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Effectiveness of as-needed antihistamines in chronic spontaneous urticaria patients under omalizumab treatment

Murat Türk^{1,2} | İnsu Yılmaz¹ | Sakine Nazik Bahçecioğlu¹ | Pelin Can³ | Ragıp Ertaş⁴ | Demet Kartal⁵ | Salih Levent Çınar⁵ | Emek Kocatürk^{3,6}

¹Division of Allergy and Clinical Immunology, Department of Chest Diseases, Erciyes University School of Medicine, Kayseri, Turkey

²Clinic of Immunological and Allergic Diseases, Kayseri Training and Research Center, Kayseri, Turkey

³Department of Dermatology, Okmeydanı Training and Research Hospital, İstanbul, Turkey

⁴Clinic of Dermatology, Kayseri Training and Research Center, Kayseri, Turkey

⁵Department of Dermatology, Erciyes University School of Medicine, Kayseri, Turkey

⁶Department of Dermatology, Koç University School of Medicine, İstanbul, Turkey

Correspondence

Murat Türk, Erciyes University Hospital, Division of Allergy and Clinical Immunology, Department of Chest Diseases, Melikgazi 38039, Kayseri, Turkey.
Email: mrttrk@gmail.com

Abstract

The question how second-generation antihistamines (sgAHs) should be used when chronic spontaneous urticaria (CSU) is under control with omalizumab is still unanswered. This study aimed to investigate the effectiveness of as-needed sgAHs in patients with well-controlled urticaria under omalizumab treatment. Patients from four different urticaria centers who were treated with omalizumab 300 mg/4 weeks for at least 3 months, had well-controlled urticaria (Urticaria Control Test: $16 > \text{UCT} \geq 12$) and were using sgAHs only if needed, were included in this study. In order to assess effectiveness of sgAHs, change in the itch, hives, and total itch-hives scores before and after sgAHs were evaluated using modified urticaria activity score-twice daily. Fifty-three patients [38 female (71.7%)] with mean age 41.1 ± 11.4 years were included in this study. Median sgAH intake per patient throughout the 4 week-intervals was 3 (2–5) tablets. sgAH intake decreased itch, hives and total itch-hives scores $45.7\% \pm 52.9$, $42.4\% \pm 39.1$, and $50.2\% \pm 51.1$, respectively ($P < .001$ for all). This decrease was similar in both isolated-urticaria and urticaria-and-angioedema phenotypes. Baseline IgE levels were positively correlated with the decrease of three symptom scores ($r = 0.31$, $P = .05$; $r = 0.375$, $P = .017$; $r = 0.31$, $P = .05$, respectively) that showed in patients with higher baseline total IgE levels, as needed sgAH intake decreased the symptom scores less. Our study showed that sgAHs may still be an effective option for the treatment of the intermittent symptoms in patients with well-controlled urticaria under omalizumab treatment. Baseline total IgE levels may be used as a potential biomarker for sgAH effectiveness in these patients.

KEYWORDS

chronic spontaneous urticaria, IgE, omalizumab, second-generation antihistamines, treatment management

1 | INTRODUCTION

Chronic spontaneous urticaria (CSU) presents itself with the development of transient hives (wheals) and/or angioedema lasting longer

than 6 weeks or more, without any external trigger. CSU affects nearly all age groups in the population. It has an estimated life time prevalence of approximately 0.5% to 1%, and its prevalence has an increasing trend.¹ CSU causes severe impairment in patients' quality of life (QoL).² The aim of treatment in CSU is complete disease control with absence of signs and symptoms, and normalization of QoL.³ Second-generation H1-antihistamines (sgAHs) are the recommended first-line treatment option for CSU and increasing sgAHs dose up to

Abbreviations: AAS, angioedema activity score; CSU, chronic spontaneous urticaria; PROM, patient reported outcome measure; QoL, quality of life; sgAH, second-generation H1-antihistamine; UAS7, urticaria activity score over 7 days; UAS_{TD}, urticaria activity score-twice daily; UCT, urticaria control test.

