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CURRENT APPROACHES TO THE TREATMENT OF FREQUENTLY RECURRENT URTICARIA

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Abstract. **Current approaches to the treatment of frequently recurrent urticaria.** Dytyatkovska E.M., Bendetska Yu.V., Rodkina I.A., Nedogibchenko N.A. The article presents summarized materials on etiology, pathogenesis, classification, clinical manifestations and treatment of chronic urticaria. The management of patients with this pathology at Dniprovsky Allergological Center was analyzed. For assessment of quality of life SKINDEX-29 questionnaire was used. The questionnaire includes three sections: symptoms, emotions and functions. Physical symptoms include six points: tenderness, heartburn or tingling, itching unpleasant sensations when contacting with water, skin irritation, sensitivity. The emotional sphere is characterized by such ten points as: concern about the condition of the skin; depression; feeling of shame; concern that scars can remain after skin disease; feelings about worsening of the skin; anxious mood; embarrassment, feeling of humiliation; skin irritation; rejection of oneself. "Features" section has twelve items: sleep quality; work and hobbies; social activity; sex life; solitude; fatigue; unwillingness to leave home; limiting intimacy with others; complexity in carrying out daily activities; difficulty in expressing feelings; obstruction to create relationships with others; limiting close communication with relatives. Gastrointestinal system was also examined: fibrogastroduodenoscopy with determination of *Helicobacter Pylori*, ultrasound diagnosis of abdominal organs, the intensity of clinical symptoms was determined on a UAS7 scale. Fifteen patients (including eight women and seven men) were successfully treated with omalizumab. The mean age was 39.1±3.6 years. The average duration of the disease in patients was 5.1±0.9 years. The intensity of symptoms was determined before treatment after the first and second injection of Omalizumab. After the first injection, there was a positive trend. The clinical effect occurred in seventy-two hours. Statistical processing of the study results was performed using Statistica v.6.1® software. (StatSoft, USA). The inclusion of omalizumab is an effective treatment for chronic urticaria in the absence of an effect from antihistamines.

Реферат. **Современные подходы к лечению часто рецидивирующей крапивницы.** Дитятковская Е.М., Бендецкая Ю.В., Родкина И.А., Недогибченко Н.А. В статье приведены обобщенные материалы по этиологии, патогенезе, классификации, клинических проявлениях и лечении хронической крапивницы. Проанализовано ведение пациентов с данной патологией в Днепровском аллергологическом центре. Для оценки показателей качества жизни использовался опросник SKINДЕКС-29 (имеет три раздела: симптомы, эмоции и функции). Физические симптомы включают шесть пунктов: болезненность, жжение или покалывание, зуд, неприятные ощущения при контакте с водой, раздражение кожи, чувствительность. Эмоциональная сфера характеризуется такими десятью пунктами, как: обеспокоенность состоянием кожи, чувство подавленности, чувство стыда; беспокойство о том, что от кожного заболевания могут остаться рубцы; переживания об ухудшении состояния кожи; тревожное настроение; смущение, чувство униженности; раздражение по

поводу состояния кожи; неприятие себя. Раздел «Функции» - имеет двенадцать пунктов: качество сна, работа и хобби, социальная активность, сексуальная жизнь; одиночество; усталость, нежелание выходить из дома, ограничение близости с другими людьми; сложность в осуществлении повседневной деятельности; сложность при проявлении чувств; препятствие создавать отношения с окружающими, ограничение тесного общения с родственниками). Также обследовали систему желудочно-кишечного тракта: фиброгастродуоденоскопия с определением *Helicobacter pylori*, ультразвуковая диагностика органов брюшной полости, интенсивность клинической симптоматики определялась по шкале UAS7. Успешно прошли лечение пятнадцать больных (из них восемь женщин и семь мужчин) с помощью омализумаба. Средний возраст составлял $39,1 \pm 3,6$ года. Средний стаж заболевания у больных $5,1 \pm 0,9$ года. Интенсивность симптомов определялась до лечения, после первой, и второй инъекции Омализумаб. Уже после первой инъекции отмечали положительную динамику. Клинический эффект наступал через 72 часа. Статистическую обработку результатов исследования проводили с использованием программного продукта Statistica v.6.1[®]. (StatSoft, США). Включение омализумаба является эффективным методом лечения хронической крапивницы при отсутствии эффекта от антигистаминных препаратов.

