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Sex differences in the efficacy of omalizumab in the treatment of chronic spontaneous urticaria

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Abstract

Background: Omalizumab is shown to be effective in the treatment of chronic spontaneous urticaria (CSU), a disease with high personal and social impact. Sex differences in CSU are recognized with women more frequently affected. Scarce is the knowledge about response to omalizumab between sex groups. We sought to identify any differences based on the sex of patients receiving omalizumab.

Methods: We evaluated data of patients diagnosed with CSU refractory to high-dose second-generation H1 antihistamines and treated with 300 mg omalizumab every 4 weeks for 6 months and then at relapse.

Results: Discussion: All patients, regardless of sex, age, or any other factor, achieved the clinical remission of the disease after the first 3 doses with a reduction of the disease activity indices and impact on the quality of life. Recurrences predominate in men, two months after the suspension of the drug. Respect to sex and recurrence we did not find any correlation with age, body mass index, peripheral eosinophil counts, total IgE levels, D-dimer, plasma prothrombine level or C-reactive protein. We found no sex differences in tolerability and safety. CSU in girls may persist longer and have worse prognosis, but no one has so far noted sex differences in response to omalizumab.

Conclusions: Although there are no certainties on the mechanism of action of omalizumab in CSU, the noticeable difference in response between males and females lead us to suppose a role of the hormonal balance both on the pathogenesis of the CSU and on the efficacy of OmAb.

Keywords

urticaria, allergy, omalizumab, gender, sex, anti-IgE, IgE, CSU

Introduction

Chronic spontaneous urticaria (CSU) is a heterogeneous inflammatory itching skin disease[1] in which the female to male ratio is approximately 2–4:1 but to date we ignore the pathogenic mechanism determining the female prevalence. Sex dependent immunological features may be responsible for this predilection.[2] CSU is a common nosological entity in older individuals, although few data are available regarding clinical features and epidemiology in the elderly.[3-5] Omalizumab (OmAb) is recommended to be added to CSU therapy if sufficient improvement does not occur after 2–4 weeks that the dose of second-generation H1

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antihistamines were increased up to fourfold.[6-8] 10–30% of patients do not achieve a satisfactory control of the disease and recurrence is possible.[9] Epidemiology shows the weight of sex's matter in CSU but sex- or gender-stratified analysis for treatment efficacy is missing. Unfortunately, in clinical practice, the sex and gender differences are still neglected in the era of precision medicine. The objective of our study was to identify any differences between female and male patients receiving OmAb, in terms of tolerability, safety, and clinical efficacy.

Materials and methods

We evaluated data of 42 patients (26 females and 16 males) (Table 1) diagnosed with CSU refractory to high-dose second-generation H1 antihistamines (AH) and treated with OmAb between January 2017 and November 2019 in a 35-month, prospective, non-interventional single-center study. We present data at baseline, at 3-month visits during therapy and at 2-months visits after each cycle with addition of 2 months of observation if no relapses occurred in the first two months after the end of therapy. The size of the sample was conditioned by the low incidence of the disease correlated to the total population of the reference area of our hospital and the need for a not excessively prolonged recruitment period. Patient recruitment took place from January to October 2017 with collection of patient's CU-related medical history, comorbidities and previous treatments. Inclusion criteria comprised adult patients (≥18 years) with confirmed CU diagnosis for ≥2 months, resistant to H1-AH treatment.

Patients with physical urticaria and angioedema were preventively excluded. The study included three visits along the 25-month follow-up period. To assess disease activity and guide assessment of therapy effectiveness we used patients reported outcomes through DLQI, Urticaria Activity Score (UAS), and CU-Q2oL. Patients received 300 mg OmAb administered every 4 weeks for 6 months. Patients relapsing after two months of observation were retreated with a second 5-month cycle. Further relapse after 2 months of observation, underwent to a third therapeutic cycle lasting 6 months with a subsequent watching time of 4 months. We compared the characteristics of patients (shown in Table 1) after discontinuation of OmAb and evaluated the possible effects of all available variables on clinical response.[10](Tables 2 and 3)

The study was conducted according to Good Clinical Practice guidelines, the Declaration of Helsinki, was approved by the local ethics committee (Internal Review Board University of L Aquila ex "Academic Ethics

Table 1. Clinical and laboratory variables of the study.