4-fold as the second-line treatment is recommended in case of inadequate control with standard dose of sgAHs. For the antihistamine refractory patients, omalizumab is the only licensed third-line approach, of which the clinical efficacy and safety in CSU has been shown in several clinical trials and real-life studies.³⁻⁵

The European Academy of Allergy and Clinical Immunology (EAACI)/Global Allergy and Asthma European Network (GA2LEN)/European Dermatology Forum (EDF)/World Allergy Organization (WAO) guideline on urticaria recommends omalizumab as an add-on treatment option to sgAHs.³ The guideline also recommends using pharmacotherapy following the principle of "as much as needed and as little as possible" aiming complete symptomatic relief.³ However, since there is no adequate literature support, the guideline does not give clear recommendations on whether sgAHs should be discontinued in order to lessen the pharmacotherapy after initiation of omalizumab. An opinion on this subject suggests rapid discontinuation of sgAHs after omalizumab is initiated in all patients since these patients were already resistant to antihistamines before.^{6,7} Supporting this idea, in a review of 16 studies, it has been shown that omalizumab was effective without the need for concomitant sgAHs in up to 60% of patients.⁵ Another opinion on how to manage sgAHs together with omalizumab opposes rapid discontinuation of sgAHs since they may still be effective.⁶ As shown in our previous studies, in clinical practice we also try rapid discontinuation of sgAHs in the first 3 months of therapy in well-controlled urticaria [urticaria activity score over 7 days (UAS7) $\leq$ 6 or urticaria control test (UCT) $\geq$ 12], and recommend the patients to use sgAHs only as-needed in case of intermittent urticarial symptoms.^{6,8} Previous studies showed that there were patients that develop intermittent symptoms although they fulfill the well-controlled urticaria criteria under omalizumab. A pooled analysis of ASTERIA-I, ASTERIA-II, and GLACIAL studies demonstrated that after treatment with omalizumab 300 mg/4 weeks for 12 weeks, complete response (UAS7 = 0) was noted in 49%, 54%, and 47%, and well-controlled urticaria (UAS7 $\leq$ 6) was noted in 67%, 76%, and 62% of the patients, respectively.⁹ The 15% to 22% difference between the complete response and well-controlled urticaria groups points out the patients who still have intermittent urticarial symptoms although the disease is under control with omalizumab.

Even though we recommend these patients to use as-needed sgAH whenever they are symptomatic, the effectiveness of this treatment is not clear. Therefore, this study aims to investigate the effectiveness of as-needed sgAHs in patients with well-controlled urticaria under omalizumab treatment.

2 | METHODS

This study involves CSU patients under omalizumab treatment from four different urticaria centers in Turkey. All patients were treated with 300 mg doses of omalizumab every 4 weeks for at least 3 months. In all centers, in order to assess the disease control in the previous interval, patients underwent UCT scoring (UCT = 16 defined complete controlled urticaria, 16 > UCT $\geq$ 12 defined well-controlled urticaria, and UCT < 12 defined poor-controlled urticaria) in every visit and

omalizumab was administered at the very same visit. To evaluate the effectiveness of as-needed sgAHs, all patients were recommended to lower and, if possible, discontinue daily sgAHs and to use sgAHs as-needed from the very first visit, which was a routine procedure, applied in all centers apart from this study. Other than this, routine medical treatments of the patients, if any, were unchanged.

Patients who consented to enroll in the study were given urticaria activity score-twice daily (UAS_{TD}) form, which was developed and validated previously to assess disease activity and modified by us for this study to evaluate the effectiveness of as-needed sgAHs.¹⁰ According to this modified scoring system, during an interval, patients assessed sgAH-free days according to the standard UAS_{TD} as itch (0 = none, 1 = mild, 2 = moderate, 3 = severe itch severity at each assessment) and hives (0 = none, 1 = 1-6, 2 = 7-12, 3 = > 12 hives at each assessment) scores for each half of the day (every 12 hours). On the days with an as-needed sgAH intake, patients scored the severity of their symptoms for the 4 hours before and after the sgAH use according to these scores. In standard UAS_{TD} evaluation, arithmetical mean of the scores from the first and second half of the day were calculated. Since the aim of our study is to determine the possible changes in the itch and hives severity with sgAH intake, arithmetical daily mean of the scores before and after the sgAH use were not calculated, instead, scores before and after sgAH use were calculated separately, compared to each other and mean percentage change between the scores after sgAH use was calculated. All patients scored their daily symptoms and recorded the number of sgAHs for a single 4-week interval. Patients who (a) had concomitant inducible urticaria, (b) had isolated-angioedema phenotype, (c) had poor-controlled urticaria at the end of 3 months of omalizumab treatment, (d) did not use any sgAH during an interval, or (e) could not discontinue routine daily sgAHs, were excluded from the study. Demographic information, baseline IgE values, and UCT scores of intervals were obtained from the patient charts. This study was approved by the institutional ethical committee (Erciyes University Medical Ethical Committee, decision no: 2020/179).

