standard deviation.

[†] Five patients with symptomatic dermatographism were associated with CSU, one patient had both symptomatic dermatographism and cold urticaria and one patient had symptomatic dermatographism, cold urticaria and cholinergic urticaria at the same time. One patient with cold urticaria also had CSU. There were no statistically significant differences between age and gender of patients with CIndU and CSU while disease duration was significantly longer and accompanying angioedema was lower in patients with CIndU than CSU ($p < 0,01$) (Mann Whitney U, Yates' Continuity Correction Test).

^{††} Three patients (one with symptomatic dermatographism, two with combined CIndU) who has been using omalizumab at the beginning of study has been included for demographic data but not for DLQI and UCT scorings.



CIndU, Chronic inducible urticaria CSU, Chronic spontaneous urticaria

Fig. 1. The spectrum of treatment taken by the patients in both groups at the time of referral.

3.4. Evaluation of response to omalizumab treatment as the third line treatment

Twenty-seven of 67 (40,3%) CIndU patients and 21 of 66 (31,8%) CSU patients were diagnosed as AH-resistant urticaria. But 15 CSU patients and 17 CIndU patients (10 patients with SD, 2 with CholU, 2 with ColdU, 2 with combined CIndU and 1 with AU) were treated with omalizumab (150mg every 2 weeks or 300mg every 4 weeks). The missing number of patients (10 of CIndU and 6 of CSU patients) is due to patients' unwillingness for omalizumab therapy or quitting follow-up. Ten (58,8%) patients with CIndU gained well control of their symptoms at week 4 while 13 (76,5%) patients at week 8, 11 patients (64,7%) at week 12 responded to treatment. 13/15 patients in CSU group and 14/17 patients in CIndU group continued follow-up until 24th week of omalizumab treatment. Eleven (78,6%) patients in CIndU group responded to omalizumab treatment at week 24 (Fig. 2).

While 6 of the 7 SD patients responded to omalizumab treatment, all patients with combined CIndU (n:2), one of two ColdU and one of two CholU patients and AU patient responded to treatment with omalizumab at week 24.

Increases in the mean UCT scores and decreases in the mean DLQI scores between baseline and 4th, 8th, 12th and 24th weeks were significant in CIndU (Fig. 3, Tables 3 and 4).

Patients with CSU showed similar response rates to omalizumab treatment as patients with CIndU (Fig. 4). Ten patients (66,7%) with CSU responded to treatment at week 12, while 11 (84,6%) responded at week 24. There were no significant differences observed between the means of UCT scores and mean changes in UCT scores from the baseline to week 12 and 24 between CIndU and CSU groups ($p > 0,05$, Mann Whitney U Test) (Table 4). But continuing omalizumab treatment for 24 weeks increased the response rates in patients who were unresponsive at week 12 (Fig. 5). When the response rates of CIndU patients were evaluated in detail; the mean DLQI scores of 17 patients with CIndU decreased from $12,12 \pm 8,05$ to $4,18 \pm 4,39$ ($p: 0,002$; $p < 0,01$, Wilcoxon Signed Ranks Test) while UCT scores increased significantly from $6,71 \pm 2,66$ to $12,24 \pm 3,56$ at week 12 ($p: 0,001$; $p < 0,01$, Wilcoxon Signed Ranks Test). At follow up, since three patients left the study, we had 14 patients to evaluate the responses. We included the results of these 14 patients for 24 week response evaluation. The UCT scores statistically increased from

