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Impact of Omalizumab Treatment on Quality of Life and Activity of Chronic Spontaneous Urticaria

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Abstract

Background: Omalizumab treatment has shown promise in managing Chronic spontaneous urticaria (CSU). This study focuses on evaluating its effect on improving the quality of life and reducing CSU activity and severity in patients of different age groups.

Material and Method: Conducted at Derince Training and Research Hospital, this observational study involved 50 CSU patients, categorized into adolescents (≤18years, n=15) and adults (>18years, n=35). Data were collected through clinical and demographic assessments, including Urticaria Activity Score (UAS), Urticaria Control Test (UCT), and Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) questionnaires, at the beginning and the third month of Omalizumab treatment.

Result: Significant improvements were observed in UAS, UCT, and CU-Q2oL scores post-Omalizumab treatment, indicating reduced symptom severity and enhanced quality of life. The median UAS at the start was 35 (28-35); at the third month, 7 (0-7); median UCT at the start was 2 (1.25-3), at the third month 16 (13-16); median CU-Q2oL at the start was 70.5 (66-74), at the third month 23 (23-28); ($p<0.001$, $p<0.001$, and $p<0.001$, respectively). In adult patients, levels of anti-TPO and anti-TG were significantly higher compared to adolescents with CSU (anti-TPO 28 (0.92-47.4) IU/mL vs. 1.73 (0.79-27.1) IU/mL, $p=0.066$; anti-TG 12.6 (1.4-31.5) IU/mL vs. 1.08 (0.74-9.66) IU/mL, $p=0.007$).

Conclusion: Omalizumab treatment improves the quality of life and reduces disease activity in CSU, demonstrating its efficacy as a therapeutic option for those resistant to antihistamines across all age groups. Further research is warranted to explore the long-term effects of Omalizumab and its potential in personalized CSU management strategies.

Keywords: Omalizumab, Chronic spontaneous urticaria, Urticaria Activity Score, Urticaria Control Test, Chronic Urticaria Quality of Life Questionnaire

Introduction

Chronic spontaneous urticaria (CSU) is a skin condition characterized by recurring, itchy skin lesions and edemas, persisting for at least six weeks. The pathophysiology of CSU still needs to be fully understood, involving a combination of immunological interactions, genetic factors, and environmental triggers.[1,2] Approximately 30-50% of cases are attributed to autoimmune causes. The most common formation of urticaria involves autoantibodies against the alpha chain of the high-affinity IgE receptor (FCεR1α) on the surface of basophils and mast cells. The second and rarer one is the anti-IgE autoantibody against the IgE antibody itself. These IgG-type autoantibodies lead to the activation of basophils and mast cells by binding to FCεR1α or IgE.[2-4]

The Urticaria Activity Score (UAS) is a widely used scoring system for assessing the severity of urticaria symptoms. UAS is based on the intensity of urticaria lesions and itchiness. UAS provides reliable information for both patients and physicians in determining the severity of the disease and assessing the response to treatment. The Urticaria Control Test (UCT) evaluates whether the condition affects the patient's daily activities.[3-7] Improving the quality of life in CSU patients is one of the goals of treatment. Therefore, the Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) has been translated into Turkish. Using this quality-of-life questionnaire is beneficial in assessing the clinic's effectiveness and treatment efficacy.[8]

Despite treatment options, including antihistamines, corticosteroids, and other immunomodulatory agents, the problem of insufficient symptom control and the emergence of side effects persists in many patients.[9,10] Omalizumab has marked significant progress in managing CSU among monoclonal antibody therapies in recent years. Omalizumab is a monoclonal anti-IgE antibody that exhibits its effect by binding to IgE, reducing the level of IgE, and consequently decreasing the receptors and expressions of IgE on mast

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cells and basophils. Various studies have provided positive findings that Omalizumab reduces symptoms of CSU and enhances quality of life.[11,12] A study by Chang et al. observed a significant reduction in UAS following Omalizumab treatment.[11] Moreover, Tharp et al.'s research examined the impact of Omalizumab on UCT scores, determining that the treatment positively influenced daily life activities.[13] However, some studies have suggested that the impact of Omalizumab on CSU symptoms could vary among patients.[14,15] Further research is needed to determine the specific effects of Omalizumab treatment on UAS and UCT.

