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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/GA^{2}LEN/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.

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 otherinducible 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; GA^{2}LEN, Global Allergy and Asthma European Network; JTFPP, Joint Task Force on Practice Parameters; LTRA, leukotriene receptor antagonists; QoL, quality of life; SD, symptomatic dermographism; 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/GA^{2}LEN/EDF/WAO) Guideline recommends using the same treatment algorithm for both CSU and CIndU which is updosing 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/GA^{2}LEN/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 updosing 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/GA^{2}LEN/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 (Kocaturk 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 $\geq$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 $\geq$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 updosing sg-AHs up to 4-folds (updosing group: ebastine 40 mg/day). The patients with a UCT score of $\geq$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 updosing 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 updosing 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