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Original Article

Evaluation of the effectiveness of anti-IgE treatment in patients with chronic urticaria with an urticarial control test

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Abstract

Aim: Chronic spontaneous urticaria (CSU) is characterized by recurrent urticaria, angioedema and a combination of both over a period of more than 6 weeks. Anti-immunoglobulin E (IgE) monoclonal antibody (omalizumab) treatment is an effective and safe treatment modality that can be applied in antihistamine-resistant cases in patients with CSU and the urticaria control test is a simple and useful test that evaluates the control level of the disease over the past 4 weeks.

Material and Methods: Following appropriate urticaria control tests, 82 test results of 41 patients with CSU (23 females, 18 males) who received subcutaneous anti-IgE treatment at a dose of 300 mg/4 weeks for 6 months were evaluated retrospectively.

Results: With each question, there was a statistically significant difference between the mean scores before treatment and at 6 months of treatment (p: 0.001 for question 1, p: 0.001 for question 2, p: 0.001 for question 3, p: 0.001 for question 4). As a result, 95.1% of the patients included in the study achieved a complete and/or partial response to treatment.

Conclusion: Omalizumab treatment in patients with chronic spontaneous urticaria (CSU), is an effective and safe treatment modality, independent of the patients' serum IgE levels, eosinophil counts, thyroid-stimulating hormone levels, C-reactive protein and sedimentation rates, presence or absence of anti-nuclear antibody (ANA) and regardless of whether angioedema is associated with chronic spontaneous urticaria. Furthermore, the urticaria control test is a practical test that can be used to evaluate the efficiency of treatment in CSU patients

Keywords: Chronic spontaneous urticaria; urticaria control test; anti-IgE treatment.

INTRODUCTION

Chronic spontaneous urticaria (CSU) is characterized by recurrent urticaria, angioedema and a combination of both over a period of more than 6 weeks (1). Angioedema occurs in about half of CSU patients and often affects the lips, neck, periorbital areas of the face, extremities and genital areas (2,3). The prevalence of CSU has been reported approximately 1% in several studies (4-6). Guidelines and practical guides for the treatment of CSU have been established by many allergy and dermatology groups around the world (7,8). A careful patient history and detection of what initiates and/or aggravates urticaria are the first steps in all of these guidelines and practical guides. Many treatment guidelines recommend non-sedating H1 antihistamines as first line therapy. If symptoms persist, increasing the dose of H1 antihistamines, changing the H1 antihistamines, or both are recommended. After this stage, treatment recommendations vary according to the guidelines, and anti-immunoglobulin E (IgE) monoclonal antibody (omalizumab) treatment is an effective and safe treatment modality that can be applied in antihistamine-resistant cases (9). Omalizumab is a monoclonal antibody developed against IgE in 2014 that has been approved for use in cases of CSU that do not respond adequately to antihistamine treatment in adolescents (12 years and older) and adult patients. With CSU, subcutaneous administration of 150 or 300 mg is recommended every 4 weeks and unlike the doses used in asthma patients: these doses are independent of serum IgE values and body weight (10). Various validated questionnaires have been developed to monitor these treatment modalities (11). Of

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these tests, the Urticaria Control Test (UCT) is often used as it is simple and easy to understand. The answers to the questions in this test are scored from 0 to 4 points (0: most common and 4: slightest), thus a score between 0 and 16 is obtained (11). A UCT score of 12 or less is considered poorly controlled urticaria. A 3-point improvement in total scoring is considered a minimal response (12). In this study, we aimed to evaluate the efficacy of the treatment by comparing urticaria control test scores before anti-IgE treatment and at 6 months of anti-IgE treatment in patients who were followed up at our clinic for CSU, who did not respond adequately to antihistamine treatment for 6 months and therefore started anti-IgE treatment.

Supplement 1. Urticaria Control Test (11)

The Urticaria Control Test

Patient name: _____ Date: (dd mm yyyy): ___ ___ ____

Date of birth (dd mm yyyy): ___ ___ ____

Instructions: You have urticaria. The following questions should help us understand your current health situation. Please read through each question carefully and choose an answer from the five options that best fits your situation. Please limit yourself to the last four weeks. Please don't think about the questions for a long time, and do remember to answer all questions and to provide only one answer to each question.