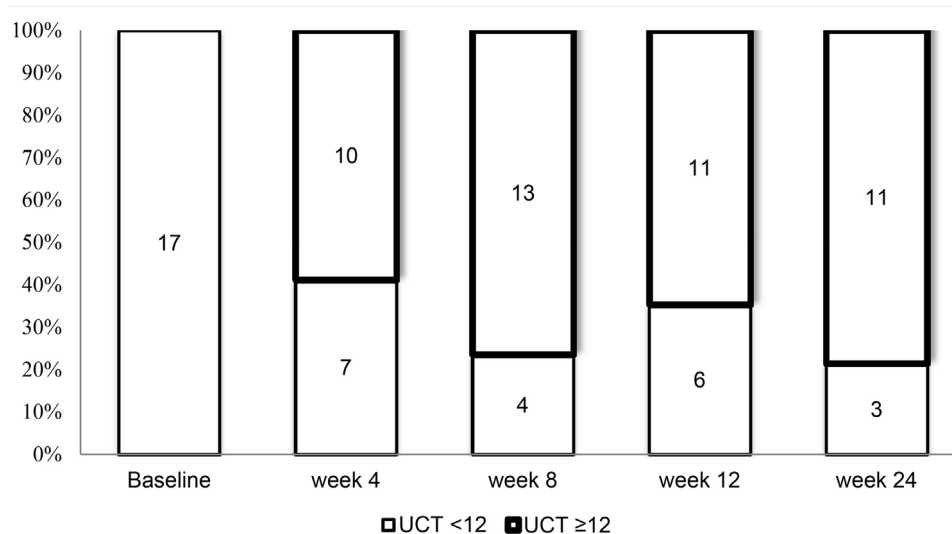
Table 2
Response rates of CIndU and CSU patients to 1st and 2nd line treatments.

1st line treatment	UCT at 1st visit	CIndU (n=67) n%	CSU (n=66) n%
Standard doses of AHS	<12	53 (79,1)	41 (62,1)
	≥12	14 (20,9)	25 (37,9)
2nd line treatment	UCT at 2nd visit	CIndU (n=53) n (%)	CSU (n=41) n (%)
Combination treatment	<12	13 (46,4)	6 (85,7)
	≥12	15 (53,6)	1 (14,3)
Updosing treatment	<12	14 (56,0)	15 (44,1)
	≥12	11 (44,0)	19 (55,9)
Response to 2nd line treatment	<12	27(50,9)	21(51,2)
	≥12	26(49,1)	20(48,8)

CIndU, Chronic inducible urticaria CSU, Chronic spontaneous urticaria.

AHS, Antihistamines, UCT, Urticaria control test.

Response to standard doses of AHS in CSU group was significantly higher than CIndU group ($p = 0,031$, $p < 0,05$, Pearson χ^2 test).



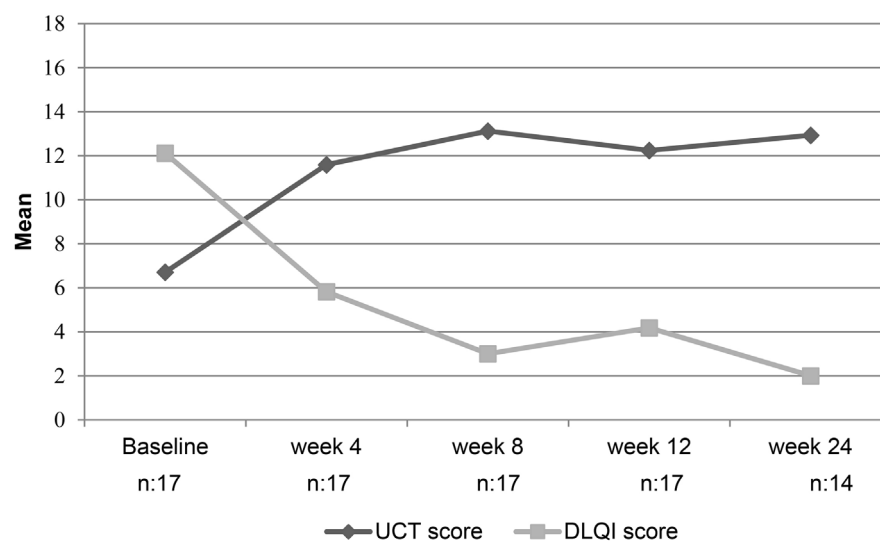
CIndU, Chronic inducible urticaria

Fig. 2. Response rates to omalizumab treatment in patients with CIndU at week 4, 8, 12 and 24.

