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Original Article

Profile of patients with chronic spontaneous urticaria treated with omalizumab in Chapecó, south of Brazil

Perfil de pacientes com urticária crônica espontânea submetidos ao tratamento com omalizumabe em Chapecó, SC

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ABSTRACT

Introduction: Chronic spontaneous urticaria is a disease characterized by erythematous maculopapular eruption, associated with itching and angioedema, that has no recognized external stimulus and is difficult to control. First- and second-line treatments, available through the Brazilian Unified Health System, do not yield meaningful results, and patients become refractory. Omalizumab, considered a third-line treatment and not widely available through the Brazilian Unified Health System, may yield meaningful results in halting disease symptoms. **Objective:** To evaluate patients with chronic spontaneous urticaria who have used or are using omalizumab. **Methods:** We conducted a cross-sectional case series observational study with a review of the medical records of 34 patients with chronic spontaneous urticaria treated with omalizumab at the Eye Institute of Santa Catarina, south of Brazil. **Results:** Most patients with chronic spontaneous urticaria receiving omalizumab were female (76.5%) with a mean age of 41 years. The disease most commonly associated with chronic spontaneous urticaria was depression (38.2%). Omalizumab treatment success was measured with the Urticaria Activity Score (UAS7). Based on data extracted from the medical records, all 34 patients had a score greater than 35 before treatment. After receiving omalizumab, 32 patients managed to reach a score of 0, differing only in the duration of treatment. **Conclusion:** Chronic spontaneous urticaria is an incurable, highly refractory disease, but its symptoms can be reduced mainly with the use of omalizumab, which proved to be effective in the cases analyzed here.

Keywords: Chronic spontaneous urticaria, omalizumab, monoclonal antibodies.

RESUMO

Introdução: A urticária crônica espontânea é caracterizada por lesões máculo-papulares eritematosas, associadas a prurido e angioedema, que não possui estímulo externo reconhecido e de difícil controle. A primeira e a segunda linha terapêutica, disponibilizadas pelo Sistema Único de Saúde, não apresentam resultados significativos, os quais se tornam refratários. O omalizumabe, considerado terceira linha terapêutica e que não é amplamente disponibilizado pelo Sistema Único de Saúde, pode apresentar resultado significativo na interrupção dos sintomas da doença. **Objetivo:** O presente estudo tem como objetivo avaliar pacientes com urticária crônica espontânea que usaram ou estão em uso de omalizumabe. **Métodos:** Trata-se de um estudo observacional transversal do tipo série de casos, cuja análise foi feita através dos prontuários, com população de 34 pacientes com urticária crônica espontânea submetidos ao tratamento com omalizumabe no Instituto de Olhos de Santa Catarina (IOSC). **Resultados:** Constatou-se no estudo que a maioria dos pacientes com urticária crônica espontânea em uso de omalizumabe é constituída do sexo feminino (76,5%) e idade média de 41 anos. A doença mais associada à urticária crônica espontânea foi depressão (38,2%). O sucesso do tratamento com omalizumabe é medido pelo questionário UAS7 (*Urticaria Activity Score*), o qual, segundo os dados dos prontuários, todos os pacientes apresentavam resultado maior que 35 pontos antes do uso da medicação, e 32 conseguiram alcançar um índice de 0 após o uso do omalizumabe, variando apenas no tempo de tratamento. **Conclusão:** A urticária crônica espontânea é uma doença que não tem cura e possui alta refratariedade, mas pode ter seus sintomas reduzidos, principalmente com o uso do omalizumabe, que se mostrou eficiente nos casos analisados.

Descritores: Urticária crônica, omalizumabe, anticorpo monoclonal.

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Introduction

Chronic urticaria is a highly morbid disease that affects between 0.5% and 1% of the population and is often difficult to control. It is characterized by erythematous maculopapular lesions associated with pruritus, which may present angioedema and generally lasts less than 24 hours.[1] Urticaria can be classified into 2 main groups: acute urticaria (AU), which lasts 6 weeks or less, and chronic urticaria (CU), which lasts 6 weeks or more. Additionally, chronic urticaria can be divided into chronic inducible urticaria (CIndU), which has an identified exogenous causal factor, and chronic spontaneous urticaria (CSU), when there is no recognized external trigger, and both forms can occur simultaneously in the same individual.[2] The diagnosis of CSU and all forms of CUs are essentially clinical, and there are no specific complementary tests.