1. How much have you suffered from the physical symptoms of the urticaria (itch, hives (welts) and/or swelling) in the last four weeks?

☐very much (o points) ☐much (1 points) ☐somewhat (2 points) ☐ a little (3 points) ☐not at all (4 points)

2. How much was your quality of life affected by the urticaria in the last 4 weeks?

☐very much ☐ much ☐somewhat ☐a little ☐not at all

3. How often was the treatment for your urticaria in the last 4 weeks not enough to control your urticaria symptoms?

☐very often ☐often ☐sometimes ☐seldom ☐not at all

4. Overall, how well have you had your urticaria under control in the last 4 weeks?

☐not at all ☐a little ☐somewhat ☐well ☐very well

MATERIAL and METHODS

The diagnosis of CSU was made with characteristic skin findings and consistent clinical history. As recommended by international guidelines (1), in the absence of any underlying disease, urticaria plaques that appeared and resolved repeatedly for more than six weeks were considered CSU. In our clinic, all patients with CSU undergo a complete blood count with differential, anti-nuclear antibody (ANA), C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR), serum IgE levels, thyroid stimulating hormone (TSH) level testing, thyroid autoantibodies (if the TSH level is abnormal) and stool examination for parasites to reveal a possible underlying disease. Also autologous serum skin test (ASST) is applied if there is no obstacle. Anti-IgE monoclonal antibody treatment is given to patients who do not respond to standard CSU treatment (second generation H1 antihistamines and in combination with leukotriene modifiers) for 6 months as recommended by international guidelines (13,14). Short term of corticosteroid therapy is given, if needed, to control exacerbations. Patients undergo urticaria control tests before and during treatment with omalizumab.

Following appropriate urticaria control tests, 82 test results of 41 patients with CSU (23 females, 18 males) who received subcutaneous omalizumab treatment at a dose of 300 mg/4 weeks for 6 months were evaluated retrospectively. Patients with drug use that may affect CSU therapy (cyclosporine, tacrolimus, mycophenolate, dapsone, sulfasalazine and hydroxychloroquine) were excluded. During omalizumab treatment, patients were allowed to receive anti-histamine treatment if needed. Also, patients with chronic diseases such as diabetes mellitus, hypertension and chronic renal disease were not included in the study. The answers that the patients gave to the UCT test questions and their total scores were scored and calculated before and after treatment.

Statistical analysis was performed with IBM SPSS Statistics Version 25 software package. Normally distributed parameters were presented as mean ± standard deviation and non-parametric parameters were expressed as median (interquartile range [minimum/maximum]). Descriptive data were presented as frequencies and percentages. The Wilxocon test was used to compare the median values of dependent variables. P values of ≤ 0.05 were considered statistically significant.
The study protocol was approved by the Ethics Committee. Informed consent was obtained from all the patients participating in the study.

RESULTS

Twenty-three patients were female (56.1%) and the mean age of the patients was 40.35 ± 10.35 years. Anti-nuclear antigen was positive in 22 patients (53.7%) and 25 patients (61%) had angioedema. All patients were euthyroid and the eosinophil values of the patients were within normal limits. Clinical, demographic and laboratory properties of study population were summarized in Table 1. UCT scores of the patients were 4.81 ± 2.96 (min: 0, max: 12) pre-treatment, and 13.34 ± 2.99 (median: 13,

min: 4, max: 16) at 6 months of treatment. There was a statistically significant difference between median pre-treatment and post-treatment UCT scores (p: 0.001). Pre-treatment mean scores of questions 1, 2, 3 and 4 in the test were 1.20 ± 0.90, 1.22 ± 0.76, 1.17 ± 0.74, and 1.17 ± 0.70, respectively. Mean scores of questions 1, 2, 3 and 4 in the test at 6 months of treatment were 3.27 ± 0.77, 3.29 ± 0.78, 3.27 ± 0.77, and 3.32 ± 0.76, respectively. With each question, there was a statistically significant difference between the mean scores before treatment and at 6 months of treatment (p: 0.001 for question 1, p: 0.001 for question 2, p: 0.001 for question 3, p: 0.001 for question 4) (Table 2). After 6 months of treatment, 37 out of 41 (90.2%) patients had a UCT of ≥12. Two patients (4.9%) achieved a partial response (3-point improvement in total scoring). Two patients (4.9%) were considered unresponsive to treatment. As a result, 95.1% of the patients included in the study achieved a complete and/or partial response to treatment.