7,07 ± 2,56 to 11,93 ± 3,73 at week 12 ($p:0,002$; $p < 0,01$) while it increased to 12,93 ± 2,67 at week 24 ($p:0,001$; $p < 0,01$), these increases were statistically significant between the baseline levels but there were no statistical significance between the mean UCT levels of week 12 and 24 ($p:0,233$; $p > 0,01$ Wilcoxon Signed Ranks Test). The DLQI scores decreased significantly from 11,14 ± 6,90 to levels 5,07 ± 4,34 at week 12 ($p:0,008$; $p < 0,01$) and 2 ± 2,18 at week 24 ($p:0,001$; $p < 0,01$). But no statistical difference observed between the levels of week 12 and 24 in terms of DLQI scores change ($p:0,11$; $p > 0,01$ Wilcoxon Signed Ranks Test).

3.5. Evaluation of total response rates of CIndU and CSU according to guidelines

Total response rates increased from 37,9% (n:25) to 68,2% (n:45) with the 2nd line treatments in CSU group while it increased from 20,9% (n:14) to 59,7% (n:40) in CIndU group. When omalizumab was introduced to AH-refractory cases as a 3rd line treatment, total response rates evaluated at the 12th week were 76,1% (n:51) in patients with CIndU and 83,3% (n:55) in CSU. At the 24th week



CIndU, Chronic inducible urticaria UCT, Urticaria control test DLQI, dermatology life quality index

Fig. 3. The mean UCT and DLQI scores of CIndU group were evaluated at baseline, and 4th, 8th, 12th and 24th weeks of the treatment. Increases in the mean UCT score and decreases in the mean DLQI score between baseline and 4th, 8th, 12th and 24th weeks were significant (Wilcoxon Signed Ranks Test, $p < 0,01$).

Table 3
Mean UCT, DLQI scores of CIndU patients at baseline (week 0) and 4th, 8th and 12th weeks of omalizumab treatment.

CIndU-Omalizumab treated patients (n = 17)	UCT Score		Disease control		DLQI Score	
	Min-Max(Median)	Mean ± SD	UCT < 12 n (%)	UCT ≥ 12 n (%)	Min-Max (Median)	Mean ± SD
Baseline	2–11 (5)	6,71 ± 2,66	17 (100)	0 (0)	2–27 (9)	12,12 ± 8,05
Week 4	5–15 (12)	11,59 ± 2,90	7 (41,2)	10 (58,8)	0–23 (3)	5,82 ± 6,80
Week 8	8–16 (14)	13,12 ± 2,64	4 (23,5)	13 (76,5)	0–14 (1)	3,00 ± 4,06
Week 12	2–16 (12)	12,24 ± 3,56	6 (35,3)	11 (64,7)	0–11 (2)	4,18 ± 4,39
p	^e 0,001**		^e 0,001**		^e 0,001**	
0.–4. week	^d p: 0,001**		^d 0,002**		^d p: 0,009**	
0.–8. week	^d p: 0,001**		^d 0,001**		^d p: 0,001**	
0.–12.week	^d p: 0,001**		^d 0,001**		^d p: 0,002**	

CIndU, Chronic inducible urticaria UCT, Urticaria control test DLQI, dermatology life quality index SD, standard deviation.

^d Wilcoxon Signed Ranks Test.

^e Friedman Test.

** p < 0,01.

these rates reached to 80,6% (n:54) in CIndU and 87,9% (n:58) in CSU (Fig. 6).

3.6. Side effects and compliance to treatments

Side effects of standard dose of H1-AHs used at referral were questioned. Twenty-two (32,8%) patients with CIndU reported at least one side effect. While sedation was reported by 25,4% (n:17) of this 67 patients, gastric complaints and cognition impairment had been reported by 2 patients. Dizziness, headache, weight gain and nervousness were the other complaints reported. Sedation was mostly reported with the use of levocetirizine [47,1% (n:8)]. Fourty-nine patients (73,1%) showed good compliance to standart doses of H1-AHs at referral. When the side effects were evaluated at the second visit, 9 (32,1%) patients taking combination of sg-AHs and 5 (20%) patients taking updosed sg-AHs stated at least one side effect but there were no significant differences between the groups (p = 0,491; p > 0,05, Yates' Continuity Correction Test). One of the patients reported flu-like symptoms after each injection of omalizumab. When the compliance to up dosing (76%, n:19) and combination (75%, n:21) of sg-AHs compared, there were also no differences between the two groups (p > 0,05, Yates' Continuity Correction Test).