This study aims to identify the effects of Omalizumab treatment on urticaria activity, severity, and quality of life in adolescent and adult patients with CSU who are resistant to antihistamine therapy and have started Omalizumab treatment. We evaluated our patients with CSU regarding clinical characteristics and laboratory parameters and analyzed factors affecting antihistamine resistance in these patients. This evaluation provides a more comprehensive understanding of the treatment's clinical efficacy and targets improving the patient's quality of life. Understanding the impact of Omalizumab on UAS and UCT could contribute to developing more effective CSU management strategies.

Material and Methods

This research was conducted at Derince Training and Research Hospital after receiving approval from the local institutional review board (IRB). The study included 50 CSU patients. They were evaluated in two separate groups: 15 adolescents (≤18 years old) and 35 adults (>18 years old). Clinical and demographic data were collected from their medical records. These records included clinical history, urticaria possible etiologic/aggravating factors, Skin Prick Tests (SPT), laboratory tests, and questionnaire assessments (UAS, UCT, and CU-Q2oL) of each patient at the beginning and the third month of Omalizumab treatment. Detailed demographic and clinical features of all CSU patients are shown in **Table 1.**

Statistical analysis: Continuous variables were presented as mean±standard deviation (SD) or median with their 25th-75th percentile. Categorical variables were expressed as numbers and percentages (n, %). We used the Chi-square or Fisher's exact test to compare categorical variables. Non-normal distributed variables were compared with the Mann-Whitney U test. The difference between the two measurements of a dependent group was tested using the Wilcoxon signed-rank test. P-values of less than 0.05 were considered significant. Statistics and visualizations were done with R version 4.3.1 (A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/.)

Table 1: The demographic and clinical data of CSU patients

Parameters; Mean (SD)	CSU patients (N-50)
Age	38.8 (16.7)
Female/ Male	36 (72.0%)/14 (28.0%)
Clinical follow-up (m)	19.2 (11.6)
Urticaria duration (m)	55.0 (91.5)
Attack frequency	
Every day	39 (78.0%)
Every week	10 (20.0%)
Monthly	1 (2.00%)
ED visit	
Yes	39 (78.0%)
No	11 (22.0%)
Follow-up ED visit	
Yes	10 (20.0%)
No	40 (80.0%)
Lesion disappearance time	
<1 hour	2 (4.00%)
1-24 hours	46 (92.0%)
>24 hours	2 (4.00%)
Angioedema	
Yes	42 (84.0%)
No	8 (16.0%)
Drug - Food	
Yes	23 (46.0%)
No	27 (54.0%)
Stress	
Yes	44 (88.0%)
No	6 (12.0%)
Infection	
Yes	6 (12.0%)
No	44 (88.0%)
Comorbidity	
Yes	14 (28.0%)
No	36 (72.0%)
Additional medication	
Yes	14 (28.0%)
No	36 (72.0%)
Smoking	
Yes	22 (44.0%)
No	28 (56.0%)
SPT result:	
None	28 (56.0%)
HDM positive	8 (16.0%)
Pollen positive	3 (6.00%)
Pollen+HDM positive	1 (2.00%)
Dermographism	4 (8.00%)
Negative	6 (12.0%)

Abbreviations: *CSU: Chronic spontaneous urticaria, M: month, ED: emergency department, SPT: skin prick test, HDM: house dust mite*

Results

The study included a total of 50 patients and assessed them in two separate groups: adolescents (n=15, ≤18 years) and adults (n=35, >18 years). The adolescent group consisted of 73% females and 27% males, with a median age of 18 (17-18 years); the adult group consisted of 71% females and 29%