Variables	Women	Men
N, (%)	26 (62%)	16 (38%)
Age, years, mean ± DS	48.8 ± [11.3]	48.1 ± [22.3]
Duration of CSU, mean ± DS	3.9 ± [3]	1.5 ± [2]
Thyroid impairment, *n* (%)	4 (15.4%)	0
GERD, *n* (%)	2 (7.7%)	0
Depression, *n* (%)	2 (7.7%)	0
Diabetes type II, *n* (%)	0	2 (12.5%)
Allergy to inhalants, *n* (%)	8 (30.8%)	10 (62.5%)
BMI kg/m2, mean ± DS	22.7 ± [1.5]	23.4 ± [1.2]
IgE baseline, mean ± DS	409 ± [76.1]	355 ± [66.8]
ASST, *n* (%)	8 (30.8%)	8 (50%)
Disease activity, mean ± DS		
UAS 7 T0	38.5 ± [3.7]	39.4 ± [3.6]
DLQI T0	27.7 ± [2.5]	28.4 ± [2.4]
CU-Q2oL T0	87.8 ± [3.6]	88.9 ± [3.9]
UAS 7 T3	13.2 ± [4.5]	10.1 ± [2.9]
DLQI T3	7.5 ± [2.6]	11.4 ± [3.4]
CU-Q2oL T3	11.2 ± [4.8]	11.4 ± [4.2]
UAS T6	0	0
DLQI T6	0	0
CU-Q2oL T6	0	0
Recurrence rate after first cycle	4 (15.4%)	8 (50%)
Recurrence rate after second cycle	0	4 (25%)

Table 2. Clinical and laboratory variables in woman.

Variables	Responder woman	Non responder woman
N, (%)	22 (84.6%)	4 (15.4%)
Age, years, mean ± DS	50 ± 12.2	41.5 ± 10.1
Menopause, *n* (%)	14 (53.8%)	None
Duration of CSU, mean ± DS	4.1 ± 3.7	3 ± 1
Thyroid impairment, *n* (%)	4 (15.4%)	None
MRGE, *n* (%)	2 (7.7%)	None
Depression, *n* (%)	2 (7.7%)	None
Diabetes type II, *n* (%)	None	None
Allergy to inhalants, *n* (%)	8 (30.7%)	None
BMI kg/m2, mean ± DS	24.8 ± 4.7	19.8 ± 4.1
IgE baseline, mean ± DS	479 ± 81.2	23.7 ± 2.4
ASST, *n* (%)	6 (23.1%)	2 (7.7%)
Disease activity, mean ± DS		
UAS 7 T0	38.2 ± 3.7	38.5 ± 3.5
DLQI T0	27.5 ± 2.5	30
CU-Q2oL T0	87.6 ± 3.6	91.5 ± 0.5
UAS 7 T3	12.9 ± 4.4	13.5 ± 1.5
DLQI T3	7.4 ± 2.6	11 ± 1
CU-Q2oL T3	10.6 ± 4.3	16 ± 4
UAS T6	0	0
DLQI T6	0	0
CU-Q2oL T6	0	0
Disease activity, mean ± DS(Second cycle)		
UAS 7 T0		38.3 ± 3
DLQI T0		28 ± 2
CU-Q2oL T0		87.5 ± 3.5
UAS 7 T3		13.4 ± 3
DLQI T3		10 ± 0.5
CU-Q2oL T3		15 ± 4
UAS T6		0
DLQI T6		0
CU-Q2oL T6		0

Committee" D.R. *n*. 206/2013 modified D.R. *n*. 46/2017) and written informed consent was obtained from each participant.