There was no statistically significant difference between the urticaria control test scores of the CSU patients with ANA and without ANA before omalizumab treatment and at the sixth month of treatment (respectively, p: 904 and p: 0.719).

There was no significant difference between urticaria control test scores before omalizumab treatment and in the sixth month of treatment between CSU patients with angioedema and CSU patients without angioedema (respectively, p: 0.259 and p: 467).

There was no significant difference in ESR, TSH level, serum IgE, CRP, and eosinophil count between patients who achieved a complete response after 6 months of omalizumab treatment and patients who did not achieve a full response. (respectively, p: 203, 0.719, 0.091, 0.237 and 0.751).

Table 1. Clinical, demographic and laboratory properties of study participants

Parameters	Results
Gender (female), n (%)	23 (56.1)
Current age	40.37 ± 10.35
Eosinophil count, median (minimum-maximum), mm³	142 (0-500)
IgE, median (minimum-maximum), IU/L	145.05 (5-1590)
Anti Nuclear Antigen (ANA) (+), n (%)	22 (53.7)
Urticaria with angioedema, n (%)	25 (61)
C-reactive protein, median (minimum-maximum), (mg/L)	5.88 (1-34)
Erythrocyte sedimentation rate, median (minimum-maximum), (mm/h)	5.5 (2.4-38)
Thyroid stimulation hormone levels, median (minimum-maximum), (mU/L)	1.59 (0.37-3)

There was no significant difference in the presence of ANA and coexistence of angioedema between patients who achieved a complete response after 6 months of omalizumab treatment and patients who didn't achieve a complete response (respectively, p: 0.610 and p: 0.645).

Table 2. Comparison of urticaria control tests pre-treatment and at 6 months of treatment

	Pre-treatment scores	Scores at 6 months of treatment	P
Question 1	1.20 ± 0.90 (min: 0 - max: 3)	3.27 ± 0.77 (min: 1 - max: 4)	0.001
Question 2	1.22 ± 0.76 (min: 0 - max: 3)	3.29 ± 0.78 (min: 1 - max: 4)	0.001
Question 3	1.17 ± 0.74 (min: 0 - max: 3)	3.27 ± 0.77 (min: 1 - max: 4)	0.001
Question 4	1.17 ± 0.70 (min: 0 - max: 3)	3.32 ± 0.76 (min: 1 - max: 4)	0.001
Total score	4.81 ± 2.96 (min: 0 - max:12)	13.34 ± 2.99 (min: 4 - max: 16)	0.001

DISCUSSION

Chronic spontaneous urticaria (CSU) is characterized by recurrent urticaria, angioedema and a combination of both over a period of more than 6 weeks (1). CSU is more common in females (F) than in males (M) (6,15,16). Although the F: M ratio in our study is higher for females, this ratio can be considered low at 1.3 to 1 compared to literature data. This is probably related to the small size of our study population. CSU often appears in the third to fifth decade of life. As the mean age of the patients in our study was 40.4 ± 10.4, our results were consistent with the literature. The mean age of patients in another study conducted in Turkey was similarly 37 ± 9.4 (17).

Our study confirms and supports other studies (18-23) showing that omalizumab is effective in the treatment of CSU. In a meta-analysis of 1312 patients, omalizumab provided a significant reduction in weekly pruritus and swelling scores in patients unresponsive to standard dose antihistamine treatment compared to the placebo group (24). In another study, omalizumab has been shown to provide a significant improvement in quality of life and sleep from the first dose (21).

Autoimmune conditions in CSU patients have been shown in several studies more frequently than in the normal population (15,25,26). These autoimmune conditions are mainly thyroid diseases, celiac disease, Sjogren's syndrome, systemic lupus erythematosus, and rheumatoid arthritis (15). The presence of autoantibodies such as ANA is considered indicative of increased production of polyclonal antibodies from immune cells (27). The presence of ANA is more common in CSU patients than in the normal population (28). Moreover, the relationship between thyroid autoimmunity and the presence of ANA has been shown in CSU patients (29,30). Since there were no patients with thyroid autoimmunity in our study, we could not evaluate the relationship between ANA and thyroid autoimmunity. But, at the end of the sixth month,

we found no significant difference in the presence of ANA between patients receiving full benefit from omalizumab and patients not receiving the full benefit (p:0.610).