Treatment can be challenging. Second-generation H1-antihistamines are considered the first-line therapy for CSU. They are minimally or non-sedating and free of anticholinergic effects and have a good safety profile, unlike first-generation H1-antihistamines, which are currently not recommended due to their adverse effects.[3] However, although these medications are available in Brazil's public health system (SUS), they have a high added value and treatment may fail, requiring a fourfold dose in an attempt to achieve the intended effect.[4] Even so, a large proportion of patients remain refractory to H1-antihistamines and have to resort to second- or third-line treatments, which include omalizumab, cyclosporine, or montelukast.[1]

Ciclosporin is an immunosuppressive and anti-inflammatory medication. It has a better risk-benefit ratio than corticosteroids, though the incidence of side effects such as nephrotoxicity and hypertension are a cause for concern and require monitoring.[5] A study found the medication to be effective in 44% of patients with moderate to severe urticaria.[6]

Montelukast, a leukotriene receptor antagonist, is perhaps the most cost-effective of the medications. However, high-quality clinical studies have not provided evidence of the efficacy and safety of this medication. Even so, it is used in some refractory cases of CSU.[7]

The use of systemic corticosteroids in exacerbations of CU is recommended for no longer than ten days and in the lowest possible dose, given the potential adverse effects of long-term treatment.[1]

CSU has an autoimmune component associated with Immunoglobulin-E, which the immunobiological omalizumab (Anti-IgE) may have some effect, as it has a direct action on the pathophysiological mechanisms of the disease; it is considered the third-line treatment option to treat CSU.[3] However, even though the medication is safe with positive results, it has a high cost, ranging from R$1,795.83 to R$2,244.79 per vial, depending on the dose required, and SUS hardly makes it available, except for the treatment of severe asthma.[8]

The patient's routine is affected due to unpredictable and chronic outbreaks and compromised body image, especially caused by pruritus and angioedema, which affect the performance of daily activities and the quantity and quality of sleep, causing direct costs in medication consumption, the use of health care services, and indirect costs associated with lower school and professional performance.[1] This study aims to evaluate patients with CSU who used or are currently using omalizumab, as well as to verify the positive and adverse effects and impacts in different cases of CSU, and to compare the efficacy of omalizumab with other medications in the treatment of CSU.

Material and methods

This is an observational case-crossover study, whose analyzed populatio-n consisted of 34 patients treated with omalizumab and with CSU, from the *Instituto de Olhos Santa Catarina (IOSC) - Hospital Dia*.

The sample included patients treated with omalizumab and with CSU between July 2018 and May 2021. Patients who had not completed 3 months of treatment with omalizumab or who did not follow the treatment protocol properly were excluded.

Data were collected from patients with CSU who had taken omalizumab, through medical record analysis to identify their clinical evolution. Subsequently, information was retrieved from medical records based on a questionnaire about the disease and the use of the medication. This information was held in confidence as per a confidentiality agreement.

Data such as sex, age, time since diagnosis of CSU, medications used before and associated with omalizumab, symptoms and diseases associated with CSU, and the time required for omalizumab to take effect were analyzed. The Urticaria Activity Score (UAS7), which assesses the symptoms and intensity

of CSU over a 7-day period, was also analyzed. It was previously applied by the attending physician to patients before and after the use of omalizumab and recorded in their medical records.

The results were calculated as means, modes, and medians of the variables mentioned above, using Microsoft Excel and Epi-Info.

The project was developed in accordance with CNS Resolution No. 466/201223 and Resolution No. 510/201624, analyzed by the Research Ethics Committee Involving Human Beings - CEP/UNOCHAPECÓ and approved according to Opinion No. 4.822.997 (CAAE 48046721.2.0000.0116).

Results and discussion

CSU manifestations result from the release of pro-inflammatory mediators from mast cells found in the dermis of mucous membranes. Different factors can induce mast cells, from the activation of nerve endings and vessels in the dermis, recruiting inflammatory cells such as endothelial cells, eosinophils, and even mast cells. CSU most commonly presents clinical signs such as erythematous papules, pruritus, and angioedema. The papules show mast cell and eosinophil degranulation, endothelial cell activation, vascular proliferation, and activation of blood coagulation. In addition, CSU produces a proliferated cytokine environment, indicating an activation of the innate interleukin (IL) response, especially IL-33 and IL-25.[1]

The study included 34 patients who had CSU and had used omalizumab between July 2018 and May 2021. As shown in Table 1, 26 (76.5%) patients were women and 8 (23.5%) were men. The mean age (SD) was 41 (5.66) years. The age group with the most patients was 41 to 60 years (44.1%). The results are consistent with Ozlem et al.,[9] who also found that women were prevalent and the mean age was 44.3 years. This age group is also similar to that of Souza et al. who reported a higher prevalence between 20 and 50 years of age.[10]

Interestingly, 4 patients (11.8%) had a family history of CSU, all third-degree relatives, although there is still no data to suggest that CSU has an associated genetic inheritance. Although most patients (82.4%) had a history of CSU progression up to 10 years, the mean age (SD) was 4 (10.38) years.