4. Discussion

Second-generation H1-AHs constitute the 1st line treatment in both CSU and CIndU, but only 4–56% of CU patients respond to standard doses [5,8,9,11–15]. In a recent systematic review and meta-analysis, response rates to standard doses of AHs was

reported in 38.6% (95% CI 34.7–42.7) of CSU patients [16]. Even though there is a lack of data in the literature showing the treatment responses, CIndU can be challenging to treat with the standard doses of AHs [17]. In this study we demonstrated that patients with CIndU respond poorer than patients with CSU to standard doses of sg-AHs (20,9% vs 37,9%). This is a common observation by urticaria experts but has not been reported elsewhere.

When the standard doses of sg-AHs fails, second step in the EAACI/GA²LEN/EDF/WAO guideline is increasing the dosage up to 4 folds [5]. In most cases of CIndU, up dosing is required to prevent the symptoms [18]. Higher dosages of sg-AHs are superior to standard dosages and they are also safe to use [4].

We wondered if responses to up dosing would be different in the CIndU group than the CSU group and found that response rates to up dosing in the CSU and CIndU groups were not significantly different from each other; even though the response rates to standard doses were very poor in the CIndU group. There are numerous studies showing efficacy of up dosing in CSU [19–24], as well as different types of CIndU [25–30] but a comparison has not been performed between CSU and CIndU before.

High doses of AHs have been reported to be effective in about 45%–50% of patients with CSU [31], and response rates increase from 45% up to more than 60% with the up dosing of sg-AHs [32]. A systematic review and meta-analysis showed that response rate to up dosing sg-AHs was 63.2% (95% CI 57–69.6%) in CSU [16]. We determined that total response rates increased from 37,9% to 68,2% with the second step of the treatment in the CSU group while it increased from 20,9% to 59,7% in CIndU group. Increasing antihistamine doses whether with up dosing or combination

Table 4
Comparison of means and mean changes in UCT scores of omalizumab treated CIndU and CSU groups at week 12 and 24.

n = 32		CIndU (n = 17)	CSU (n = 15)	p-value
UCT score before omalizumab treatment (baseline, week 0)	Min-Max(Median)	2–11 (5)	0–11 (6)	0,893
	Mean ± SD	6,71 ± 2,66	6,47 ± 2,92	
UCT scores at week 12	Min-Max (Median)	2–16 (12)	3–16 (13)	0,715
	Mean ± SD	12,24 ± 3,56	12,60 ± 3,37	
Mean change from baseline to week 12 in UCT score	Min-Max (Median)	–3– 13 (5)	–5– 14 (5)	0,530
	Mean ± SD	5,53 ± 3,90	6,13 ± 4,50	
n = 27		CIndU (n = 14)	CSU (n = 13)	
UCT score before omalizumab treatment (baseline, week 0)	Min-Max (Median)	4–11 (6,5)	0–10 (6)	0,604
	Mean ± SD	7,07 ± 2,56	6,08 ± 2,84	
UCT scores at week 24	Min-Max (Median)	6–16 (13)	5–16 (15)	0,362
	Mean ± SD	12,93 ± 2,67	13,54 ± 3,07	
Mean change from baseline to week 24 in UCT score	Min-Max (Median)	1–11 (6)	–3–14 (7)	0,223
	Mean ± SD	5,86 ± 3,39	7,46 ± 4,23	

CIndU, Chronic inducible urticaria UCT, Chronic spontaneous urticaria Urticaria control test SD, standard deviation.

