# РЕЗУЛЬТАТЫ ТЕРАПИИ ХРОНИЧЕСКОЙ КРАПИВНИЦЫ У ПАЦИЕНТОВ С IgE-ЗАВИСИМЫМ И IgE-НЕЗАВИСИМЫМ ПРОФИЛЕМ ЗАБОЛЕВАНИЯ

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**Резюме.** Главным механизмом возникновения крапивницы является дегрануляция тучных клеток. Доказано, что вне зависимости от пути активации клинические проявления не будут отличаться. По данным литературы до половины случаев хронической спонтанной крапивницы имеют аутоиммунный характер, могут сочетаться с аутоиммунной патологией щитовидной железы, СКВ и др. и имеют более тяжелое течение. В терапии традиционно используются антигистаминные препараты в стандартных или увеличенных дозировках. Однако часть пациентов не реагирует на проводимое лечение даже при кратном увеличении доз.

В терапии резистентной к традиционному лечению антигистаминными препаратами крапивницы рекомендовано применение генно-инженерной таргетной терапии препаратом Омализумаб. Целью исследования было определение профиля пациентов с хронической крапивницей (ХК) и сравнение эффективности лечения препаратом Омализумаб у пациентов с IgE-зависимой (1-я группа) и IgE-независимой (2-я группа) крапивницей. Обследован 81 пациент с хронической крапивницей (60 взрослых, 21 ребенок). Пациенты до начала терапии имели длительный стаж ХК: от 1 года до 20 лет. Все пациенты до начала таргетной терапии получали лечение антигистаминными препаратами в стандартных и кратно увеличенных дозах, однако контроля получено не было. Повышение уровня сывороточного IgE выявлено в 51,7% случаев у взрослых и 42% у детей. Сопутствующая сенсибилизация определялась у 48,3% взрослых, и 76,2% детей. У детей наиболее распространенной была пищевая, эпидермальная и пыльцевая сенсибилизация. У взрослых чаще встречалась пыльцевая и эпидермальная сенсибилизация. Уровень эозинофилии в 1-й группе был более выражен, чем во 2-й группе – 302,6 и 116,4 клеток/мкл ($U = 61,5$; $p = 0,0097$). Через 6 месяцев в 1-й группе отмечено улучшение балла симптомов (UCT) с 3,1 баллов ДИ (1,5-4,6) до 12,2 ДИ (10,8-13,7), ($p = 0,0001$). Во 2-й группе улучшение симптомов с 0,63 баллов ДИ (0,36-1,6), до 8,1 ДИ (5-11,2) через 6 месяцев. После 6 месяцев генно-инженерной биологической терапии (ГИБТ) полный контроль над симптомами ХК в 1 группе получен у 66,7% больных, частичный – у 33,7%. Во второй группе в 33,3% случаев положительных результатов лечения добиться не удалось. Таким образом, ГИБТ препаратом Омализумаб повышает контроль над течением ХК. Результаты лечения выше у пациентов с IgE-зависимым профилем заболевания.

*Ключевые слова: хроническая крапивница, омализумаб, IgE, биологическая терапия, эозинофилы, UCT-тест*

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# RESULTS OF THERAPY OF CHRONIC URTICARIA IN PATIENTS WITH IgE-DEPENDENT AND IgE-INDEPENDENT DISEASE PROFILE

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**Abstract.** The main mechanism for the occurrence of urticaria is the degranulation of mast cells. It has been proven that, regardless of the activation pathway, clinical manifestations will not differ. According to the literature, up to half of cases of chronic spontaneous urticaria are autoimmune in nature, can be combined with autoimmune thyroid disease, SLE, etc., and have a more severe course.

In therapy, antihistamines are traditionally used. However, some patients do not respond to the treatment, even with a multiple increase in doses. In the treatment of urticaria resistant to traditional antihistamines, the use of Omalizumab is recommended. The purpose of the study: to determine the profile of patients with chronic urticaria, as well as to evaluate the effectiveness of treatment with Omalizumab in patients with IgE-dependent and IgE-independent chronic urticaria.

