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Chronic urticaria in theory and practice. Experience of UCARE-centers for clinicians

N.I. Ilyina[1], I.V. Danilycheva[1], I.V. Dorofeeva[1], O.G. Elisyutina[1], O.M. Kurbacheva[1], E.A. Latysheva[1], L.S. Litvin[2], I.A. Manto[1], E.V. Nazarova[1], K.S. Pavlova[1], A.S. Primak[1], E.S. Fedenko[1], R.V. Shchubelko[1]

[1] National Research Center – Institute of Immunology Federal Medical-Biological Agency of Russia, Moscow, Russian Federation
[2] Novartis Pharma LLC, Moscow, Russian Federation

ABSTRACT.
Chronic urticaria (CU) is an urgent medical and social problem. The instruments of everyday clinical practice are international and domestic guidelines which briefly reflect modern ideas about various aspects of CU. Recently, a new opportunity has emerged to expand theoretical and practical experience in the management of patients with CU, to carry out educational activities to disseminate modern knowledge about urticaria, to conduct research in the field of studying the pathogenesis, treatment, and prevention of exacerbations of the disease. This opportunity is realized through the centers of excellence for working with such patients (GA²LEN UCARE centers). One of the five Russian centers, have prepared and conducted an online training program "Chronic urticaria: scientific and medical achievements and practical aspects of patient management" at the Federal State Budgetary Institution State Research Center "Institute of Immunology" FMBA of Russia. The event was held by the employees of the Federal State Budgetary Institution State Research Center "Institute of Immunology" of the FMBA of Russia on November, 2020.

Keywords: chronic urticarial; GA²LEN; UCARE centers

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Хроническая крапивница в теории и практике. Опыт UCARE-центров — практическим врачам

Н.И. Ильина[1], И.В. Данилычева[1], И.В. Дорофеева[1], О.Г. Елисютина[1], О.М. Курбачева[1], Е.А. Латышева[1], Л.С. Литвин[2], И.А. Манто[1], Е.В. Назарова[1], К.С. Павлова[1], А.С. Примак[1], Е.С. Феденко[1], Р.В. Щубелко[1]

[1] Государственный научный центр «Институт иммунологии» Федерального медико-биологического агентства, Москва, Российская Федерация
[2] ООО «Новартис Фарма», Москва, Российская Федерация

АННОТАЦИЯ.
Хроническая крапивница (ХК) — актуальная медико-социальная проблема. Инструментами повседневной клинической практики являются международные и отечественные согласительные документы, кратко отражающие современные представления о разных аспектах ХК. В настоящее время расширение теоретического и практического опыта по ведению пациентов с ХК, осуществление образовательной деятельности по распространению современных знаний о крапивнице, проведение научных исследований патогенеза, лечения, профилактики обострений заболевания реализуются с помощью центров передового опыта по работе с такими пациентами (GA²LEN UCARE centers). В одном из пяти российских центров, организованном в ФГБУ «ГНЦ "Институт иммунологии"» ФМБА России, была подготовлена и выполнена в ноябре 2020 года онлайн обучающая научно-практическая программа для врачей «Хроническая крапивница: научно-медицинские достижения и практические аспекты ведения пациентов».

Ключевые слова: хроническая крапивница; GA²LEN; UCARE centers

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List of abbreviations

GCS — glucocorticosteroid
nsH_1-AH — non-sedating antihistamines
CU — chronic urticaria
CSU — chronic spontaneous urticaria
CU-Q2oL — Chronic Urticaria Quality of Life Questionnaire
DLQI — Dermatology Life Quality Index
GA²LEN — Global Allergy and Asthma European Network
GA²LEN UCARE Centers (GA²LEN urticaria centers) — GA²LEN centers of excellence in urticaria
UAS7 — Urticaria Activity Score 7
UCT — Urticaria Control Test.

Background

Chronic urticaria (CU) represents one of the topical medical and social problems due to its widespread prevalence, rapid increase in morbidity, frequent resistance to traditional methods of therapy, negative impact on the quality of life, and financial burden on the healthcare system and patients. The CU prevalence in the population ranges from 0.1% to 1.5%, and it mainly affects people of working age [1, 2]. Prolonged and persistent course of the disease, severe itching, and cosmetic problems result in the loss of earning capacity and a decrease in the quality of life of CU patients.