As shown in Table 2, the most common symptom associated with CSU was pruritus, reported by 27 (79.4%) patients, followed by angioedema (55.9%), pain in the lesions (23.5%), positive dermographism (14.7%), and oropharyngeal edema (11.8%). The least common symptoms were joint pain (5.9%), changes in sleep (5.9%), abdominal pain (4.2%), and fever (4.2%).

Table 1
Clinical and demographic characteristics of patients with chronic spontaneous urticaria (CSU)

Variable	n = 34	%
Sex		
Female	26	76.5
Male	8	23.5
Age group		
Up to 20 years	2	5.9
21-40 years	12	35.3
41-60 years	15	44.1
61-72 years	5	14.7
Time since CSU		
Up to 10 years	28	82.4
More than 10 years	6	17.6
Family history of CSU		
Yes	4	11.8
No	32	88.2

The high prevalence of pruritus as a symptom of CSU is mainly due to the release of histamine and inflammatory cytokines. Acute pruritus is primarily mediated by histamine H1 and H4 receptors, which trigger other symptoms such as edema and erythema.[11]

Although histamine is the most common mast cell mediator in CSU, the ineffectiveness of first-line medications shows that other pro-inflammatory mediators are involved, such as platelet activating factor, leukotrienes, prostaglandins, chemokines, and cytokines, among others. These mediators are increased in the peripheral blood during urticarial activity.[1]

Angioedema was higher than the findings of Souza et al.[10] (2019), who reported 28.6% of patients

with angioedema. As for the pathophysiology of angioedema and pruritus in CSU, it is related to the release of histamine as an inflammatory mediator, called histaminergic angioedema. It has a better prognosis and generally responds well to treatment with antihistamines and corticosteroids.[12] This study found less positive dermographism than Duarte P.P., whose sample included 20%.[13]

Table 2 also shows that the most prevalent chronic diseases affecting the patients studied concomitantly with CSU were depression (38.2%), hypothyroidism (17.8%), hypertension (14.7%), dyslipidemia (14.7%), and anxiety (11.8%). Neuropathic pain, vasculitis, rhinitis, cardiovascular disease, thrombosis, angina pectoris, and hepatitis B showed results below 8.8%. The results for depression were higher than those of Vieira,[14] whose population had a prevalence of psychiatric illnesses of 22.5%, including depression and/or panic disorder and/or anxiety. As for anxiety, the rate of patients is similar to the study above.

Table 2
Diseases associated with chronic spontaneous urticaria (CSU) in patients taking omalizumab

Variable	Female	Male	Total	%
Diseases associated with CSU				
Depression	10	3	13	38.2
Hypothyroidism	4	2	6	17.8
Hypertension	4	1	5	14.7
Dyslipidemia	4	1	5	14.7
Anxiety	3	1	4	11.8
Neuropathic pain	2	1	3	8.8
Vasculitis	1	0	1	4.2
Rhinitis	2	0	2	5.9
Cardiovascular disease	1	1	2	5.9
Thrombosis	1	0	1	4.2
Angina Pectoris	1	0	1	4.2
Hepatitis B	1	0	1	4.2
Signs and symptoms associated with CSU				
Pruritus	20	7	27	79.4
Angioedema	15	4	19	55.9
Pain in the lesions	7	1	8	23.5
Dermographism +	3	2	5	14.7
Oropharyngeal edema	4	0	4	11.8
Joint pain	2	0	2	5.9
Sleeping disorders	2	0	2	5.9
Abdominal pain	0	1	1	4.2
Fever	1	0	1	4.2

The study by Farril-Romanillos et al.[15] (2019) found better results than this study in relation to the association of CSU with hypothyroidism, with 82% of the patients studied having both diseases. However, 28% of these patients had positive antibodies and were all women, which also differs from ours, in which 2 patients (5.9%) were men.[15] This association between CSU and hypothyroidism occurs because mast cells are activated in urticaria and are responsible for releasing inflammatory mediators such as histamine, mainly due to the binding of various types of IgE antibodies, including anti-thyroperoxidase IgE (anti-TPO) to their surface. These antibodies sensitize mast cells and induce degranulation after exposure to the specific circulating antigen, and anti-TPO are the same as those produced against the thyroid in diseases that cause hypothyroidism, in which they are released as a result of autoimmune damage to thyroid. Therefore, we cannot say that there is only 1 relationship between both diseases, but rather that they coexist.[16]

The most prevalent aggravating factors for CSU were non-steroidal anti-inflammatory medication use (23.0%), viral infection (15.4%), summer (15.4%), sweating (11.5%), and stress (7.7%).