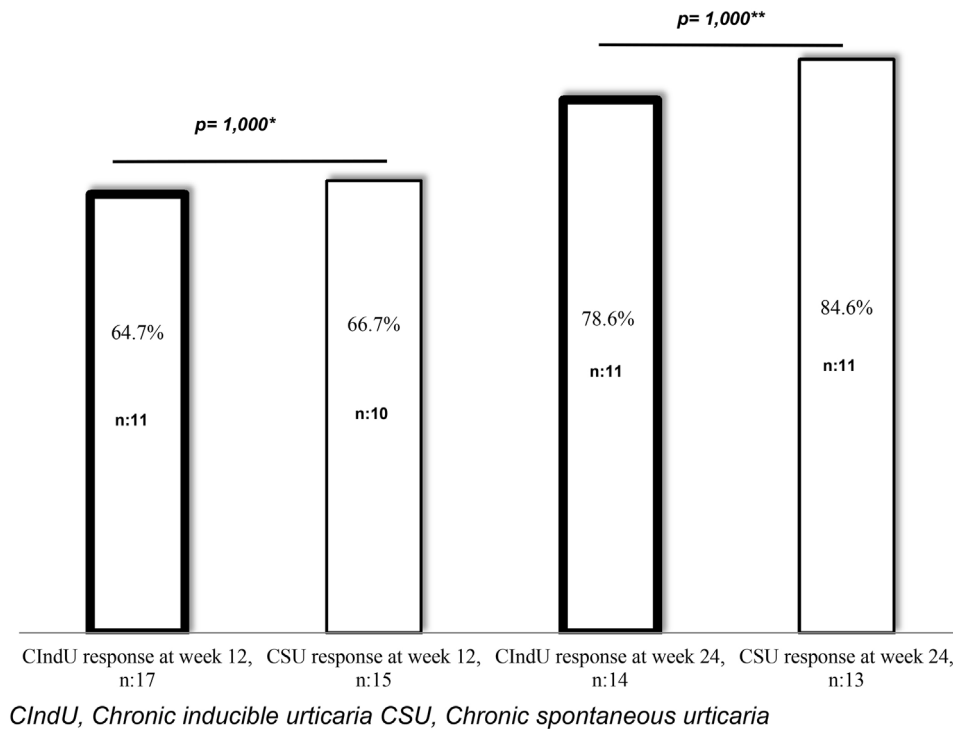


Fig. 4. Similar response rates to omalizumab in patients with CIndU and CSU at week 12 and 24 (*Yates' Continuity Correction Test, **Fisher exact test $p > 0.05$).

showed an undisputed efficacy and increased quality of life in both groups; and this increase was very prominent in the CIndU group.

Safety and drug interactions are the common concerns of the combination therapies or up dosing of AHs although there are trials showing the safety of up dosing AHs [19,20,28,29,33–35]. Ebastine was shown to be effective and safe at high doses in CSU [22] while

20 mg doses of ebastine was shown to be effective and safe in the patients with SD [25]. We did not observe in our cohorts any side effects that were significantly different between combination and up dosing of sg-AHs.

About 30–50% of CU patients are refractory to AHs and require alternative treatments [31,36–38]. Third line treatment choices for