Currently, the incidence of chronic urticaria continues to grow rapidly, with doctors of different specialties facing it and treatment is not always effective [6]. In this case, the influence of chronic urticaria on the life of the patient is much wider than severe external manifestations on the skin [5]. Chronic urticaria leads to anxiety and depression, sleep problems, poor quality of life and work performance [2].

The article summarizes the materials of our own clinical observations on the optimization of treatment of chronic urticaria with the use of modern biological drugs. The analysis showed that in patients hospitalized, chronic urticaria occupies the 1st place (30% of all hospitalizations) among nosologies. In outpatients - takes 2nd place (28% of all references to a doctor). Chronic urticaria is a pathology that leads to work decrement and deterioration of quality of life, which is easy to detect using the SKINDEX-29 questionnaire [7]. Urticaria has an allergic mechanism in its pathogenesis (insect allergy, drug allergy, food allergy), may have an autoimmune mechanism or accompany infectious disease [3]. In 40% it is idiopathic. Chronic and idiopathic urticaria as a rule deteriorates quality of life. Therefore, experts from different countries are studying different methods to control the symptoms of the disease [6], while ensuring the safety of each patient. In the absence of the effect from different combinations of antihistamines, a medicine omalizumab or cyclosporine or montelukast should be included in therapy [8]. The use of montelukast, cyclosporine when added to antihistamines results in a short effect [5]. According to the literature data, omalizumab was not used in our country.

The purpose of this study was to study the efficacy of omalizumab (Xolar) in patients with frequently recurrent urticaria.

MATERIALS AND METHODS OF RESEARCH

Under our supervision there were 15 patients aged from 18 to 67 years, of which 8 women and 7

men. The mean age was 39.1 ± 3.6 years. The average length of the disease in patients was 5.1 ± 0.9 years.

For all patients, the intensity of clinical symptoms was determined by UAS7 scale:

- 0 - no symptoms
- 1 - mildly expressed
- 2 - expressed
- 3 - clearly expressed

The intensity of symptoms was determined before treatment, after the first and second injection of omalizumab.

The SKINDEX-29 questionnaire was used to assess quality of life [7]. The questionnaire was filled in by each patient independently at the initial examination. The structural unit of SKINDEX-29 [7] consists of 29 questions and has three sections: symptoms, emotions and functions. Physical symptoms include 6 points: tenderness, heartburn or tingling, itching, unpleasant sensations on contact with water, skin irritation, sensitivity. The emotional sphere is characterized by the following ten points: concern about the condition of the skin; depression; feeling of shame; concern that scars can remain after skin disease; feelings about worsening of the skin; anxious mood; embarrassment, feeling of humiliation; skin irritation; rejection of oneself. The "Features" section has twelve points: sleep quality; work and hobbies; social activity; sex life; solitude; fatigue; unwillingness to leave home; limiting intimacy with others; complexity in carrying out daily activities; difficulty in expressing feelings; obstacle to building relationships with those around you; limitation of close communication with relatives. Answers to the questions were evaluated by a conditional five-point scale. Points correspond to the patient's condition at the time of filling in questionnaire and are represented by the following values: 0 – never, 25 – rarely, 50 – sometimes, 75 – often, 100 – always. The more points scored in each

section, the lower the patient's psychological quality of life. And the total score for the sections was calculated as the arithmetic mean of the number of

questions. The interpretation and categorization of SKINDEK-29 sections [7] is presented in Table 1.

Table 1

Interpretation and categorization of SKINDEK-29 sections

Severity degree	Sections SKINDEK-29			Total SKINDEK-29
	emotions	functions	symptoms	
Mild	0-23,9	0-20,9	0-38,9	0-24,9
Moderate	24-34,9	21-31,9	39-41,9	25-31,9
Severe	35-38,9	32-36,9	42-51,9	32-43,9
Very severe	≥ 39	≥ 37	≥ 52	≥ 44

In addition, all patients underwent examination of the gastrointestinal tract: fibrogastroduodenoscopy with the determination of *Helicobacter pylori*, ultrasound diagnostics of abdominal organs, since chronic urticaria is often accompanied by pathology of the gastrointestinal tract, namely GERD, ulcer disease and chronic duodenitis

Serum IgE level by the enzyme-linked immunosorbent assay on DRG test systems (Germany) using the anti-IgE serum was defined in all patients before the treatment.