Eight-one patients with chronic urticaria (60 adults, 21 children) were examined. Patients before the start of therapy had a long history of CU: from 1 to 20 years. Patients before the start of therapy were treated with antihistamines, but no control was obtained. An increase in the level of serum IgE was detected in 51.7% of cases in adults and 42% in children. Concomitant sensitization was determined in 48.3% of adults and 76.2% of children. In children, food, epidermal and pollen sensitization was the most common. Pollen and epidermal sensitization were more common in adults. The level of eosinophilia in the group with IgE-dependent was more pronounced than in other group ($p = 0.0097$). After 6 months, the group with IgE-dependent showed an improvement in the symptom score (UCT) from 3.1 CI (1.5-4.6) to 12.2 CI (10.8-13.7), ($p = 0.0001$). In other group, symptoms improved from 0.63 CI (0.36-1.6) to 8.1 CI (5-11.2) after 6 months (no control). After 6 months of genetically engineered biological therapy (GIBT), complete control over the symptoms of CU in group 1 was obtained in 66.7% of patients, partial – in 33.7%. In the second group, in 33.3% of cases, positive treatment results could not be achieved. Thus, genetically engineered biological therapy with Omalizumab increases the control over the course of CU. Treatment outcomes are higher in patients with an IgE-dependent disease profile.

*Keywords: chronic urticaria, omalizumab, IgE, biological therapy, eosinophils, UCT test*

## Introduction

Chronic spontaneous urticaria is a disease lasting more than 6 weeks, characterized by the appearance of blisters and/or angioedema, passing without a trace within 24 hours. Several pathways of mast cell activation have been proven. However, the mechanisms by which urticaria occurs are not fully understood. It has been shown that, regardless of the activation pathway, clinical manifestations in all types will be the same.

Mast cell degranulation may be associated with activation of high-affinity receptors (FcεRI) by immunoglobulin E or autoreactive anti-IgE or anti-FcεRI IgG, as well as autoreactive IgE [2, 6, 8].

Degranulation can also occur due to disruption of mast cell activation signaling mechanisms, for example, when exposed to complement components or unknown factors [3, 7].

According to the literature, up to half of cases of chronic spontaneous urticaria are autoimmune in nature, can be combined with autoimmune thyroid disease, SLE, etc., and have a more severe course.

In therapy, antihistamines are traditionally used in standard or increased dosages. However, some patients do not respond to the treatment, even with a multiple increase in doses [4].

According to current concepts, genetically engineered biological therapy (GIBT) Omalizumab therapy can be prescribed already on the second line [1]. And although this therapy is not disease-modifying, it is widely used to achieve disease control and improve the quality of life. The duration of therapy has not yet been determined, but should be at least 6 months. Early termination of therapy is not recommended, because there is a risk of losing patients with a late response. Even long-term therapy with Omalizumab does not eliminate the risk of relapse after treatment is stopped. The drug is characterized by a good safety profile and high efficacy.

**The purpose of the study:** to determine the profile of patients with chronic urticaria, as well as to evaluate the effectiveness of treatment with Omalizumab in patients with IgE-dependent and IgE-independent chronic urticaria.

## Materials and methods

A total of IgE level, peripheral blood eosinophil count, and association with comorbidities were assessed in 81 patients with CU. Of the patients who did not respond to antihistamine therapy at standard and elevated doses, 27 patients received biological therapy with Omalizumab, including 17 women and 10 men. The mean age of patients receiving GIBT was 45.4±12.6. Patients were divided into 2 groups: with IgE-dependent (gr 1; 18 patients) and IgE-independent urticaria (gr 2; 9 patients). All patients were treated with Omalizumab (as a lyophilisate for solution for subcutaneous administration) subcutaneously at a dosage of 300 mg once every four weeks. When dosing the drug, the initial level of IgE was taken into account. Efficacy was assessed after 3 and 6 months of therapy clinically and using the UCT questionnaire, where values of 16 points indicated complete control of the disease, more than 12 points – partial control, and values ≤ 11 – no control of urticaria [11].

Statistical data processing was carried out using generally accepted methods of variation statistics. Methods of nonparametric statistics were used, the Mann–Whitney U test (U), and the cross-tabulation method ($\chi^2$) were used. The critical value of the significance level was taken equal to 5%. The data obtained were processed using the application package AtteStat, version 10.5.1, Statistical formulas of the Microsoft Excel program, version 5.0.