Results

After 3 months of treatment (T3) with OmAb, the mean value of UAS 7 improved to 13.2 ± [4.5] points (range 5–22) for women, and then zeroed at the end of the treatment when nobody showed signs or disease symptoms. Similar trend for male patients who at T3 had an average UAS 7 value of 10.1 ± [2.9] points (range 6–14) and 0 points at the end of the treatment. The mean DLQI value at time 0 (T0) was 27.7 ± [2.5] points (range 30–25) for women and 28.4 ± [2.4] points (range 30–24) for men. At T3 the same value was 7.5 ± [2.6] points (range 3–12) for women and 11.4 ± [3.4] points (range 6–16) for men. Average of CU-Q2oL score at T0 was 87.8 ± [3.6] (range 80–92) for women and 88.9 ± [3.9] (range 80–92) for men, at T3 was 11.2 ± [4.8] (range 5–22) for women and 11.4 ± [4.2] (range 5–20) for men. After six months of treatment patients achieved in both scale 0 points with clinical remission in all patients. To the next evaluations, 8 males (50%) resorted to a second cycle of therapy and 4 (25%) to a third OmAb cycle. Only 4 (25%) men definitively recovered after the first cycle. Instead among females, 22 (84.6%) were in complete remission and 4 (15.4%) underwent a second cycle. After 4 months of observation by the end of the last therapeutic cycle no women showed recurrence. Among the six male subjects with the highest relapse rate, then undergoing the third therapeutic cycle with OmAb, four were positive for autologous serum skin test (ASST) (25%), two (12.5%) of the six with only one recurrence, and two (12.5%) of the four first cycle responders were ASST positive. In the female sample, half

Table 3. Clinical and laboratory variables in men.

Variables	Responder men	Men non responder at first cycle OmAb	Men non responder at second cycle OmAb
N, (%)	4 (25%)	8 (50%)	4 (25%)
Age, years, mean ± DS	21 ± 8	51 ± 17.6	69.5 ± 0.5
Duration of CSU, mean ± DS	0.3 ± 0.05	2.4 ± 1.5	0.7 ± 0.3
Thyroid impairment, *n* (%)	None	None	None
GERD, *n* (%)	None	None	None
Depression, *n* (%)	None	None	None
Diabetes type II, *n* (%)	None	2 (12.5%)	None
Allergy to inhalants, *n* (%)	4 (25%)	4 (25%)	2 (12.5%)
BMI kg/m2, mean ± DS	21.7 ± 3.1	28.4 ± 4.1	26 ± 1.1
IgE baseline, mean ± DS	141.40 ± 58.6	569.2 ± 95.4	140 ± 100
ASST, *n* (%)	2 (12.5%)	2 (12.5%)	4 (25%)
Disease activity, mean ± DS			
UAS 7 T0	38.5 ± 3.5	40.2 ± 3.5	38.5 ± 3.5
DLQI T0	27.5 ± 2.5	28.7 ± 2.5	27.5 ± 2.5
CU-Q2oL T0	86.5 ± 3.5	90 ± 3.4	88.5 ± 2.5
UAS 7 T3	10 ± 3	9.2 ± 2.2	5.5 ± 0.5
DLQI T3	10 ± 5	10 ± 2.8	19 ± 9
CU-Q2oL T3	12.5 ± 0.5	12.5 ± 5.2	8.5 ± 0.5
UAS T6	0	0	0
DLQI T6	0	0	0
CU-Q2oL T6	0	0	0
Disease activity, mean ± DS(Second cycle)			
UAS 7 T0		39.5 ± 1	38 ± 4
DLQI T0		28.2 ± 2.3	27 ± 2
CU-Q2oL T0		87.6 ± 3.4	86.5 ± 3.5
UAS 7 T3		8.7 ± 2.3	6 ± 0.5
DLQI T3		9.5 ± 3	15 ± 5
CU-Q2oL T3		11 ± 2	8.3 ± 0.7
UAS T6		0	0
DLQI T6		0	0
CU-Q2oL T6		0	0
Disease activity, mean ± DS(Third cycle)			
UAS 7 T0			38.2 ± 2.8
DLQI T0			26.5 ± 3
CU-Q2oL T0			87.5 ± 2
UAS 7 T3			5.7 ± 1
DLQI T3			17 ± 6
CU-Q2oL T3			8.4 ± 0.5
UAS T6			0
DLQI T6			0
CU-Q2oL T6			0