Global Allergy and Asthma European Network Centers of Excellence in Urticaria (GA²LEN UCARE Centers)

In the last decade, attempts have been made to unify the approach to the diagnostics and management of CU based on the principles of evidence-based medicine. The instruments of everyday clinical practice are international and Russian consensus papers that briefly present the contemporary outlooks about various aspects of CU [3, 4]. A new opportunity, which is implemented in the centers of excellence for working with such patients (GA²LEN UCARE centers), has recently appeared to expand the theoretical and practical experiences in managing CU patients [5]. Similar centers are already functioning for patients with other diseases.

The urticaria reference centers aim to conduct scientific research on the pathogenesis, treatment, and prevention of the disease exacerbations and educational activities to increase the current knowledge about urticaria. The network of centers of excellence in urticaria is the first experience of the GA²LEN in the accreditation, promotion, and cooperation of institutions. To date, approximately one hundred GA²LEN UCARE centers have been globally certified[1]. Their creation requires the fulfillment of a number of conditions. In particular, the infrastructure of a medical institution should include an in-patient facility and a polyclinic with an allotted time for receiving patients with urticaria (children and adults) and available specialists in the field of urticaria led by an expert. The team of the center must adhere to the principles of an interdisciplinary approach to patients (the presence of professionals of different specialties in a medical institution would be an asset), a responsible attitude to documentation, archiving of the patient data, and adherence to current protocols for the diagnostics and treatment of urticaria. The center doctors must know and use the current nomenclature and classification of urticaria in their daily work and recognize and apply modern therapeutic algorithms. Their tasks include history taking, conducting differential diagnostics, standardized assessments and monitoring of activity and control of the disease, identifying concomitant diseases, and performing provocative and threshold testing in patients with induced urticaria. The center team should be involved in the dissemination of knowledge on urticaria to colleagues and patients. An annual Urticaria Day[2] represents a good example of the educational activities of the staff of UCARE centers and at the same time a care token to their patients. The event form is diverse (virtual meetings of patients with doctors, educational webinars, campaigns in social networks, etc.), but its essence consists of raising the disease awareness of patients

[1] Urticaria Centers of Reference and Excellence. Available from: http://www.ga2len-ucare.com/centers.html
[2] Available from: www.urticariaday.org

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and their family and friends, the mechanisms of urticaria development, prognosis, and diagnostic and treatment options. Patients should be able to realize that they are not alone in combating with their illness. Within this event, on October 1, 2020, an online educational program dedicated to Urticaria Day was prepared and conducted with the active participation of the team of the Urticaria Reference Center of the Institute of Immunology in State Scientific Center Institute of Immunology of the Federal Medical and Biological Agency of Russia (hereinafter the Institute of Immunology) (Figs. 1 and 2).

Another necessary aspect of the center's activities is its scientific work. According to the most recent official figures, urticaria reference centers are involved in more than 12 international research projects that are at various stages of implementation[3] and several of them, such as UVERSI-CU (urticaria and urticarial vasculitis), CURICT (use of information and communication technologies for medical purposes in management of patients with CU), PREG-CU (pregnancy and CU), have already been completed.

The PREG-CU project (Pregnancy and Chronic Urticaria: characteristics and outcomes of pregnancy in CU patients) is a prospective international multicenter observational study which involved 27 UCARE centers and used a questionnaire (47 items) to analyze the course of pregnancy in 288 CU patients (with chronic spontaneous urticaria (CSU), chronic inducible urticaria, or a combination of these subtypes) from 13 countries, including Russia. The results were reported at the Global Urticaria Forum [6].

The large-scale active project, the global Chronic Urticaria Registry, is a prospective international multicenter observational study aimed at further understanding the course of CU in children and adults, evaluating therapeutic approaches used by doctors in real clinical practice, their efficiency, and safety for the subsequent planning of rational medical care for patients with this disease. The register is aimed at collecting primary data on CU patients and subsequent information over time. Participation in the registration is voluntary. As of February 26, 2020, 39 GA²LEN UCARE centers around the world have joined the registry, and 35 of them have entered baseline data on 2,946 patients. The data on 461 CU patients were entered into the register from Russian centers [7].

Thus, the scope of interaction between the members of GA²LEN UCARE center teams is expanding globally. Such collaborative work leads to the personal development of each team member and an increase in the knowledge about the different aspects of urticaria.