The percentages in the table do not total 100% because some patients have more than one disease and/or associated symptom. These medications cannot be said to directly induce CSU due to the prevalence of the disease's autoimmune factor; however, these factors can be powerful triggers for worsening the clinical condition.

All the patients followed the recommended standard of treatment, took second-generation antihistamines, had their doses boosted up to 4 times, and then resorted to omalizumab as a third-line treatment. In addition, 4 patients tried to use fourth-line medications before omalizumab, such as cyclosporine and montelukast, but their condition failed to improve.

Omalizumab is a humanized anti-IgE monoclonal antibody that is capable of reducing the release of inflammatory mediators from CSU. It acts by binding to the C3 domain of free IgE, preventing this immunoglobulin from binding to the receptors present on the membranes of mast cells.[17] Omalizumab also has the ability to reduce levels of free IgE and high-affinity IgE receptors, which are located on the surface of mast cells and basophils.[18]

Omalizumab is administered subcutaneously at intervals of 2 to 4 weeks, depending on the patient's needs. In Brazil, SUS has widely approved it since 2012 as the fifth step in the treatment of severe asthma refractory to the usual medications.[19]

As Table 3 shows, most patients (41.2%) took up to 1 year to start omalizumab after being diagnosed with CSU. The mean (SD) was 3.8 (59.1) years. It took a mean (SD) of 2.3 (1) months to start having an effect. Most patients (32.4%) took 3 months to show a response. This differs from the results of Labrador-Horrillo et al.[20] (2013) and Büyüköztürk et al.[21] (2012), whose patients (53.4%) took 1 week to respond to omalizumab.

Another 2 patients did not respond to the medication, as they discontinued it because it was inaccessible to the general public, and they could not afford to continue with the treatment. In the study by Ensina et al.[22] (2016), 2 patients also discontinued the medication for the same reason. As this is also a Brazilian study, it confirms that users find the high cost and difficulty of obtaining the medication in the SUS a limitation.[22]

Only 1 patient had an adverse effect (hypotension) associated with the use of omalizumab, and it was later found that their urticaria was due to vasculitis, for which the medication has no effect. Most of the patients (35.3%) had been taking the medication for 2 years, whereas the mean was 1 year.

As for the success of treatment with omalizumab, as measured by the UAS7 score, all the patients scored more than 35 points before using first-line medication, up to 25 points even after using second-generation antihistamines, and 32 managed to reach an index of 0 after using omalizumab, only varying the length of treatment. These results showed that omalizumab was more effective than the study by Su et al.[23] (2020), which reported that the mean UAS7 score before taking omalizumab was 31 points, and after 6 months of taking the medication, patients achieved a mean score of 3.9, in a sample of 50 patients.

The high UAS7 scores before taking omalizumab, even after a maximum dose of antihistamines, reflect the considerable worsening of patients' quality of life, since this score measures the signs and symptoms they experience during a week of CSU exacerbation. As a consequence, in addition to self-medication and taking improper medication, emergency health services are in high demand to try to relieve the

worst symptoms, such as angioedema, pruritus, and oropharyngeal edema, which consequently lead to reduced productivity.

Figure 1 shows the medications used in combination with omalizumab in exacerbations of CSU. Most patients (67.3%) took second-generation antihistamines, and 8 patients (16.3%) did not need any associated medication. In relation to the studies by Su et al.[22] (2020), our results show that fewer patients required simultaneous use of antihistamines and omalizumab, since the comparative study reported that 46% of patients took antihistamines regularly and 44% did so irregularly and for a short time, totaling 90% of the sample. In addition, only 5 patients in the other study required no treatment associated with omalizumab, which is less than our findings.

Conclusion

CSU is a disease with high morbidity, caused by autoimmune disorders, with periods of worsening and remission, whose exacerbation can last for years. The profile of patients affected by the disease is mostly made up of young women of working age who have taken up to 10 years to be diagnosed with CSU, leading to decreased quality of life during this period and less productivity. In many cases, these patients are not responsive to the usual first- and second-line treatments.