Statistical processing of the study results was performed using Statistica v.6.1® software. (StatSoft, USA), serial number AGAR 909E415822FA. The mean values are represented as arithmetic mean and its error ($M \pm m$) or median and interquartile range – Me (25-75 percentile). The significance of differences in the mean values was estimated by the Student's criterion for the dependent samples, relative values by the Pearson χ^2 criterion with Yates' correction. The critical level of statistical significance of differences (p) was assumed to be <0.05 . [1]

RESULTS AND DISCUSSION

In all patients clinical symptoms before treatment, expressed by urticarial generalized rash (mean intensity – 3.0 points) with marked itching (mean 2.9 ± 0.1 points) which significantly deteriorated quality of life of patients (SKINDEK-29 questionnaire) – 43.4 ± 4.2 were marked. Total IgE level ranged from 23 IU/ml to 1800 IU/ml, with a median of 200 (79-714) IU/ml.

After examination of the gastrointestinal tract, the following comorbid conditions were identified:

- gastroesophageal reflux disease;

- chronic cholecystitis;
- duodenitis.

In the period of the disease before administering the study drug omalizumab all patients were prescribed H1 blockers of the last generation at a standard dose, in the absence of the effect the dose was increased by 4 times. In addition, therapy for identified concomitant diseases of the gastrointestinal tract by recommendations of a gastroenterologist was prescribed: PPI, prokinetics, *Helicobacter pylori* eradication.

The effect of a fourfold dose of H1 blocker occurred on the second day of drug taking. However, with decreasing dose to the standard one, urticaria appeared again, being accompanied by itching of the skin. The quality of life of patients (the SKINDEK-29 questionnaire) averaged 31.9 ± 2.6 points.

In accordance with European guidelines for the diagnosis and treatment of urticaria, we prescribed omalizumab (Xolar), 150 mg. The effect after administration occurred in 72 hours.

As can be seen from table 2, after the first injection, the rash completely disappeared only in 2 patients, but its intensity decreased by 1.7 times on average – from 2.9 ± 0.1 points to 1.7 ± 0.2 points ($p < 0.001$). After the second injection, the number of patients with symptoms of rash reduced by half (from 15 to 8 patients; $p < 0.05$). Therewith rash mostly was mildly expressed – 1.0 ± 0.2 points in 5 patients and 2.0 ± 0.2 points in 3. After the third injection, not-critical rash remained in only 3 patients.

Table 2

Dynamics of rash intensity under the influence of omalizumab (M±m)

Indicator	Observation period			
	before treatment	after 1 injection	after 2 injection	after 3 injection
Number of patients with symptom, n /%	15/ 100	13/ 87	8/ 53 *	3/ 20 **
The mean symptom severity score, M ± m	2,9±0,1	1,7±0,2**	0,7±0,2**	0,3±0,2**

Notes: * – p<0.05; ** – <0.001 compared to baseline.

The dynamics of itching severity in patients with chronic urticaria under the influence of omalizumab was similar (Table 3).

Already after the first injection a decrease in the incidence of itching from 3 points to 1.7±0.2 points (p<0.001) and the complete disappearance of symptoms in half of the patients after the second procedure was observed.

Quality of life of patients (SKINDEX-29 questionnaire) was 16.8±1.2.

It should be noted that we did not establish a statistically significant correlation between the levels of total IgE and the dynamics of clinical symptoms

under the influence of omalizumab in patients with chronic urticaria - Spearman correlation coefficients (r) did not exceed 0.27 (p> 0.05) at critical r = 0.55 at p <0.05.

The effectiveness of repeated courses of omalizumab therapy in patients with chronic urticaria confirms the safety and efficacy of this treatment modality.

100% of patients achieve control of chronic spontaneous urticaria symptoms in recure after initially responding well (patients reported rapid and complete response within the first 4 weeks after omalizumab injection and in the first days of recure).

Table 3

Dynamics of itching intensity under the influence of omalizumab in patients with chronic urticaria

Indicator	Observation period			
	before treatment	after 1 injection	after 2 injection	after 3 injection
Number of patients with symptom, n /%	15/100	13/87	8/53 *	2/13**
The mean symptom severity score, M ± m	3,0±0,0	1,7±0,2**	0,7±0,2**	0,2±0,1**

Notes: * – p <0.05; ** – p <0.001 compared to baseline.

CONCLUSIONS

1. The inclusion of omalizumab is an effective treatment modality for chronic urticaria in the absence of antihistamines.

2. The level of total IgE is not a criterion for the mandatory administration of omalizumab to patients with chronic urticaria.