of the non-responders in the first treatment cycle were positive for ASST (7.7%), while six (23.1%) of the twenty-two responders were positive. Although there was a greater ASST positivity among men with more relapses, a greater response to treatment was found among women despite the higher ASST positivity rate. The mean IgE level in women with remission in the first cycle of therapy was 478.69 while the non-responders in the first cycle had an average level of IgE less than 23.7. On the contrary in the male sample, the highest level of IgE was found in patients with a relapse after the first therapeutic cycle with a mean value of 749, mean values equal to 155.1 were documented in patients with double relapse and then underwent the third therapeutic cycle, while the lowest values (mean 14.4) were detected in the responders at the first OmAb cycle. Although in the literature it is documented high basal IgE levels (above 100

KU/l) in CSU patients responsive to treatment and with a faster relapse after discontinuation of therapy, this seems to happen in our sample only for the female population while the data relating to men would seem not to comply with what is reported, offering a further reason for reflection on the possible implication of gender difference.[11,12] Our analysis laboratory is not equipped for distinguishing free IgE from those linked to OmAb or to effector cells this makes IgE assay after therapy of little significance.[13] All patients, regardless of sex, age, or any other factor, achieved a partial clinical remission of the disease after the first 3 doses of OmAb with a reduction of the disease activity indices and impact on the quality of life measured by UAS7, DLQI, and CU-Q2oL.[14,15] Thus confirming effectiveness of the therapy and improvement of the patient's quality of life.[16]

Discussion

The identification of response biomarkers to therapy in CSU is a key topic and was showed as the combination of eosinopenia and basopenia is a better predictor of non-response to second-generation H_1 AH than eosinopenia alone.[17]Several biomarkers have been indicated to differentiate severity and prognosis in CSU patients: older patients have more severe disease, females have a longer remission, duration of urticaria is directly linked to severity, such as with less evidence positivity of ASST, the coexistence of angioedema seem to have a less favorable prognosis.[18,19] In our patients, recurrences predominate in men, two months after the suspension of the drug. Respect to sex and recurrence, we did not find any correlation with age, body mass index, peripheral eosinophil counts, total IgE levels, D-dimer, plasma prothrombine level or C-reactive protein. We found no sex differences in tolerability and safety. No one has so far noted these sex differences as well as recently in the study by Özyılmaz-Bozat G. et al. that found no differences with respect to sex between recurring and not recurring patients although in a previous research they showed that CSU in girls may persist longer and have worse prognosis.[20] Gouder C. et al., analyzing the difference between men and women in terms of effectiveness, tolerability, and response rate of OmAb found no difference in their study on the patients Maltese with asthma.[21] Recently Johal KJ et al. explored if under OmAb treatment of CSU the rate of clinical remission is concordant with baseline basophil features or the rate of change of IgE-dependent functions of basophils and/or plasmacytoid dendritic cells. Their data show as changes in basophil IgE based HR, surface IgE or FcεRI, bear no relationship to the kinetics in the change in clinical symptoms while the baseline basophil count and basophil functional phenotype may be predictive of responsiveness to OmAb. Analyzing their data, it should be noted that among 7 non-responders basopenic patients 4 are males out of 6; of the other two one is basopenic unclassified and the last is non-basopenic responder.[22] These numbers are consistent with our personal experience showing a better response to OmAb in women than in men with CSU: 84.6% of complete remissions in women versus 25% in men after the first cycle of OmAb. A recent review on the predictors of treatment response in CSU show a strong level of evidence for no association of sex as a possible markers of non-response to OmAb.[23] In their recent work, Yu et al.[24] observed that gender is not linked to the speed of achieving complete control with OmAb treatment.