## Results and discussion

Under observation were 81 people with chronic urticaria: 60 adults and 21 children. Among adults, in 34 people (56.7%), urticaria was combined with angioedema, among children, a combination with angioedema was observed in 8 people (38.1%).

In 51.7% of adult patients and 42% of children, an increase in the level of total IgE was not detected. The mean values of serum IgE in patients with elevated values of this indicator did not differ significantly in children and adults and amounted to 405.4 IU/mL CI (205-605.6) and 480.25 IU/mL CI (257.5-703), respectively (U = 144, p = 0.22).

Concomitant sensitization to one or more allergens was detected in 55.6% of patients: in adults in 48.3% of cases (29/60), in children in 76.2% (16/21). In children with CU, food, epidermal and pollen sensitization was most common: 38%, 38%, 33.3%, respectively. In adult patients with urticaria, pollen sensitization was most often noted – 33.3%, and epidermal sensitization – 18.3%.

All patients, before the start of GIBT, according to clinical guidelines, received treatment with antihistamines in standard and multiple-fold increased doses, however, no control was obtained against the background of this therapy. Patients before the start of therapy had a long history of CU: from 1 to 20 years. The average experience of urticaria in group 1 was 3.3 years, CI (2.2-4.4), in group 2 – 6.28, CI (0.13-12.43). The level of eosinophilia in group 1 was more pronounced and averaged 302.6 cells/μL CI (159-445), in group 2 – 116.4 cells/μL CI (65-179), (U = 61.5; p = 0.0097).

In group 1, at the beginning of therapy, the average symptom intensity score according to the UCT questionnaire was 3.1 points CI (1.5-4.6). There was a statistically significant increase in the mean symptom intensity score after 3 months to 10.6 CI (8.6-12.5), (U = 296.5, p = 0.0001), and after 6 months to 12.2 CI (10.8-13.7), (U = 353.5, p = 0.0001) – the disease acquired a well-controlled course. Complete control over the symptoms of urticaria was achieved in 66.7% of patients, partial control – in 33.3% of cases. In some patients who had not previously responded to GCS therapy, an improvement in sensitivity to this group of drugs was noted (Table 1).

In group 2, by the beginning of treatment, the intensity of symptoms according to UCT averaged 0.63 points CI (0.36-1.6), after 3 months of therapy 8.75 CI (6.92-10.6), and after 6 months 8.1 CI (5-11.2). In the group as a whole, the intensity of symptoms according to the UCT questionnaire increased already after 3 months of treatment (U = 64, p = 0.0007), however, in 33.3% of patients, the disease had an uncontrolled course after 6 months of therapy. Complete control over the symptoms of CU after 6 months of GIBT was obtained in 11.1% of cases, partial – in 55.6% of cases.

In a comparative analysis of the effectiveness of GIBT with Omalizumab, in general, in group 1, the positive effect of treatment (disease control) was more pronounced than in group 2 ($\chi^2 = 7.4$; p = 0.0245).

The high efficacy of Omalizumab in urticaria has been shown in numerous studies; it improves the condition of more than half of patients after 2 months. According to the literature, a more pronounced effect of Omalizumab therapy is observed in patients with clinically associated sensitization to

**TABLE 1. DYNAMICS OF THE INTENSITY OF SYMPTOMS OF URTICARIA AFTER 6 MONTHS OF THERAPY WITH OMALIZUMAB**

| | Group 1 | | | Group 2 | | |
|---|---|---|---|---|---|---|
| | before | after | p | before | after | p |
| UCT test | 3.1 points (1.5-4.6) | 12.2 (10.8-13.7) | p = 0.0001 | 0.63 points (0.36-1.60) | 8.1 (5.0-11.2) | p = 0.0040 |

allergens, confirmed by skin prick testing and/or serological methods, the level of eosinophilia more than 260 cells/μL, the duration of treatment with Omalizumab for more than 12 months, which is consistent with our results [5, 9].

## Conclusion

Thus, GIBT with Omalizumab increases the control over the course of CU. The results of treatment are higher in patients with an IgE-dependent disease profile: the presence of a higher level of eosinophilia, the presence of concomitant sensitization, confirmed by serology or skin tests.