A close relationship exists between Russian centers of excellence on urticaria. To date, five certified centers are actively operating in Russia, and two of them are in Moscow (at the Institute of Immunology and the City Clinical Hospital No. 52 of the Moscow City Health Department); one each in Smolensk (at the City Clinical Hospital No. 1, the Department of Allergology and

[3] Urticaria Centers of Reference and Excellence. Available from: www.ga2len-ucare.com

Fig.1. Information for patients with urticaria about the upcoming International Urticaria Day educational event.

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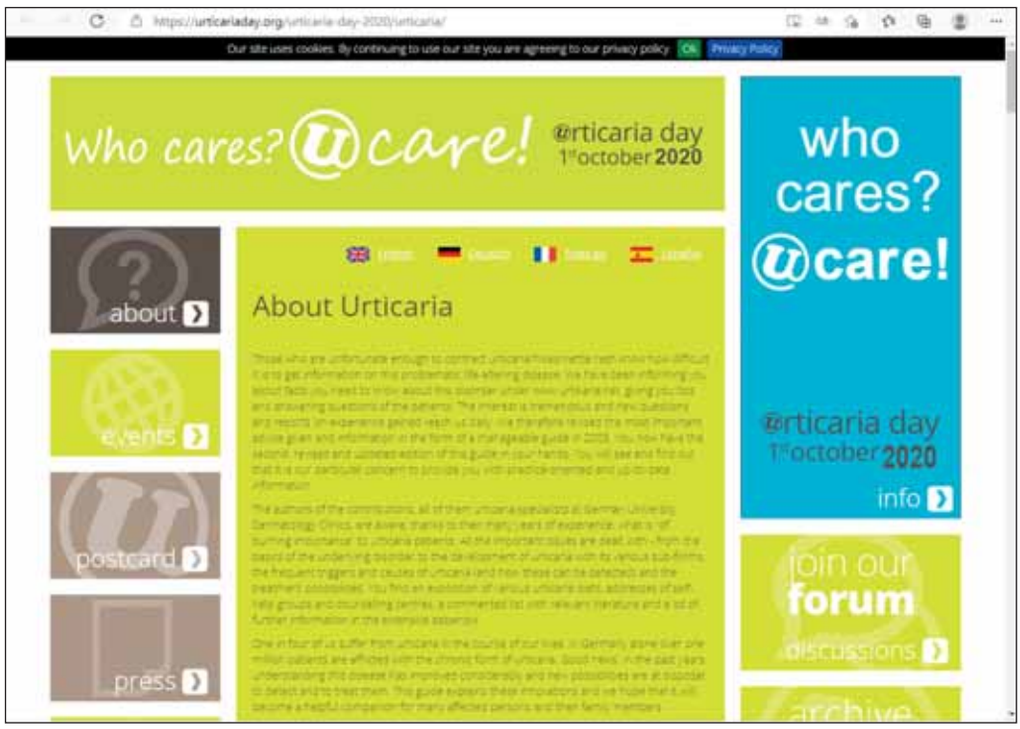

Fig. 2. International Urticaria Day Announcement. (https://urticariaday.org/urticaria-day-2020/urticaria/).

Immunology of the Smolensk State Medical University), Chelyabinsk (at the Chelyabinsk Regional Clinical Dermatovenerologic Dispensary), and Kazan (at the Republican Center of Clinical Immunology of the Republican Clinical Hospital, Department of Clinical Immunology and Allergology, Kazan State Medical University). Hospitals that aim to become a center of excellence in urticaria can contact any of the existing Russian centers for advice and information or check out the website *www.ga2len-ucare.com*.

Program for Doctors: "Chronic Urticaria: Scientific and Medical Achievements and Practical Aspects of Patient Management"

One of the most important tasks of the UCARE centers is the dissemination of knowledge about urticaria, contemporary methods of examination, therapy, and promising scientific fields. The training programs come in various forms, including intramural, extramural, or those focused on one or more aspects of the problem. The specialists of our center prepared and conducted an online training program for doctors in November 2020, "Chronic urticaria: scientific and medical achievements and practical aspects of patient management" (sponsored by Novartis Pharma).