Although there are no certainties on the mechanism of action of OmAb in with CSU,[25,26] the noticeable difference in response between males and females lead us to suppose a role of the hormonal balance both on the pathogenesis of the CSU[27,28] and on the efficacy of OmAb. In fact, CU is at least twice as frequent in women than in men and may be associated with several diseases and conditions characterized by sex hormones fluctuations as female hormones have immunologic effects and modulate the inflammatory response while gender differences in the expression profiles of histamine receptors and of mast cells exists. Recent studies revealed that a female predominance of urticaria is observed only in specific age groups. Hyun-Sun Yoon et al. also showed a clear female predominance for new-onset urticaria only for those aged 20×10^{44} and 45×10^{64} years. A female predominance of urticaria in specific age groups could be due to estrogen. Estrogen is believed to enhance humoral immunity and antibody synthesis. The fact that CU is twice as frequent in women than in men and may be associated with some diseases and conditions characterized by sex hormone changes, include hormonal contraceptives, pregnancy, menstrual cycle, menopause, and or hormone replacement therapy, suggest that fluctuations in hormonal milieu may play a role in pathogenesis of the disease. A support of this hypothesis is that, like estradiol, low concentrations of environmental estrogens are capable of causing mast cell degranulation, suggesting their role in the pathogenesis of mast cell-dependent diseases. A gender difference in the expression profiles of histamine receptors and of mast cells was demonstrated, also, in experimental studies. These characteristics lead to the hypothesis that OmAb may affect differently depending on the gender, explaining the lower recurrence rate in women present in our study.[29,30] The limitations of the study are the paucity of the sample as conducted in a small peripheral center and based on a disease with a low incidence in the population. A further limitation is that sample power analysis was not performed. Although limited by a small sample this study offers the possibility to reflect on the gender difference in the context of therapy with OmAb.[31-34] It will be a future objective to expand the series over time to evaluate the influence of gender on a larger sample.

Conclusions

In conclusion, OmAb is an effective and safe drug in the treatment of CSU and our results show a better response in women than in men. Further studies would be useful in order to confirm our data and to highlight possible mechanisms underlying the sex differences of OmAb effectiveness. It is important to increase the awareness of potential sex-specific effectiveness of therapy also in allergies.

Declaration of conflicting interests

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Ethics approval

This type of study does not require specific approval from our ethics committee. We have strictly adhered to the rules laid down in these cases by our Internal Review Board of the University of L'Aquila, Italy, (ex "Comitato etico di Ateneo" D.R. *n*. 206/2013 modified D.R. *n*. 46/2017) and conducted in accordance with the 1975 Helsinki Declaration and its subsequent amendments.

Informed consent

Written informed consent was obtained from all subjects before the study.