2.1 | Statistical analysis

Data were analyzed using the SPSS software version 17 (SPSS Inc, Chicago, Illinois). Since all variables were not normally distributed, within-group comparisons were made using Wilcoxon test and between-group comparisons were made using the Mann-Whitney *U* test. Correlations between continuous variables performed using Pearson correlation. *P* < .05 was considered significant.

3 | RESULTS

Fifty-three patients [38 female (71.7%)] with the mean age of 41.1 $\pm$ 11.4 years were included in this study. Twenty-eight patients (53%) had isolated-urticaria and 25 (47%) had urticaria-and-angioedema phenotype. Mean baseline total IgE level prior to omalizumab treatment was 333.1 $\pm$ 508.9 IU/mL.

Mean UCT scores in the evaluation visits was 13.05 ± 1.19 points. Omalizumab was administered 300 mg every 4 weeks, and during a single interval all patients used as-needed sgAHs 188 times in total. Median sgAH intake during 4 weeks-intervals was 3 (2-5) tablets per patient. UCT scores and sgAH intake frequency of the same interval showed a negative correlation ($r = -0.441$; $P = .003$).

Mean itch, hives, and total itch-hives scores before and after as-needed sgAH intake were listed in Table 1. Mean total itch-hives

TABLE 1 Results of itch, hives, and total itch-hives scores before and after sgAH intake

	Before sgAH	After sgAH	P
Itch score			
Mean $\pm$ SD	1.62 ± 0.83	0.97 ± 1	<.001
Median (IQR)	2 (1-2)	1 (0-2)	
Hives score			
Mean $\pm$ SD	1.06 ± 0.88	0.68 ± 0.82	<.001
Median (IQR)	1 (0-2)	0.5 (0-1)	
Total itch-hives score			
Mean $\pm$ SD	2.69 ± 1.45	1.64 ± 1.58	<.001
Median (IQR)	2 (2-4)	2 (0-2)	

Abbreviations: IQR, interquartile range; SD, standart deviation; sgAH, second generation antihistamines.

score was 2.69 ± 1.45 points before as-needed sgAH intake, and decreased to 1.64 ± 1.58 points after sgAH intake ($P < .001$). When itch and hives scores were evaluated separately, both scores decreased significantly similarly after sgAH intake (Table 1).

Mean decrease in itch, hives, and total itch-hives scores after sgAH intake was found $45.7\% \pm 52.9$; $42.4\% \pm 39.1$ and $50.2\% \pm 51.1$, respectively. All three scores before and after sgAH intake and decrease in these scores after sgAH intake were similar for isolated-urticaria and urticaria-and-angioedema phenotypes (Table 2). When evaluated separately, all three parameters (itch, hives, total itch-hive scores) showed significant decrease after sgAH intake ($P < .001$ for all).

In addition, patients with higher baseline total IgE levels showed significantly less improvement in itch, hives and total itch-hives scores after as-needed sgAH intake ($r = 0.31$, $P = .05$; $r = 0.375$, $P = .017$; $r = 0.31$, $P = .05$, respectively) (Figure 1). No such correlation was found between baseline total IgE levels and sgAH intake frequency or UCT scores.