This study showed that omalizumab, a third-line medication for CSU, was effective in controlling patients' symptoms, some as early as when the first dose was administered, reducing the use of antihistamines. As a result, this immunobiological reduced self-medication, the misuse of other medications, and health costs, such as frequent visits to emergency departments and other specialized consultations.

Table 3
Analysis of the use of omalizumab in patients with CSU

Variable	n = 34	%
Time between CSU diagnosis and initiation of omalizumab		
Up to 1 year	14	41.2
2-5 years	12	35.3
6-10 years	4	11.8
More than 10 years	4	17.6
Response time after initiating omalizumab		
1 month	8	23.5
2 months	10	29.4
3 months	11	32.4
4 months	3	8.8
No response	2	5.9
Time of treatment with omalizumab		
Less than 1 year	5	14.7
1 year	14	41.2
2 years	12	35.3
3 years or more	3	8.8

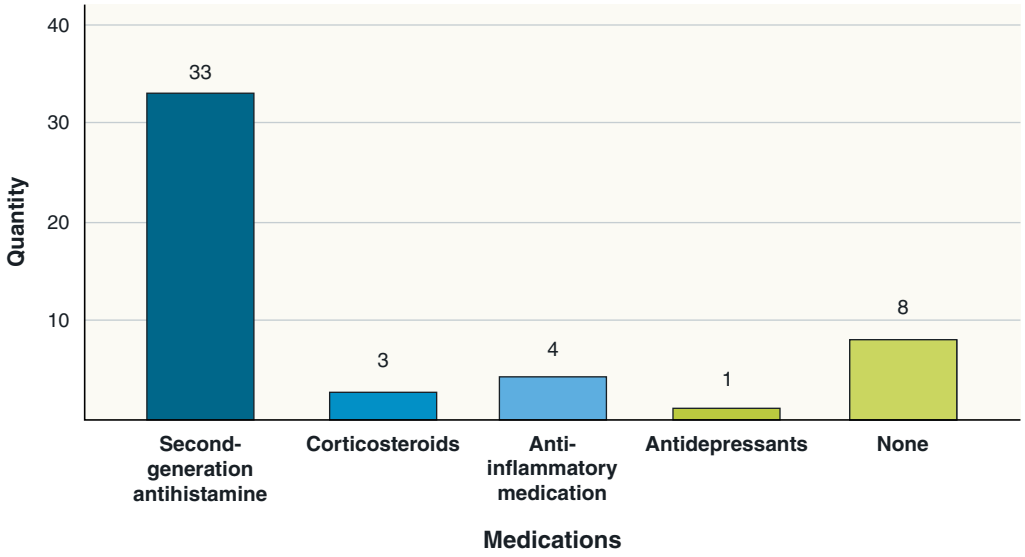

Figure 1
Medications associated with treatment with omalizumab

References

1. Costa AC, Campina S, Andrade P, Filipe P, Guilherme A, Gonçalo M. Urticária crônica - do Diagnóstico ao Tratamento. Revista SPDV. 2016;74(4):315-25.
2. Magerl M, Borzova E, Giménez-Arnau A, Grattan CEH, Lawlor F, Mathelier-Fusade P, et al. The definition and diagnostic testing of physical and cholinergic urticaria - EAACI/GA2LEN/EDF/UNEV consensus panel recommendations. Allergy. 2009;64(12):1715-21.
3. Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B, et al. The AACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy. 2018;73(3):1393-414.
4. Valle SOR, Motta AB, Amaral CSF, Ensina LFC, Mallozi MC, Spengler MGMT, et al. O que há de novo na urticária crônica espontânea? Braz J Allergy Immunol. 2016;4(1):9-25.
5. Viegas LP, Ferreira MB, Kaplan AB. The maddening itch: an approach to chronic urticaria. J Investig Allergol Clin Immunol. 2014;24(1):1-5.
6. Ferreira BR, Ribeiro MI, Gonçalo M. Ciclosporina no Tratamento da Urticária Crónica Espontânea na Era do Omalizumab. Revista SPDV. 2018;76(2):157-64.
7. Barbosa AM, Araújo FM, Vieira L. Eficácia, segurança e custo-efetividade do omalizumabe para urticária crônica espontânea em pacientes maiores de 12 anos refratários aos anti-histamínicos: revisão rápida de evidências. Revista Científica da Escola Estadual de Saúde Pública de Goiás. 2019;5(2):64-82.
8. Agência Nacional de Vigilância Sanitária. Preços máximos de medicamentos por princípio ativo [internet]. Available from: https://www.gov.br/anvisa/pt-br/assuntos/medicamentos/cmed/precos/arquivos/lista_conformidade_2021_03_v2.pdf. Accessed March 17 2021.
9. Ozlem S, Bahali AG, Onsun N. The effect of at least 1-year use of omalizumab without interruption on relapse in patients with chronic spontaneous urticaria. Dermatologic therapy. 2020;33(6):1-5.
10. Souza DL, Muniz JP, Sakae TM, Menezes MM. Efetividade da administração de omalizumabe para tratamento de pacientes com urticária crônica espontânea. Revista Brasileira de Análises Clínicas. 2019;51(6):81-6.