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References

1. Ghazanfar MN, Kibsgaard L, Thomsen SF, et al. (2020) Risk of comorbidities in patients diagnosed with chronic urticaria: A nationwide registry-study. Published 2020 Jan 25. *World Allergy Organization Journal* 13(1): 100097. DOI: 10.1016/j.waojou.2019.100097.
2. De Martinis M, Sirufo MM, Suppa M, et al. (2020) Sex and gender aspects for patient stratification in allergy prevention and treatment. Published 2020 Feb 24. *International Journal of Molecular Sciences* 21(4): 1535. doi: 10.3390/ijms21041535.
3. Ventura MT, Scichilone N, Paganelli R, et al. (2017) Allergic diseases in the elderly: biological characteristics and main immunological and non-immunological mechanisms. *Clinical and Molecular Allergy* 15: 2. DOI: 10.1186/s12948-017-0059-2.
4. De Martinis M, Sirufo MM, Viscido A, et al. (2019) Food Allergies and Ageing. *International Journal of Molecular Sciences* 20(22): 5580. DOI: 10.3390/ijms20225580.
5. De Martinis M, Sirufo MM and Ginaldi L (2017) Allergy and aging: an old/new emerging health issue. *Aging and disease* 8(2): 162–175. DOI: 10.14336/AD.2016.0831.
6. Sirufo MM, Ginaldi L and De Martinis M (2019) Successful treatment with omalizumab in a child with asthma and urticaria: a clinical case report. Published 2019 Jun 5. *Frontiers in Pediatrics* 7: 213. DOI: 10.3389/fped.2019.00213.
7. De Martinis M, Sirufo MM and Ginaldi L (2019) A "stadium" urticaria, cold urticaria is still a mostly unknown disease, with a wide spectrum of severity degrees and few therapeutic certainties: is omalizumab one of these? reflections from a clinical case report. *Iran Red Crescent Med J* 21(1): e84250.
8. De Martinis M, Sirufo MM and Ginaldi L (2019) Solar urticaria, a disease with many dark sides: is omalizumab the right therapeutic response? Reflections from a clinical case report. *Open Medicine* 14: 403–406. DOI: 10.1515/med-2019-0042.
9. Sánchez J, Alvarez L and Cardona R (2020) Cyclosporine and omalizumab together: a new option for chronic refractory urticaria. *The Journal of Allergy and Clinical Immunology: In Practice* 8(6): 2101–2103. DOI: 10.1016/j.jaip.2020.02.012.
10. Curto-Barredo L, Archilla L, Vives G, et al. (2018) Clinical features of chronic spontaneous urticaria that predict disease prognosis and refractoriness to standard treatment. *Acta Dermato Venereologica* 98(7): 641–647. DOI: 10.2340/00015555-2941.
11. Grieco T, Dies L, Sernicola A, et al. (2020 Nov) Potential clinical and serological predictors of chronic spontaneous urticaria relapse in patients under omalizumab treatment. *Immunotherapy* 12(16): 1173–1181. DOI: 10.2217/imt-2020-0088. Epub 2020 Sep 7. PMID: 32892673
12. Ertas R, Ozyurt K, Ozlu E, et al. (2017) Increased IgE levels are linked to faster relapse in patients with omalizumab-discontinued chronic spontaneous urticaria. *Journal of Allergy and Clinical Immunology* 140(6): 1749–1751.
13. Sirufo MM, De Martinis M and Ginaldi L (2018) Omalizumab an effective and safe alternative therapy in severe refractory atopic dermatitis. *Medicine* 97(24): e10897. DOI: 10.1097/MD.0000000000010897.
14. Weller K, Zuberbier T and Maurer M (2015) Chronic urticaria: tools to aid the diagnosis and assessment of disease status in daily practice. *Journal of the European Academy of Dermatology and Venereology* 29(Suppl 3): 38–44. DOI: 10.1111/jdv.13200.
15. Hollis K, Proctor C, McBride D, et al. (2018) Comparison of Urticaria Activity Score Over 7 Days (UAS7) Values Obtained from Once-Daily and Twice-Daily Versions: Results from the ASSURE-CSU Study. *American Journal of Clinical Dermatology* 19(2): 267–274. DOI: 10.1007/s40257-017-0331-8.
16. Ghazanfar MN, Holm JG and Thomsen SF (2018) Effectiveness of omalizumab in chronic spontaneous urticaria assessed with patient-reported outcomes: a prospective