Since 2017, routine measurements of TSH and thyroid autoantibodies have not been recommended in CSU patients (15). Nevertheless, some clinicians continue to measure TSH and thyroid autoantibodies in CSU patients, while others recommend that thyroid autoantibodies be checked in case of abnormal TSH levels (31). In the past years, Configo-Cohen et. al. have shown that hypothyroidism and hyperthyroidism have been higher in CSU patients than in the normal population (15). In our study, all patients were euthyroid. Therefore, although we did not make an assessment on this point, we did not find a significant difference in thyroid hormone levels between patients who were accepted to respond completely after six months of omalizumab treatment and those who did not respond completely (p: 0.719).

C-reactive protein and erythrocyte sedimentation rate values are often normal in CSU patients (15). In a study examining the utility of comprehensive laboratory tests in CSU patients, only ESR and a complete blood count with differential were found to be useful (31). Abnormal rates in these values should be stimulating for systemic diseases such as underlying infection, autoimmunity, and rheumatologic diseases. In our study, at the end of the sixth month, no significant difference was found between ESR and CRP values between patients who benefited from omalizumab and those who did not (p: 0.203 and p:0.751).

Immunoglobulin E plays a central role in the pathogenesis of many allergic diseases and is, therefore, the target of many treatment modalities. One of these treatments, omalizumab binds free IgE and downregulates IgE receptors on the basophil and mast cell surface (22). Ertaş et al. showed that CSU patients who did not respond to omalizumab had lower levels of IgE than those who responded partially and fully to treatment, that those who did not respond to omalizumab treatment during the treatment had mild serum IgE elevation compared to those who responded partially or fully to omalizumab treatment (32). Similarly, Deza et al. found lower IgE levels in patients who did not respond to omalizumab treatment than patients who responded (33). In our study, there was no significant difference in serum IgE levels between patients who fully responded to treatment and those who did not respond completely. This may be due to the relatively small size of our study population.

Angioedema is observed in about half of CSU patients (4,6). Deza et al. reported that CSU cases with angioedema have higher disease activity and are more resistant to omalizumab treatment (33). However, Ertaş et al. weren't able to show this relationship (32). In our study, no significant difference was found in the presence of angioedema between patients who responded and did not respond to omalizumab treatment (p: 0.645).

The urticaria control test is a simple and useful test that evaluates the control level of the disease over the past 4 weeks (11,34). It mostly evaluates the patient's quality of life over the past 4 weeks. Although it is claimed to be not as sensitive as urticaria activity score over 7 Days (UAS7) in detecting minimal clinical improvement and deterioration, several studies have demonstrated a strong linear correlation between UCT and UAS7 scores, and quality of life questionnaires (12).

In a meta-analysis examining real-life data results of 67 observational studies analyzing the benefits and harms of omalizumab treatment in patients with CSU receiving omalizumab treatment, 72% of patients reported a complete response while 18% reported a partial response to treatment. In the same study, the incidence of adverse events, including anaphylaxis in 3 patients, was 4% (23). The complete and partial response rates obtained in our study can be considered consistent with these meta-analysis results. In a study reviewing the time when patients began to benefit from omalizumab treatment and the duration of this benefit, Kaplan et al (35). reported that a significant improvement was observed in 60% of patients in the first 12 weeks and that the benefit from treatment began within the first month.

The cross-sectional design of our study, our study being a single-center study, and not including patients that could not fill out the UCT due to various reasons are among the limitations of the study.

CONCLUSION

As a result, omalizumab treatment in patients with chronic spontaneous urticaria (CSU), is an effective and safe treatment modality, independent of the patients' serum IgE levels, eosinophil counts, thyroid-stimulating hormone levels, C-reactive protein and sedimentation rates, presence or absence of anti-nuclear antibody (ANA) and regardless of whether angioedema is associated with chronic spontaneous urticaria. Furthermore, the urticaria control test is a practical test that can be used to evaluate the efficiency of treatment in CSU patients.

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