4 | DISCUSSION

Our study showed that in CSU patients with well-controlled urticaria under omalizumab treatment, sgAHs decreased itch and hives scores

TABLE 2 Results comparing itch, hives, and total itch-hives scores and their changes after sgAH intake in isolated-urticaria and urticaria-and-angioedema phenotypes

	Isolated-urticaria phenotype n = 28	Urticaria-and-angioedema phenotype n = 25	P
Itch score before sgAH			
Mean $\pm$ SD	1.69 ± 0.76	1.54 ± 0.91	.219
Median (IQR)	2 (1-2)	1 (1-2)	
Hives score before sgAH			
Mean $\pm$ SD	0.95 ± 0.87	1.2 ± 0.87	.051
Median (IQR)	1 (0-2)	1 (1-2)	
Total itch-hives score before sgAH			
Mean $\pm$ SD	2.64 ± 1.34	2.74 ± 1.57	.797
Median (IQR)	2 (2-4)	2 (2-4)	
Itch score after sgAH			
Mean $\pm$ SD	0.99 ± 1	0.94 ± 0.85	.982
Median (IQR)	1 (0-2)	1 (0-1)	
Hives score after sgAH			
Mean $\pm$ SD	0.65 ± 0.88	0.71 ± 0.76	.277
Median (IQR)	0 (0-1)	1 (0-1)	
Total itch-hives score after sgAH			
Mean $\pm$ SD	1.62 ± 1.7	1.66 ± 1.43	.501
Median (IQR)	1 (0-2)	2 (0-2)	
Change in itch score with sgAH (%)			
Mean $\pm$ SD	-52.9 ± 54.6	-39.3 ± 51.7	.365
Median (IQR)	$-64.7 (-100-4.3)$	$-39.3 (-100-0)$	
Change in hives score with sgAH (%)			
Mean $\pm$ SD	-37.8 ± 41.5	-46.9 ± 37.1	.522
Median (IQR)	$-40.1 (-75.3-0)$	$-50 (-87.5-4.9)$	
Change in total itch-hives score with sgAH (%)			
Mean $\pm$ SD	-51.9 ± 53.4	-48.4 ± 49.8	.783
Median (IQR)	$-64.6 (-100-5.7)$	$-50 (-100-15.6)$	

Abbreviations: IQR, interquartile range; SD, standard deviation; sgAH, second generation antihistamines.