study. *Journal of the European Academy of Dermatology and Venereology* 32(10): 1761–1767.
17. Kolkhir P, Church MK, Altrichter S, et al. (2020) Eosinopenia, in chronic spontaneous urticaria, is associated with high disease activity, autoimmunity, and poor response to treatment. *The Journal of Allergy and Clinical Immunology: In Pract* 8(1): 318–325. e5. DOI: 10.1016/j.jaip.2019.08.025.
18. Alizadeh Aghdam M, Pieterse RH, Kentie PA, Rijken F, Knulst AC and Röckmann H (2020) Effective omalizumab interval prolongation in the treatment of chronic urticaria. *The Journal of Allergy and Clinical Immunology: In Practice* 8(20): 3667–3668. DOI: 10.1016/j.jaip.2020.06.056.
19. Alizadeh Aghdam M, van den Broek F, Rijken F, et al. (2020) High-dose omalizumab use in patients with chronic spontaneous urticaria. *The Journal of Allergy and Clinical Immunology: In Practice* 8(4): 1426–1427. DOI: 10.1016/j.jaip.2019.10.018.
20. Özyılmaz-Bozat G, Şahiner ÜM, Buyuktiryaki B, et al. (2020) Children with chronic spontaneous urticaria: recurrence after remission and its predictors. *The Journal of Allergy and Clinical Immunology: In Pract* 8(2): 796–798. DOI: 10.1016/j.jaip.2019.08.010.
21. Gouder C, Asciak R and Montefort S (2017) Sex differences in the efficacy, safety, and tolerability of omalizumab after 1 year in Maltese patients with asthma. *Annals of Allergy, Asthma & Immunology* 118(4): 513–514. DOI: 10.1016/j.anai.2017.01.019.
22. Johal KJ, Chichester KL, Oliver ET, et al. (2021) The efficacy of omalizumab treatment in chronic spontaneous urticaria is associated with basophil phenotypes. *Journal of Allergy and Clinical Immunology* 147(21): 2271–2280. DOI: 10.1016/j.jaci.2021.02.038.
23. Fok JS, Kolkhir P, Church MK and Maurer M (2021) Predictors of treatment response in chronic spontaneous urticaria. *Allergy* 76: 2965–2981. DOI: 10.1111/all.14757.
24. Yu M, Terhorst-Molawi D, Altrichter S, et al. (2021) Omalizumab in chronic inducible urticaria: a real-life study of efficacy, safety, predictors of treatment outcome and time to response. *Clinical & Experimental Allergy* 51: 730–734. DOI: 10.1111/cea.13838. Epub ahead of print. PMID: 33522024
25. Alizadeh Aghdam M, Knol EF, den Elzen M, et al. (2020) Response of FcεRI-bearing leucocytes to omalizumab in chronic spontaneous urticaria. *Clinical & Experimental Allergy* 50(3): 364–371. DOI: 10.1111/cea.13566.
26. Kaplan AP, Giménez-Arnau AM and Saini SS (2017) Mechanisms of action that contribute to efficacy of omalizumab in chronic spontaneous urticaria. *Allergy* 72(4): 519–533. DOI: 10.1111/all.13083.
27. Kasperska-Zajac A, Brzoza Z and Rogala B (2008) Sex hormones and urticaria. *Journal of Dermatological Science* 52(2): 79–86. DOI: 10.1016/j.jdermsci.2008.04.002.
28. Amsler E, Augey F, Soria A, et al. (2016) Chronic urticaria and hormones: is there a link?. *Journal of the European Academy of Dermatology and Venereology* 30(9): 1527–1530. DOI: 10.1111/jdv.13644.
29. Kasperska-Zajac A, Brzoza Z and Rogala B (2008) Sex hormones and urticaria. *Journal of Dermatological Science* 52(2): 79–86. DOI: 10.1016/j.jdermsci.2008.04.002.
30. Ridolo E, Incorvaia C, Martignago I, et al. (2019) Sex in respiratory and skin allergies. *Clinical Reviews in Allergy & Immunology* 56(3): 322–332. DOI: 10.1007/s12016-017-8661-0.
31. Sussman G, Hébert J, Gulliver W, et al. (2020) Omalizumab re-treatment and step-up in patients with chronic spontaneous Urticaria: OPTIMA Trial. *The Journal of Allergy and Clinical Immunology: In Pract* 8(7): 2372–2378. e5. DOI: 10.1016/j.jaip.2020.03.022.
32. Gimenez-Arnau A, Bartra J, Ferrer M, et al. (2020) A specialized therapeutic approach to chronic urticaria patient's refractory to H1-Antihistamines Improves the Burden of the Disease. The Spanish AWARE Experience. *Journal of Investigational Allergology and Clinical Immunology* 32. doi: 10.18176/jiaci.0661.
33. Sirufo MM, De Pietro F, Bassino EM, Ginaldi L and De Martinis M (2021) Translational Allergy and Omalizumab: The Pioneer. *Indian Journal of Pharmaceutical Education and Research* 55(1): s259–s264.
34. Irelli A, Sirufo MM, D'Ugo C, Ginaldi L and De Martinis M (2020) Sex and Gender Influences on Cancer Immunotherapy Response. Published 2020 Jul 21. *Biomedicines* 8(7): 232. DOI: 10.3390/biomedicines8070232.