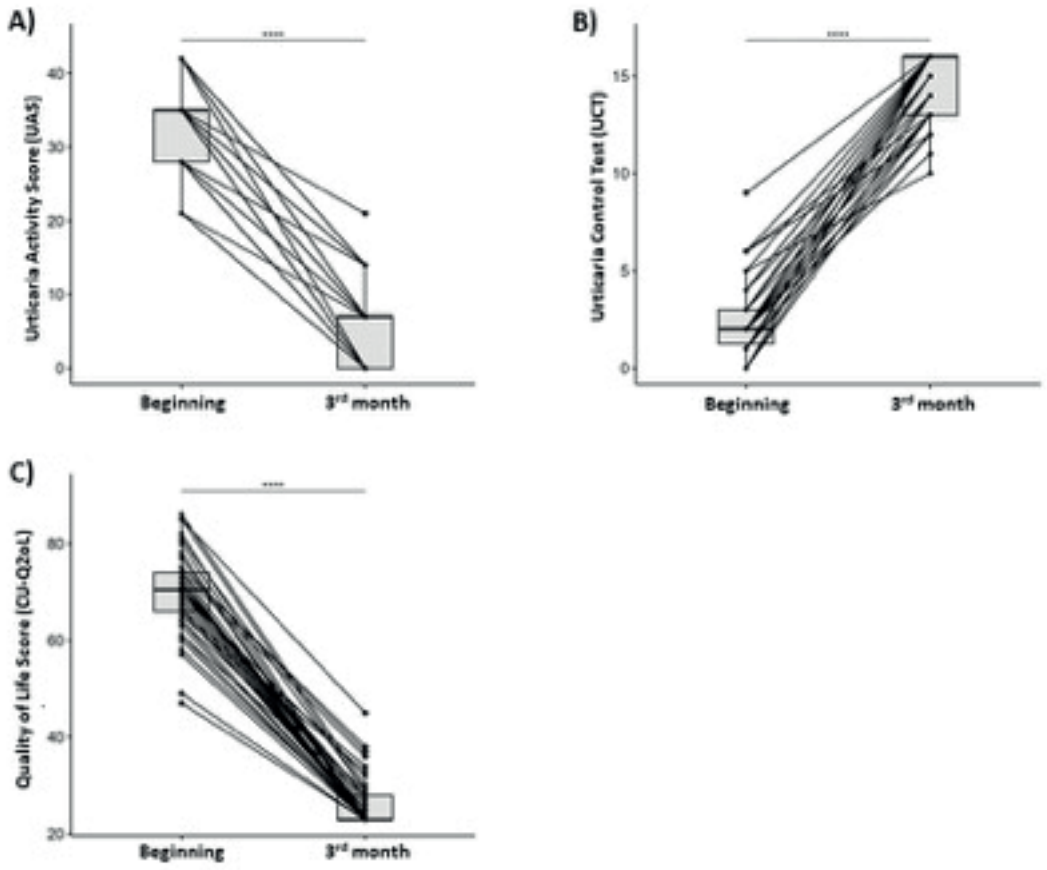

Figure 1: Patients were administered UAS, UCT, and CU-Q2oL questionnaires at the initiation of Omalizumab treatment and the third month of the treatment

males, with a median age of 48 (39.5-57 years). The average clinical follow-up period (19.2±11.6 months, p=0.695) and the duration of urticaria (55±91.5 months, p=0.655) were similar among all patients. The mean duration of Omalizumab treatment for all patients was 12 (±8.6) months **(Table 1).**

Patients were administered UAS, UCT, and CU-Q2oL questionnaires at the initiation of Omalizumab treatment and the third month of the treatment **(Figure 1).** Pre-treatment UAS questionnaire results indicated that 94% of patients had severe urticaria, and 6% had moderate urticaria. Initial UCT questionnaire results showed that all individuals in both groups had poorly controlled disease activity. According to the quality of life questionnaire, 40% were mild to moderately affected, and 60% were severely affected; it was observed that adolescents were more likely to be mild to moderate, while adults were more severely affected (p=0.345). The median UAS at the start was 35 (28-35); at the third month 7 (0-7); the median UCT at the start was 2 (1.25-3); at the third month 16 (13-16); median CU-Q2oL at the start was 70.5 (66-74), at the third month 23 (23-28); ($p<0.001$, $p<0.001$, and $p<0.001$, respectively).