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## References

1. Agache I., Rocha C., Pereira A., Song Y., Alonso-Coello P., Solà I., Beltran J., Posso M., Akdis C.A., Akdis M., Brockow K., Chivato T., del Giacco S., Eiwegger T., Eyerich K., Giménez-Arnau A., Gutermuth J., Guttman-Yassky E., Maurer M., Ogg G., Ong P., O'Mahony L., Schwarze J., Werfel T., Canelo-Aybar C., Palomares O., Jutel M. Efficacy and safety of treatment with omalizumab for chronic spontaneous urticaria: A systematic review for the EAACI Biologicals Guidelines. *Allergy, 2021, Vol. 76, no. 1, pp. 59-70.*
2. Bracken S.J., Abraham S., MacLeod A.S. Autoimmune theories of chronic spontaneous urticaria. *Front. Immunol., 2019, Vol. 10, 627.* doi: 10.3389/fimmu.2019.00627.
3. Gibbs B.F., Rathling A., Zillikens D., Huber M., Haas H. Initial Fc epsilon RI-mediated signal strength plays a key role in regulating basophil signaling and deactivation. *J. Allergy Clin. Immunol., 2006, Vol. 118, pp. 1060-1067.*
4. Guillen-Aguinaga S., Jauregui Presa I., Aguinaga-Ontoso E., Guillen-Grima F., Ferrer M. Updosing nonsedating antihistamines in patients with chronic spontaneous urticaria: a systematic review and meta-analysis. *Br. J. Dermatol., 2016, Vol. 175, pp. 1153-1165.*
5. Hasal E., Baskan E.B., Yazici S., Aydogan K., Saricaoglu H. Factors related to omalizumab drug survival and treatment responses in chronic urticaria. *Int. Arch. Allergy Immunol., 2022, Vol. 183, no. 11, pp. 1198-1208.*
6. Kolkhir P., Church M.K., Weller K., Metz M., Schmetzer O., Maurer M. Autoimmune chronic spontaneous urticaria: what we know and what we do not know. *J. Allergy Clin. Immunol., 2017, Vol. 139, no. 6, pp. 1772-1781.*
7. Luquin E., Kaplan A.P., Ferrer M. Increased responsiveness of basophils of patients with chronic urticaria to sera but hypo-responsiveness to other stimuli. *Clin. Exp. Allergy, 2005, Vol. 35, pp. 456-460.*
8. Maurer M., Altrichter S., Schmetzer O., Scheffel J., Church M.K., Metz M. Immunoglobulin E-mediated autoimmunity. *Front. Immunol., 2018, Vol. 9, 689.* doi: 10.3389/fimmu.2018.00689.
9. Nenasheva N.M., Kurbacheva O.M., Avdeev S.N., Fedosenko S.V., Emelyanov A.V., Belevskiy A.S., Ilyina N.I., Knyazheskaya N.P., Zyryanov S.K., Ignatova G.L., Demko I.V., Shulzhenko L.V., Leschenko I.V., Fassahov R.S., Chernyak B.A., Nedashkovskaya N.G., Bobrikova E.N., Demina D.V. Practical recommendations for choosing an immunobiological preparation for the treatment of seveendotype. *Russian Pulmonology, 2020, Vol. 30, no. 2, pp. 227-244.* (In Russ.)
10. Pereverzina N.O, Kruglova L.S., Musaev I.E. Present and future in the treatment of chronic spontaneous urticaria. *Clinical Dermatology and Venereology, 2020, Vol. 19, no. 5, pp. 604-612.* (In Russ.)
11. Weller K., Groffik A., Church M.K., Hawro T., Krause K., Metz M., Martus P., Casale T.B., Staubach P., Maurer M. Development and validation of the Urticaria Control Test: a patient-reported outcome instrument for assessing urticaria control. *J. Allergy Clin. Immunol., 2014, Vol. 133, pp. 1365-1372.*
12. Zhao Z.T., Ji C.M., Yu W.J., Meng L., Hawro T., Wei J.-F., Maurer M. Omalizumab for the treatment of chronic spontaneous urticaria: a meta-analysis of randomized clinical trials. *J. Allergy Clin. Immunol., 2016, Vol. 137, pp. 1742-1750.*

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