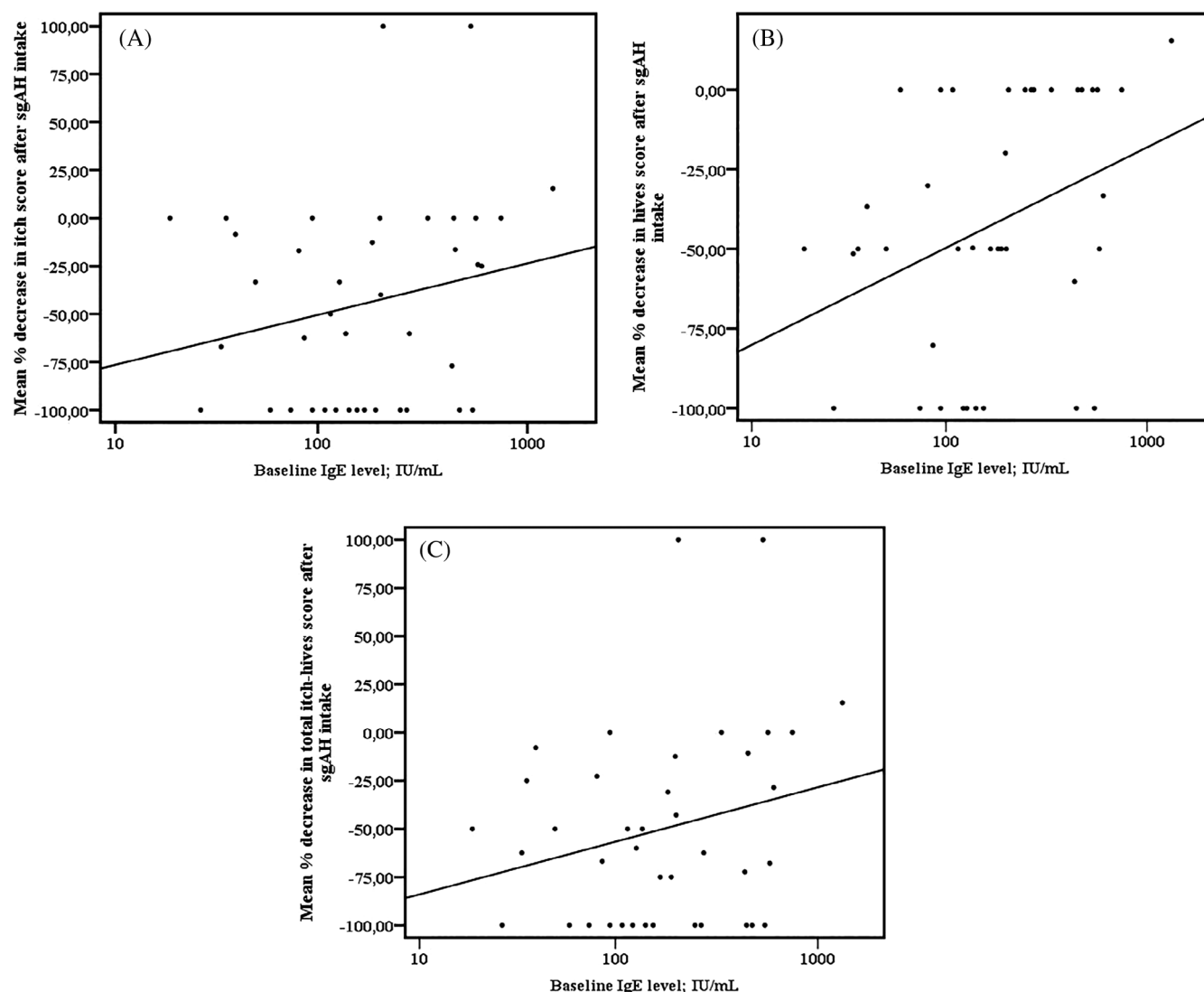


FIGURE 1 Baseline total IgE levels were correlated with the changes in itch, hives and total itch-hives scores ($r = 0.31$, $P = .05$; $r = 0.375$, $P = .017$; $r = 0.31$, $P = .05$, respectively). In patients with higher baseline total IgE levels, the mean improvement in itch. A, hives; B, and total itch-hives; C, scores after as-needed sgAH intake were lower

approximately 45% when needed during an omalizumab treatment interval. This decrease was similar in both isolated-urticaria and urticaria-and-angioedema phenotypes.

Release of histamine following mast cell degranulation plays a central role in the development of signs and symptoms of CSU.¹¹ Thus, H1-antihistamines have been the standard care of CSU. However, it was shown that rate of response to standard doses of antihistamines in CSU patients was 38.6% and increasing the dose of antihistamines were likely to increase the response rate in up to 60% of the patients.¹² Omalizumab, the first humanized anti-IgE monoclonal antibody, has become the mainstay treatment option for the antihistamine refractory patients in recent years. Although effectiveness of omalizumab in CSU has been shown in several studies, there are still many unanswered questions on how to manage omalizumab treatment in CSU. One of these questions is whether sgAHs should be discontinued in cases where the disease is under control with

omalizumab. In our previous review, we discussed on this question despite most of our answers were based on expert opinions.⁶ As far as we know, there is no study directly dealing with this subject. In their recent study, *Ensina et al.* performed a retrospective analysis and showed that over 24 months treatment with omalizumab, 27.2% of the patients were able to stop taking sgAHs and their urticaria were still continued to be controlled only with omalizumab monotherapy.⁷ They also found that accompanying angioedema or response rate to omalizumab did not create a difference in the use of sgAHs and proposed that sgAHs may be no longer necessary in some patients once the disease is controlled with omalizumab. In another retrospective real-life data, *Andaç et al.* also showed that it was possible to treat 33% of their study group with omalizumab monotherapy without antihistamines.¹³ A review dealing with this subject showed that omalizumab was effective without the need for concomitant sgAHs in up to 60% of patients.⁵ It was shown that up to 70% complete

response (UAS7 = 0 or UCT = 16) rate could be achieved with omalizumab treatment^{4,14} and it is clear that when complete response was achieved with omalizumab, sgAHs may no longer be necessary. However, as in our study, there is also a patient group that has well controlled urticaria but not complete response ($0 < \text{UAS7} \leq 6$ or $16 > \text{UCT} \geq 12$) with omalizumab. Our results showed that as the disease control rate decreased during intervals, these patients used more sgAHs, and this as-needed sgAH intake was effective on suppressing urticarial symptoms, independent from the presence of accompanying angioedema.