Adult patients had a higher frequency of attacks before Omalizumab treatment compared to adolescents (n=28, 71.8% daily; n=6, 60% weekly vs. n=11, 28.2% daily; n=4, 40% weekly, respectively, p=0.629), but this was not statistically significant. Adults constituted 70% of emergency department visits. The number of pre-treatment emergency department visits (adults median n=4 (3-10), adolescents median n=5 (3-10), p=0.730) decreased during the follow-up (adults average n=3 (1.5-3), adolescents average n=1 (1-3), p=0.721) in both groups, but was not statistically significant. Most patients experienced lesion disappearance within 1-24 hours (p=1.000). It was found that 71.4% of patients with accompanying angioedema were adults, and 28.6% were adolescents (p=0.683) **(Table 2).**

Most patients associated with triggers were adults (n=18, 78.3% adults vs. n=5, 21.7% adolescents; p=0.386). NSAIDs were predominant in adults (n=11, 78.6% adults, n=3, 21.4% adolescents), but no significance was found (p=0.911). Relationships with stress, infection, presence of additional illness, additional medication usage, and smoking were insignificant (p=0.654, p=0.348, p=0.179, p=0.179, p=0.576, and p=0.275, respectively). A skin prick test (SPT) was conducted on 44% of the patients. Of these, 16% tested positive for house dust mites, 6% for pollen, 2% for both pollen and house dust mites, 8% was dermographism, and 12% was negative. No significant correlation was found with the SPT results (p=0.275).

Table 2: Comparison of clinical parameters between adolescent CSU and adult CSU patients

	Adolescents (<18 y) N=15	Adults (>18 y) N=35	P Overall
Age	18.0 [17.0 - 18.0]	48.0 [39.5 - 57.0]	<0.001
Female/Male	11 (30.6%)/4 (28.6%)	25 (69.4%)/10 (71.4%)	1.000
Clinical follow-up (m)	17.0 [11.5 - 28.5]	14.0 [9.00 - 30.0]	0.695
Urticaria duration (m)	15.0 [7.0 - 42.0]	18.0 [7.50 - 73.0]	0.655
Attack frequency			0.629
Every day	11 (28.2%)	28 (71.8%)	
Every week	4 (40.0%)	6 (60.0%)	
Monthly	0 (0.00%)	1 (100%)	
ED visit			0.468
Yes	13 (33.3%)	26 (66.7%)	
No	2 (18.2%)	9 (81.8%)	
Follow-up ED visit			1.000
Yes	3 (30.0%)	7 (70.0%)	
No	12 (30.0%)	28 (70.0%)	
Lesion disappearance time			1.000
<1 hour	0 (0.00%)	2 (100%)	
1-24 hours	15 (32.6%)	31 (67.4%)	
>24 hours	0 (0.00%)	2 (100%)	
Angioedema:			0.683
Yes	12 (28.6%)	30 (71.4%)	
No	3 (37.5%)	5 (62.5%)	
Drug - Food			0.386
Yes	5 (21.7%)	18 (78.3%)	
No	10 (37.0%)	17 (63.0%)	
Stress :			0.654
Yes	14 (31.8%)	30 (68.2%)	
No	1 (16.7%)	5 (83.3%)	
Infection			0.348
Yes	3 (50.0%)	3 (50.0%)	
No	12 (27.3%)	32 (72.7%)	
Comorbidity			0.179
Yes	2 (14.3%)	12 (85.7%)	
No	13 (36.1%)	23 (63.9%)	
Smoking			0.576
Yes	8 (36.4%)	14 (63.6%)	
No	7 (25.0%)	21 (75.0%)	
SPT result:			0.275
None	7 (25.0%)	21 (75.0%)	
HDM positive	1 (12.5%)	7 (87.5%)	
Pollen positive	1 (33.3%)	2 (66.7%)	
Pollen+HDM positive	1 (100%)	0 (0.00%)	
Dermographism	2 (50.0%)	2 (50.0%)	
Negative	3 (50.0%)	3 (50.0%)	