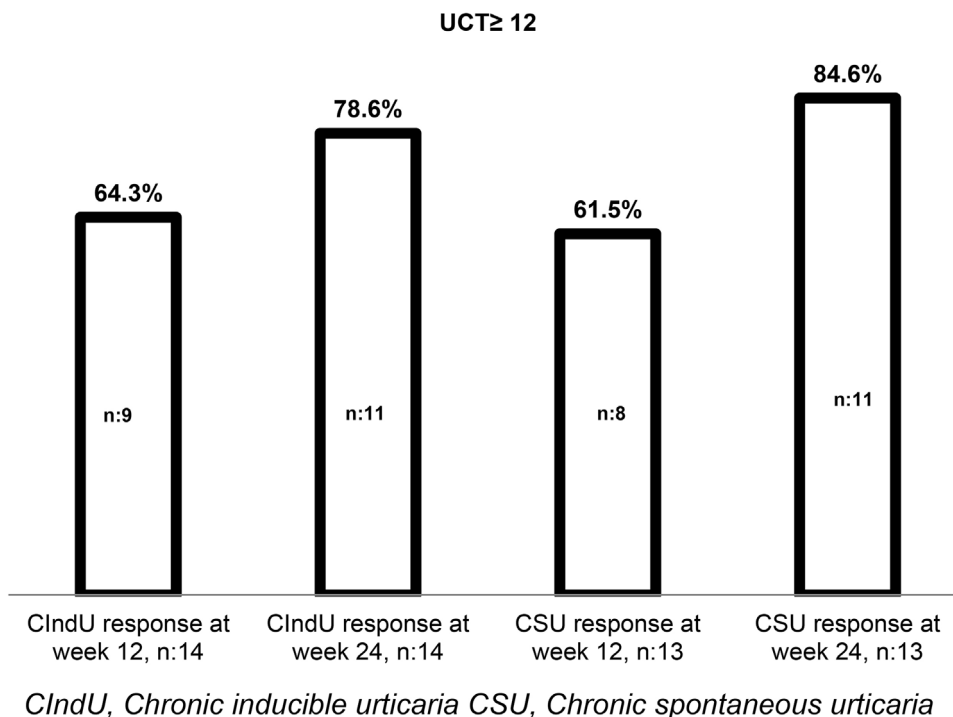
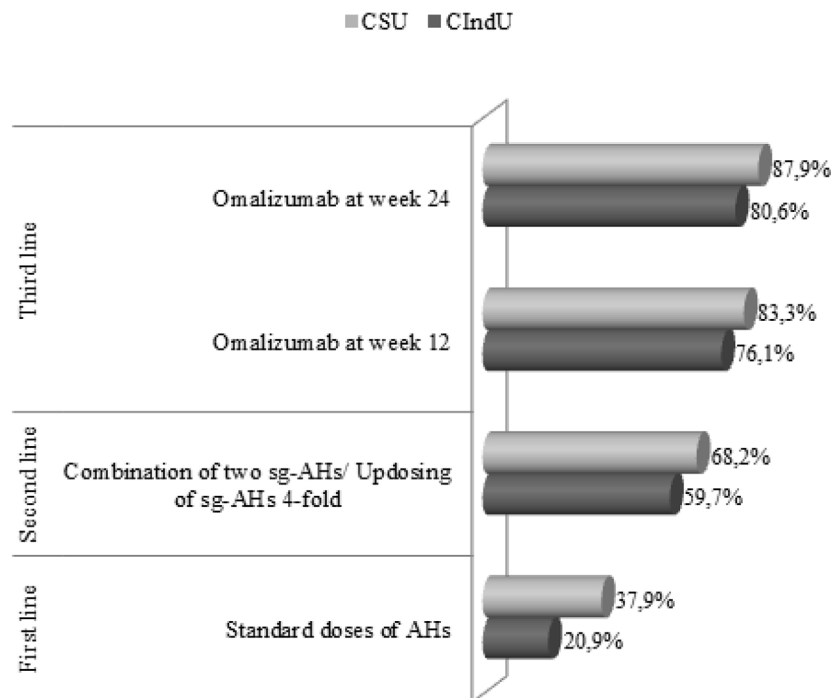


Fig. 5. There was an increase in response rates when omalizumab treatment had been continued to 24th week in CIndU and CSU groups. But 13/15 patients in CSU group and 14/17 patients in CIndU patients had continued follow-up until 24th week of omalizumab treatment.