Another interesting finding of our study is that as-needed sgAHs were less effective in patients with higher baseline total IgE levels. Over the past years, two endotypes of CSU were postulated: type-I autoimmune (autoallergic) CSU and type IIb-autoimmune CSU.¹⁵ Indirect line of evidence suggests that these two endotypes differ in their serum biomarker profiles and response to treatments. Type-I autoimmune endotype have been suggested to have higher baseline total IgE levels, have faster and higher rates of response to omalizumab treatment and higher response rates to sgAHs.¹⁴⁻¹⁶ Similar to previous studies our patients' baseline total IgE levels were high,¹⁷ and they had a rapid and high response rate with omalizumab in the first 3-months of treatment. Therefore, we believe majority of our patient group consisted of type-I autoimmune endotype. It was reported that patients with type IIb-autoimmune endotype, which were classified with indirect markers of type IIb-autoimmune endotype like higher baseline CRP levels, lower blood basophil counts and antinuclear antibodies positivity, were more likely to have resistance to antihistamines when compared with type-I autoimmune endotype.¹⁸⁻²⁰ Although it might seem to interfere with our results, it would be inappropriate to compare our results with these findings since it is important to note that previous findings reflect the antihistamine resistance prior to omalizumab treatment. A possible explanation for the lower sgAH effectiveness in patients with higher baseline total IgE levels may be that these patients had better symptomatic improvement after omalizumab and had lower symptomatic scores before sgAHs, thus the possible decrease with sgAH intake would be less. However, we eliminated this possibility since we found no such correlation between baseline total IgE levels and symptomatic scores prior to sgAH or number of sgAH intake during the interval. Another hypothetical explanation is that despite the significant suppression of mast cell degranulation, and therefore, urticarial symptoms after omalizumab treatment, intermittent degranulation of mast cells and histamine release still continues at a minimal level, and this time standard dose sgAHs may be sufficient to block action of histamine and competes with it at receptor level. However, we do not have any explanatory data on this subject and further studies investigating the underlying mechanisms are needed.

Our study has some limitations. First is the low number of the patients enrolled in the study. Second, we used UAS_{TD} to score symptoms before and after sgAH intake. Although it has been modified for our study, we are aware that this patient reported outcome measure (PROM) was not mainly validated for such purpose, but we had to use

this tool since there was no other PROM that was feasible for our study. Third, we did not evaluate the possible effects of sgAHs on angioedema in patients with urticaria-and-angioedema phenotype. Although angioedema activity score (AAS) was a validated tool to determine disease activity in recurrent angioedema patients,²¹ we did not use this PROM. Fourth, since this was an observational study, we did not change the antihistamines that have been already used by the patient, which might have resulted in efficacy diversities between different sgAHs.²² Therefore, it would be more appropriate to use the same agent in future studies. Finally, it is known that H1-antihistamines are inverse agonists and also have anti-inflammatory activities.²³ Although our study showed that as-needed sgAHs were effective in symptomatic improvement, further studies are needed to investigate whether this inverse-agonist and anti-inflammatory effects of sgAHs cause any significant difference between as-needed and daily regimes. To answer this question, comparative studies are needed.

In conclusion, our study showed that in patients with well controlled urticaria under omalizumab, as the UCT scores decreased during an interval, patients tended to use more as-needed sgAHs and these sgAHs had significantly decreased itch and hives scores. In addition, we also found that baseline total IgE levels may be used as a potential biomarker for sgAH effectiveness in patients under omalizumab treatment. We believe our findings may provide guidance for individualized treatment planning and antihistamine management in CSU patients under omalizumab treatment.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTION

All author equally participated in the design of the study and data collection. Dr Türk made the analysis of the data. All authors made substantial contributions to the interpretation of the results. Dr Türk and Dr Yılmaz wrote the draft of the manuscript. Dr Bahçecioglu, Dr Can, Dr Ertaş, Dr Kartal, Dr Çınar and Dr Kocatürk made critical review. All authors has seen and approved the final version to be published, agreed to be accountable for all aspects of the work related to its accuracy or integrity and all of them meet the requirements for authorship.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions

ORCID

Murat Türk  <https://orcid.org/0000-0002-3290-2661>

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