Abbreviations: *CSU: Chronic spontaneous urticaria, y: years, m: month, ED: emergency department, SPT: skin prick test, HDM: house dust mite*

In adult patients diagnosed with CSU, levels of anti-TPO and anti-TG were significantly higher compared to adolescents with CSU (anti-TPO 28 (0.92-47.4) IU/mL vs. 1.73 (0.79-27.1) IU/mL, p=0.066; anti-TG 12.6 (1.4-31.5) IU/mL vs. 1.08 (0.74-9.66) IU/mL, p=0.007). No significance was found in the other laboratory parameters examined **(Table 3).**

Discussion

This study rigorously evaluates the impact of Omalizumab on quality of life and urticaria activity levels in patients with CSU, characterized by morbidity and challenging management barriers. The findings are consistent with and extend the existing literature; It shows significant improvements in UAS and UCT following Omalizumab treatment. These improvements indicate a reduction in the physical symptoms of CSU and an increase in quality of life, as noted by the CU-Q2oL Questionnaire.[15,16] The importance of these results cannot be overstated, given the debilitating impact that CSU exerts on patients' daily lives, underscoring the need for effective management strategies.

Our study's cohort, including adolescents and adults, is well characterized, and dual assessment via UAS, UCT, and CU-Q2oL questionnaires before and after Omalizumab treatment reflects a robust design to capture objective

Table 3: Comparison of clinical parameters between adolescent CSU and adult CSU patients

	Adolescents (<18 y) N=15	Adults (>18 y) N=35	P Overall
Anti_TPO (IU/mL)	1.73 [0.79;27.1]	28.0 [0.92;47.4]	0.066
Anti_TG (IU/mL)	1.08 [0.74;9.66]	12.6 [1.40;31.5]	0.007
D-dimer (µg/L)	0.38 [0.35;0.45]	0.65 [0.34;1.48]	0.125
CRP (mg/L)	3.03 [2.00;7.44]	5.00 [3.03;11.8]	0.198
Lymphocyte (/µl)	2200 [1700;2845]	2100 [1784;2495]	0.368
Neutrophil (/µl)	4000 [3770;5850]	5000 [3320;6310]	0.695
Eosinophil (/µl)	200 [100;230]	200 [100;200]	0.514
Hgb (gr/dL)	14.1 [13.0;14.6]	13.4 [12.5;14.8]	0.518
Platelet (/µl)	292000 [247500;319000]	273000 [246500;337500]	0.727
Total IgE (IU/mL)	83.4 [61.3;232]	130 [37.2;211]	0.922
ANA			0.652
Positive	1 (16.7%)	5 (83.3%)	
Negative	14 (32.6%)	29 (67.4%)	

Abbreviations: *CSU: Chronic spontaneous urticaria, y: Years, Anti-TPO: Anti-Thyroid Peroxidase antibodies, Anti-TG: Anti-Thyroglobulin antibodies, CRP: C reactive protein, Hgb: Hemoglobin, ANA: Antinuclear Antibody*

and subjective treatment measures. It supports the role of Omalizumab in improving patients' quality of life.[11] The distinction between adolescents and adults regarding attack frequency, emergency department visits, and precipitating relationship is a nuanced contribution to the existing literature. A comprehensive evaluation of potential confounding factors such as medication or food triggers, stress, infection, and comorbidities adds depth to the study's results.