On the eve of the event, all participants, through video lectures, became familiarized with the epidemiology of CU, the causes and triggers of CU, methods of patient examination, aspects of the differential diagnostics of CU, and modern theories of the pathogenesis of CU (I.V. Danilycheva, Ph.D., E.A. Latysheva, MD, PhD, M.D, E.V. Nazarova, Ph.D., and O.G. Elisyutina, MD, PhD). Professor N.I. Ilyina opened the first day of the training by lecturing about the key urgent problems of doctors and CU patients and the aims and plan of the event and highlighting the scientific and practical orientation of the online meeting. The two-day program envisaged and implemented a virtual visit to the clinic of the Institute of Immunology, considered the issues of routing CU patients in the institution, and included the sharing of experiences and the organization of the UCARE center operating at the institution.

Urticaria: concept definition and classification

Urticaria represents a group of diseases characterized by the development of itching bullae and/or angioedema [8]. The prevalence of urticaria in the population is 15%–25%, whereas 1/4 of patients develop a chronic form of the disease [9, 10], i.e., the symptoms (itching bullae and/or angioedema) persist for more than 6 weeks. The regional, gender, and age differences in the disease prevalence have been revealed; Asian studies showed a higher incidence of CU (1.4%) than those reported in Europe (0.5%) and the United States (0.1%).

To a certain extent, CU is diagnosed more often in women than in men, whereas among children under 15 years of age, no gender differences in prevalence have been revealed (1.0% and 1.1% among girls and boys, respectively). Four studies of temporal trends have shown an increase in the CU prevalence over time [1].

The clinical phenotypes of CU, namely, CSU and chronic induced urticaria, are of particular interest and

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may or may not be accompanied by angioedema. Several CU patients develop isolated angioedemas without bullas. Any variant of induced urticaria (aquagenic, cold, delayed-pressure, dermographic, heat, solar, vibratory, cholinergic, or contact urticaria) is characterized by the presence of a specific trigger. CSU has no specific trigger, but comorbid diseases and conditions indicating a probable pathomechanism can be identified. CSU is the most common clinical phenotype of CU (it is registered in 2 out of 3 CU patients) [8]. According to M. Maurer et al., the prevalence of CSU in the population is 0.5%–1% [11].

Pathogenesis

One of the video lectures, which were offered for preview to the trainees of the educational program, presented modern outlooks about the pathogenesis of CU. Mast cells play a major role in the development of urticaria. Activated mast cells release a variety of preformed mediators (histamine, tumor necrosis factor, and protease) and *de novo*-synthesized lipid mediators, cytokines, and chemokines. Mediators cause vasodilation, increased vascular permeability, and release of the plasma liquid into the surrounding tissues, induce cell migration, and activate sensitive nerve fibers. The signals that activate mast cells are diverse, and they implement their function through a number of receptors located on their surface.

To date, two mechanisms of pathological activation of mast cells and basophils mediated through high affinity receptors for immunoglobulin E (IgE) (FcεRI) have been well studied in CSU patients (Fig. 3) [12].

Studies over the past 5 years have confirmed the autoallergy mechanism (type I autoimmunity or type I autoimmune response) in the activation of mast cells and basophils. In CSU patients, auto-IgE antibodies to more than 200 autoallergens (thyroperoxidase, interleukin (IL) 24, thyroglobulin, double-stranded (native) DNA, tissue factor, etc.) have been determined [13–16]. The auto-IgE antibodies in CSU patients are functional. Crosslinking of FcεRI through auto-IgE antibodies that bind the autoallergen leads to the degranulation of mast cells/basophils [17]. The IgE anti-thyroid peroxidase antibodies are often detected in CSU patients and have a pronounced capability to induce thyroid peroxidase-mediated skin reactions in CSU patients compared with practically healthy individuals [18].

In their studies, P. Staubach et al. [19] and S. Altrichter et al. [20] observed that CSU patients have an increased level of total IgE compared with healthy individuals.

The mechanism of type IIb autoimmune response (type IIb autoimmunity) in the activation of mast cells in CSU patients is well understood. The hypothesis was proposed approximately 30 years ago. The theory was confirmed based on the identification of circulating and functionally active autoantibodies of class G (IgG) aimed against FcεRI and mast cell membrane-bound antibodies of class E (IgE). This mechanism is detected in approximately 30% of CSU patients [9, 21]. An indirect evidence of this mechanism is the presence of concomitant autoimmune pathology and a positive intradermal test with autoserum [13, 22, 23].

The pathological activation of mast cells in CSU can also be associated with "defects" of intracellular signaling pathways, which can lead to the spontaneous degranulation of mast cells/basophils with the subsequent release of histamine and other protein and lipid mediators. A number of other mechanisms, namely, the mechanism implemented through the Mas-linked G-protein coupled to the X2 (MRGPRX2) receptor, are currently being actively studied [12, 17].