3. The administration of omalizumab was effective in patients with frequently recurrent urticaria in whom total IgE was within the age range.

4. Administration of omalizumab is a promising method of treating severe urticaria.

REFERENCES

1. Antomonov MYu. [Mathematical processing and analysis of biomedical data]. Kyiv: Medinform. 2018;579. Russian.

2. Cezmi AA, Agache I, Abdel-Gadir A. [Global atlas of allergy]. European Academy of Allergy and Clinical Immunology. 2014;206-11.

3. Sussman G, Hébert J, Gulliver W. [Omalizumab Retreatment of Patients with Chronic Idiopathic Urticaria/Spontaneous Urticaria (CIU/CSU) Following Return of Symptoms: Primary Results of the OPTIMA Study]. *SKIN The Journal of Cutaneous Medicine*. 2017;1(3.1):127. doi: <https://doi.org/10.25251/skin.1.suppl.126>
4. Metz M, Ohanyan T, Church MK. [Retreatment with omalizumab results in rapid remission in chronic spontaneous and inducible urticaria]. *JAMA Dermatology*. 2014;150(3):288-90. doi: <https://doi.org/10.1001/jamadermatol.2013.8705>
5. Zuberbier T, Aberer W, Asero R. [The EAACI/GA²LEN/EDF/WAO Guideline for the Definition, Classification, Diagnosis and Management of Urticaria. The 2017 Revision and Update]. *Allergy*. 2018;73:1393-414.
6. Zuberbier T, Aberer W, Asero R. [The EAACI/GA²LEN/EDF/WAO urticaria guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update]. *Allergy*. 2014;69:868-87. doi: <https://doi.org/10.1111/all.12313>
7. Maurer M, Kaplan A, Rosén K. [The XTEND-CIU study: Long-term use of omalizumab in chronic idiopathic urticaria]. *Journal of Allergy and Clinical Immunology*. 2018;141:1138-9. doi: <https://doi.org/10.1016/j.jaci.2017.10.018>
8. Türk M, Yılmaz İ, Bahçecioğlu SN. [Treatment and retreatment with omalizumab in chronic spontaneous urticaria: Real life experience with twenty-five patients]. *Allergology International*. 2018;67(1):85-89. doi: <https://doi.org/10.1016/j.alit.2017.05.003>

СПИСОК ЛІТЕРАТУРИ

1. Антомонов М.Ю. Математическая обработка и анализ медико-биологических данных. Киев: Мединформ, 2018. 579 с.
2. Global atlas of allergy / A. A. Cezmi et al. *Eur. Academy of Allergy and Clin. Immunology*. 2014. P. 206-211.
3. Omalizumab Retreatment of Patients with Chronic Idiopathic Urticaria/Spontaneous Urticaria (CIU/CSU) Following Return of Symptoms: Primary Results of the OPTIMA Study / G. Sussman et al. *SKIN The Journal of Cutaneous Medicine*. 2017. Vol. 1. No. 3.1. P. 127. DOI: <https://doi.org/10.25251/skin.1.suppl.126>
4. Retreatment with omalizumab results in rapid remission in chronic spontaneous and inducible urticaria / M. Metz et al. *JAMA Dermatology*. 2014. Vol. 150. No. 3. P. 288-290. DOI: <https://doi.org/10.1001/jamadermatol.2013.8705>
5. The EAACI/GA²LEN/EDF/WAO Guideline for the Definition, Classification, Diagnosis and Management of Urticaria. The 2017 Revision and Update / T. Zuberbier et al. *Allergy*. 2018. Vol. 73. P. 1393-1414.
6. The EAACI/GA²LEN/EDF/WAO urticaria guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update / T. Zuberbier et al. *Allergy*. 2014. Vol. 69. P. 868-887. DOI: <https://doi.org/10.1111/all.12313>
7. The XTEND-CIU study: Long-term use of omalizumab in chronic idiopathic urticaria / M. Maurer et al. *Journal of Allergy and Clinical Immunology*. 2018. Vol. 141. P. 1138-1139. DOI: <https://doi.org/10.1016/j.jaci.2017.10.018>
8. Türk M., Yılmaz İ., Bahçecioğlu S. N. Treatment and retreatment with omalizumab in chronic spontaneous urticaria: Real life experience with twenty-five patients. *Allergology International*. 2018. Vol. 67, No. 1. P. 85-89. DOI: <https://doi.org/10.1016/j.alit.2017.05.003>

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