Despite advances in understanding the pathophysiology of CSU, treatment remains complex, and many patients respond poorly to conventional treatments such as antihistamines.[17,18] In this context, Omalizumab, a monoclonal anti-IgE antibody, is emerging as a promising alternative that potentially alters the course of the disease for those resistant to standard treatments.[7,19] Interestingly, our analysis revealed no significant difference in treatment response between adolescents and adults, demonstrating Omalizumab's broad effectiveness across age groups. This observation is particularly noteworthy given the limited number of studies focusing on pediatric and adolescent populations with CSU.[20] Additionally, the study illuminates the subtle interaction between CSU and various demographic and clinical factors, such as gender, age, and autoimmune markers, which may affect the course of the disease and treatment outcomes. The higher prevalence of anti-TPO and anti-TG in adult patients suggests a link between thyroid autoimmunity and CSU severity in adults; considering the significance found in anti-TG levels, this correlation deserves further investigation. This relationship is consistent with existing studies suggesting a higher prevalence of autoimmunity in adult CSU patients.[9,10,21] This correlation not only enriches our understanding of the etiological complexity of CSU but also points to further research on the potential therapeutic effects of targeting autoimmune pathways in managing CSU. Although the study is limited due to sample size and the inherent variability of CSU delivery, it adds valuable information to the management of CSU. The relatively small sample size and short follow-up period may limit our findings' generalizability and interpretative depth. Additionally, the observational design of the study precludes causal inferences. It necessitates randomized controlled studies to prove Omalizumab's efficacy further and investigate its effect's mechanistic basis in CSU.[6,22] Omalizumab is emerging as a valid treatment option, particularly for antihistamine-refractory cases, and the study's findings support its inclusion in CSU treatment protocols, especially given the significant improvement in quality of life.

In summary, our study strengthens the therapeutic potential of Omalizumab to improve quality of life and alleviate disease activity in CSU patients resistant to antihistamines. It also paves the way for personalized treatment approaches by shedding light on the complex network of factors that affect the treatment response and the disease's emergence. The study's findings support its inclusion in CSU treatment protocols, especially given the significant improvement in quality of life.

In conclusion, the study supports the use of Omalizumab in patients refractory to CSU treatment and underlines the importance of personalized treatment strategies. More longitudinal studies with larger groups are needed to elucidate the long-term effects and safety profile of Omalizumab, the mechanistic basis of its efficacy, and identify biomarkers predictive of treatment response. This will ultimately promote a more nuanced and compelling management paradigm for CSU. Additionally, investigating the connections between autoimmune markers and CSU may unlock new avenues for therapeutic intervention.

Author contributions

NK, CO conceptualized and wrote the manuscript. NK, CO followed up with the patients, collected the clinical and laboratory data, and provided samples. NK, CO made an intellectual contribution to the discussion.