Recently, experts have been focusing on identifying the mechanisms underlying the pathogenesis of various forms of chronic induced urticaria. One of the theories suggested is related to the study of the role of autoallergy mechanism, which has been confirmed by the results of published studies and the successful practices of the use of anti-IgE therapy in patients with chronic induced urticaria [22].

The identification of comorbid diseases, especially of the autoimmune range, is important in the considered pathogenetic variants of the disease development. The prevalence of certain autoimmune diseases in CSU patients has increased (⩾1% in most studies versus ⩽1% in the general population). The incidence of concomitant autoimmune diseases in most studies was 1% or higher for insulin-dependent diabetes mellitus, rheumatoid arthritis, psoriasis, and celiac disease, 2% or higher for Graves' disease, 3% or higher for vitiligo, and 5% or higher for pernicious anemia and Hashimoto thyroiditis. Organ-specific autoimmune diseases are more common in CSU patients than systemic ones. Autoimmune thyroiditis is

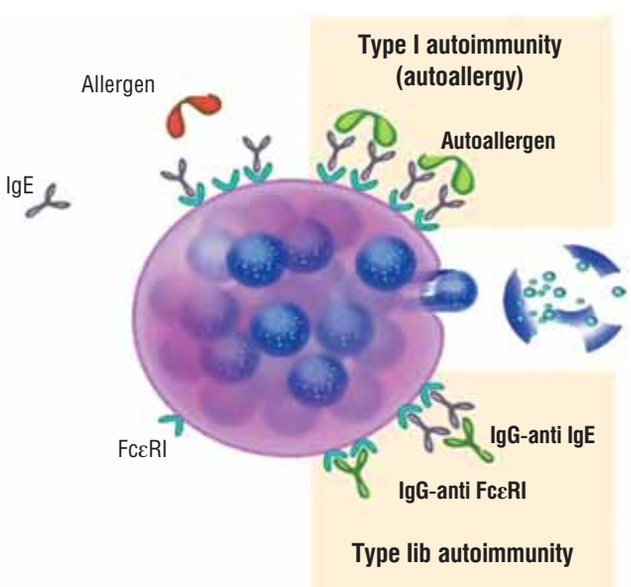

Fig. 3. Studied mechanisms of mast cell and basophil activation in CSU (adapted from [12]).

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the most common form of organ-specific autoimmune disease, and it has been registered among CSU patients. More than 15% of CSU patients have a positive family history of autoimmune diseases [24].

CSU is not an atopic disease, although atopy is relatively common in CSU patients (16.9%), especially in the pediatric population [25].

Given the debilitating nature of the CSU course, more than 30% of patients experience concomitant mental disorders, including anxiety, depression, and somatoform conditions, which have a significant negative impact on their quality of life [2].

The CSU course can be accompanied by periods of spontaneous remission or relapse over time. Among adults, the average duration of CSU is estimated at 11.5 ± 10.8 years, whereas remission within 1 year from the disease onset is registered in 20%–75% of patients; the remission reaches 30%–55% within 5 years [2]. Chronic induced urticaria has a lower probability of resolution than CSU, with 13% and 50% of patients with chronic induced urticaria being symptom-free within 1 and 5 years, respectively [26].

The factors affecting the disease duration include severe course of CU, onset at the age of over 45 years, insufficient response to standard doses of non-sedating H_1-antihistamines (nsH_1-AH), concomitant angioedema, concomitant inducible urticaria, intolerance to non-steroidal anti-inflammatory drugs, and recurrent course. Several laboratory biomarkers (high levels of C-reactive protein and D-dimer) can be used to predict the disease severity, although they are not associated with the disease duration [2, 11]. A severe and moderate course of the disease was noted in 5 out of 10 patients [27], whereas angioedema is often not diagnosed by doctors [27]; the same applies to concomitant induced urticaria, which is registered in less than 30% of CSU patients [28].