11. Valente C, Rosmaninho I. Prurido crônico - da etiologia ao tratamento. Rev Port Imunoalergologia. 2019;27(3):219-32.
12. Ferraro MF, Arruda LK, Maia LSM, Moreno AS. Angioedema hereditário e outras formas de angioedema por bradicinina: atualização no diagnóstico e tratamento. Arq Asma Alerg Imunol. 2014;1(1):6-20.
13. Duarte PP. Urticária crônica: experiência de consulta nos CHUC [dissertação]. Coimbra: Faculdade de Medicina da Universidade de Coimbra; 2014.
14. Vieira HAS. Avaliação da relação entre a gravidade da urticária crônica e o impacto na qualidade de vida (tese). Florianópolis: Faculdade de Medicina, Universidade Federal de Santa Catarina; 2021.
15. Farril-Romanillos PMO, Álvarez-Chávez FE, Xichihua-García JJ. Thyroid disorders in spontaneuos chronic urticaria. Rev Alerg Méx. 2019;66(4):403-8.
16. Rottem M. Chronic urticaria and autoimmune thyroid disease: is there a link? Autoimmun Rev. 2003;2(2):69-72.
17. Silva NL, Damayanthi H, Rajapakse AC, Rodrigo C, Rajapakse S. Leukotriene receptor antagonists for chronic urticaria: a systematic review. Allergy Asthma Clin Immun. 2014;10(4):1-6.
18. Arruda LKP, Juliana AS, Mendonça TN, Melo JML, Ferriani MPL. Mecanismo de ação da terapia com omalizumabe na urticária crônica espontânea: há um papel para autoimunidade? Arq Asma Alerg Imunol. 2016;1(4):1-8.
19. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention [Internet]. 2022. Available from: www.ginasthma.org.

20. Labrador-Horrillo M, Valero A, Velasco M, Jáuregui I, Sastre J, Bratra J, et al. Efficacy of omalizumab in chronic spontaneous urticaria refractory to conventional therapy: analysis of 110 patients in real-life practice. Expert Opinion Biol Ther. 2013;13(9):1225-8.
21. Buyukozturk S, Gelincik A, Demirturk M, Kocaturk E, Colakoglu B, Dal M. Omalizumab markedly improves urticaria activity scores and quality of life scores in chronic spontaneous urticaria patients: A real life survey. Dermatol J. 2012;39(5):439-42.
22. Ensina LF, Valle SOR, Juliani AP, Galeane M, Santos RV, Arruda LK, et al. Omalizumab in Chronic Spontaneous Urticaria: a Brazilian Real-Life Experience. Int Arch Alergia Immunol. 2016;169(1):121-4.
23. Su O, Bahali AG, Onsun N. O efeito de pelo menos 1 ano de uso de omalizumabe sem interrupção na recidiva em pacientes com urticária crônica espontânea. Dermatologic therapy. 2020;33(6).
24. Brasil. Ministério da Saúde. Gabinete do Ministro. Resolução nº 466, de 12 de dezembro de 2012. Dispõe sobre as diretrizes e normas regulamentadoras de pesquisa envolvendo seres humanos. Diário oficial da república federativa do Brasil [internet]. Brasília (DF):MS; 2012. Available from: https://conselho.saude.gov.br/resolucoes/2012/Reso466.pdf.
25. Brasil. Ministério da Saúde. Gabinete do Ministro. Resolução nº 510, de 07 de abril de 2016. Dispõe sobre as normas aplicáveis a pesquisas em Ciências Humanas e Sociais. Diário oficial da república federativa do Brasil [internet]. Brasília (DF): MS; 2016. Available from: https://conselho.saude.gov.br/resolucoes/2016/Reso510.pdf.

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