References

1. Khakoo G, Sofianou-Katsoulis A, Perkin MR, Lack G. Clinical features and natural history of physical urticaria in children. *Pediatr Allergy Immunol*. Jun 2008;19(4):363-6. doi:10.1111/j.1399-3038.2007.00667.x
2. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA(2) LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy*. Jul 2014;69(7):868-87. doi:10.1111/all.12313
3. Sanchez-Borges M, Asero R, Ansotegui IJ, et al. Diagnosis and treatment of urticaria and angioedema: a worldwide perspective. *World Allergy Organ J*. Nov 2012;5(11):125-47. doi:10.1097/WOX.0b013e3182758d6c
4. Powell RJ, Leech SC, Till S, et al. BSACI guideline for the management of chronic urticaria and angioedema. *Clin Exp Allergy*. Mar 2015;45(3):547-65. doi:10.1111/cea.12494
5. Hawro T, Ohanyan T, Schoepke N, et al. The Urticaria Activity Score-Validity, Reliability, and Responsiveness. *J Allergy Clin Immunol Pract*. Jul-Aug 2018;6(4):1185-1190 e1. doi:10.1016/j.jaip.2017.10.001
6. Bernstein JA, Lang DM, Khan DA, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. *J Allergy Clin Immunol*. May 2014;133(5):1270-7. doi:10.1016/j.jaci.2014.02.036
7. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA(2)LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy*. Jul 2018;73(7):1393-1414. doi:10.1111/all.13397
8. Baiardini I, Braido F, Bindslev-Jensen C, et al. Recommendations for assessing patient-reported outcomes and health-related quality of life in patients with urticaria: a GA(2) LEN taskforce position paper. *Allergy*. Jul 2011;66(7):840-4. doi:10.1111/j.1398-9995.2011.02580.x
9. Maurer M, Rosen K, Hsieh HJ, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med*. Mar 7 2013;368(10):924-35. doi:10.1056/NEJMoa1215372
10. Saini S, Rosen KE, Hsieh HJ, et al. A randomized, placebo-controlled, dose-ranging study of single-dose Omalizumab in patients with H1-antihistamine-refractory chronic idiopathic urticaria. *J Allergy Clin Immunol*. Sep 2011;128(3):567-73 e1. doi:10.1016/j.jaci.2011.06.010
11. Chang J, Cattelan L, Ben-Shoshan M, Le M, Netchiporouk E. Management of Pediatric Chronic Spontaneous Urticaria: A Review of Current Evidence and Guidelines. *J Asthma Allergy*. 2021;14:187-199. doi:10.2147/JAA.S249765
12. Vadasz Z, Tal Y, Rotem M, et al. Omalizumab for severe chronic spontaneous urticaria: Real-life experiences of 280 patients. *J Allergy Clin Immunol Pract*. Nov-Dec 2017;5(6):1743-1745. doi:10.1016/j.jaip.2017.08.035
13. Tharp MD, Bernstein JA, Kavati A, et al. Benefits and Harms of Omalizumab Treatment in Adolescent and Adult Patients With Chronic Idiopathic (Spontaneous) Urticaria: A Meta-analysis of "Real-world" Evidence. *JAMA Dermatol*. Jan 1 2019;155(1):29-38. doi:10.1001/jamadermatol.2018.3447
14. Labrador-Horrillo M, Valero A, Velasco M, et al. Efficacy of Omalizumab in chronic spontaneous urticaria refractory to conventional therapy: analysis of 110 patients in real-life practice. *Expert Opin Biol Ther*. Sep 2013;13(9):1225-8. doi:10.1517/14712598.2013.822484
15. Sussman G, Hebert J, Barron C, et al. Real-life experiences with Omalizumab for the treatment of chronic urticaria. *Ann Allergy Asthma Immunol*. Feb 2014;112(2):170-4. doi:10.1016/j.anai.2013.12.005
16. Weller K, Groffik A, Church MK, et al. Development and validation of the Urticaria Control Test: a patient-reported outcome instrument for assessing urticaria control. *J Allergy Clin Immunol*. May 2014;133(5):1365-72, 1372 e1-6. doi:10.1016/j.jaci.2013.12.1076
17. Greaves MW. Pathology and classification of urticaria. *Immunol Allergy Clin North Am*. Feb 2014;34(1):1-9. doi:10.1016/j.iac.2013.07.009
18. Kaplan AP. Treatment of chronic spontaneous urticaria. *Allergy Asthma Immunol Res*. Nov 2012;4(6):326-31. doi:10.4168/aair.2012.4.6.326
19. Maurer M, Bindslev-Jensen C, Gimenez-Arnau A, et al. Chronic idiopathic urticaria (CIU) is no longer idiopathic: time for an update. *Br J Dermatol*. Feb 2013;168(2):455-6. doi:10.1111/j.1365-2133.2012.11171.x
20. Godse K, De A, Zawar V, et al. Consensus Statement for the Diagnosis and Treatment of Urticaria: A 2017 Update. *Indian J Dermatol*. Jan-Feb 2018;63(1):2-15. doi:10.4103/ijd.IJD_308_17
21. Leznoff A, Sussman GL. Syndrome of idiopathic chronic urticaria and angioedema with thyroid autoimmunity: a study of 90 patients. *J Allergy Clin Immunol*. Jul 1989;84(1):66-71. doi:10.1016/0091-6749(89)90180-2
22. Vestergaard C, Deleuran M. Chronic spontaneous urticaria: latest developments in aetiology, diagnosis and therapy. *Ther Adv Chronic Dis*. Nov 2015;6(6):304-13. doi:10.1177/2040622315603951