AHs, antihistamines sg-AHs, second generation antihistamines CIndU, Chronic inducible urticaria CSU, Chronic spontaneous urticaria

Fig. 6. Total response rates of CIndU and CSU to 1st line, 2nd line and 3rd line therapies.

refractory cases include short-term corticosteroids, add-on therapy with cyclosporine, LTRA or omalizumab in the EAACI/GA²LEN/EDF/WAO guideline [5]. In 2014, omalizumab was approved by the FDA for AH-refractory CSU patients [39,40] and it was recommended by JTFPP, EAACI/GA²LEN/EDF/WAO and BSACI guidelines due to its efficacy and safety [5,8,9]. Efficacy of omalizumab for CSU has been shown by placebo controlled clinical trials [39,40–45], while there are just case reports and case series in the literature for CIndU [11,17,46–50]. There are on-going trials evaluating the efficacy of omalizumab in different types of CIndU which have not been published yet [CUTEX (NCT01580592), UFO (NCT02169115), XOLUS (NCT02262130), CUN-OMAL-UCOL (NCT02012387)]. In the current study 40,3% of CIndU patients and 31,8% CSU patients were AH-refractory and were given omalizumab treatment.

In a retrospective clinical analysis complete remission was achieved in 83% of CSU and 70% of CIndU patients by the administration of omalizumab. Patients with CIndU showed similar response rates with CSU patients to omalizumab [11]. Another cohort showed that 90% of patients with CSU responded to treatment while 53% of CIndU had a complete or almost complete response to treatment [46]. In our study, 64,7% CIndU and 66,7% CSU patients responded to omalizumab at week 12 while these rates increased to 78,6% in CIndU and 84,6% in CSU at week 24. This shows that treatment responses to omalizumab was similar in the CSU and CIndU groups and continuing omalizumab treatment for 24 weeks may increase response rates in patients who were unresponsive at week 12.

In recent reports; DPU and SD were found to be more responsive while patients with ColdU and CholU seem to be less responsive to omalizumab treatment [11]. In a case series, three of five patients with DPU; two of five patients with ColdU; three of four patients with CholU and one of two patients with SD showed response, patient with SU had no response to treatment [46]. In our

series, SD patients (6/7) and combined CIndU (2/2) showed the best response to treatment with omalizumab while one of two ColdU and CholU patients responded to omalizumab treatment at week 24. While a patient with AU did not respond to omalizumab treatment at week 12, same patient responded to treatment at week 24.

Total response rates increased from 37,9% (n:25) to 68,2% (n:45) with the 2nd line treatments in CSU group while it increased from 20,9% (n:14) to 59,7% (n:40) in CIndU group. When omalizumab was introduced to AH-refractory cases as a 3rd line treatment, total response rates evaluated at the 12th week were 76,1% (n:51) in patients with CIndU and 83,3% (n:55) in CSU. At the 24th week these rates reached to 80,6% (n:54) in CIndU, 87,9% (n:58) in CSU.

These findings suggest that updosing/combining antihistamines as well as adding omalizumab markedly increases response rates in CIndU.

5. Limitations of the study

Limitations of our study are 1. The design of CIndU group is prospective while CSU is retrospective. 2. In the second step treatments, we used levocetirizine plus rupatadine as the combination of sg-AH group while we used ebastine four-folds as the updosing group. These treatment groups were not appropriate to compare, that is why a comparison of combination and updosing of antihistamines could not be carried out. 3. When the patients reached the third line treatment, 10 of 27 CIndU patients and 6 of 21 CSU patients could not be enrolled because of unwillingness of getting omalizumab or quitting follow-up, loss of 5 more patients at the 24th week evaluation could have effected to total response rates. 4. Although omalizumab is recommended as an add-on therapy, we gave omalizumab alone without antihistamines. The reason for this was; at the beginning of our study we

started omalizumab with antihistamines but we later realised that the patients quitted taking their antihistamines. Because of this we had to treat other consequent patients as the same way with the former patients. That is why we gave omalizumab alone without antihistamines. The response rates would be higher in Figs. 4 and 5 if omalizumab and antihistamines were given together.

6. Conclusion

Although the response rates to first line treatment is lower than CSU, patients with CIndU showed similar response rates to 2nd and 3rd line treatments as CSU patients. In conclusion, the same guidelines for CSU may be implemented to patients with CIndU.

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Conflict of interest disclosure

Dr. Emek Kocatürk reports advisory board fees from Novartis. The other authors have no conflict of interest to declare.

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