Diagnostics

The diagnostics of CU is based on the detection of typical urticaria and/or angioedema, which is noted in patients for more than 6 weeks. Structured history taking and physical examination are key steps in determining the further scope of patient examination. The range of compulsory laboratory diagnostics of CSU patients is represented by an extensive general clinical blood test, a study of the erythrocyte sedimentation rate (ESR), and a study of the level of the C-reactive protein. Extended laboratory diagnostics is necessitated by the clinical situation, the patient's history, and may include tests to rule out infectious diseases (e.g., *Helicobacter pylori*), parasitic invasion, and atopy; determination of the levels of thyroid hormones and antibodies to the thyroid gland structures [thyroglobulin, free thyroxine, free triiodothyronine, and antibodies to thyroperoxidase and thyroglobulin]; tests to rule out physical urticaria with medications; oral food tests, autologous serum test, determination of tryptase and the intake of a skin biopsy sample; determination of D-dimer, antinuclear antibodies, C3/C4 component of the complement, and protein fractions. Routine diagnostic tests for inducible urticaria are recommended to be limited until a threshold for the provoking factor is determined [8].

As part of the online sessions, the program trainees "visited" the treatment room and the functional diagnostics room, where they were informed about the provocative tests for the diagnostics of induced urticaria (cold, cholinergic, dermographic, and delayed-pressure urticaria), autoserum test, diagnostic testing with allergens, skin biopsy, and assessment of CU treatment monitoring tests.

We diverted the listeners' attention to the monitoring of the disease as the most objective method for assessing the condition of patients and the efficiency of therapy. The inclusion of several questionnaires in the plan of examination and monitoring of the disease course and the efficiency of therapy are required urgently. The assessment of urticaria activity is recommended for use in clinical and research activities. For this purpose, a simple scoring system, Urticaria Activity Score 7 (UAS7) or urticaria activity index, is used to assess the severity of the disease and the treatment results for spontaneous urticaria. UAS7 assumes a total assessment of the main symptoms of the disease (the number of eruptions and intensity of itching) by the patient himself every 24 h for 7 consecutive days (Table). This assessment is convenient for the patient and the doctor and enables the objective assessment of the patient's condition and his individual response to the therapy (strong recommendation/high-quality evidence) [8]. The total points are 0 to 6 per day, with a maximum of 42 points per week.

An urticaria diary has been developed to monitor the course of the disease, the influence of factors and triggers on the disease symptoms, and the control of drug intake. This activity score cannot be used to assess the activity of physical urticaria or isolated angioedema.

An important tool for assessing the course of the disease is the Urticaria Control Test (UCT), which is generally used in patients with CSU and induced urticaria to control the disease over the past 4 weeks. This test requires answering four questions concerning the control of the disease symptoms, the impact on the quality of life, treatment efficiency, and the general control of the disease. Each answer to a question is appraised by points from 0 to 4. The maximum score for answering the questions is 16, which corresponds to complete control of the disease. The threshold value is 12 points. The UCT of 11 points or lower indicates an uncontrolled course of CU (Fig. 4) [29].

Differential diagnostics

Differential diagnostics is conducted with a number of diseases manifested by urticarial or urticarial-like elements, angioedema, and frequent symptoms that are unusual for urticaria.

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Such diseases include urticarial vasculitis. Bullas with urticarial vasculitis persist for more than 24 h and is accompanied by purpura, secondary hyperpigmentation, burning, and soreness sensations. Angioedema, livedo reticularis, fever, ailment, myalgia, and arthralgia may also be noted. A histological examination of a biopsy specimen of the affected skin is required, with the identification of typical histological signs of urticarial vasculitis, to confirm the diagnosis of urticarial vasculitis.

Herpes iris is an acute disease of the skin and mucous membranes, and it is characterized by the sudden appearance of a polymorphous eruption represented by papules, patches, bullas, and less common elements of the types of palpable purpura. A part of the eruption turns into typical and/or occasionally atypical nodular target-like elements. The lesion of the mucous membranes is typical for the large form of the disease.

T-cell lymphoma often presents with a widespread itching of the skin. In the early stages, the disease infiltrates skin, but the condition resolves within 24–48 h. T-cell lymphoma is accompanied by itching and occasionally by angioedema and can be interpreted as urticaria.

Urticaria pigmentosa (also known as macula-papular cutaneous mastocytosis) is characterized by reddish-brown patches and papules that form a bulla when rubbed (positive Unna–Darier symptom).

An early localized form of tick-borne borreliosis (Lyme disease) may manifest as chronic erythema migrans which must be differentiated from urticaria.

Polymorphic eruptions in pregnant women are characterized by the appearance on the skin of intensely itchy edematous erythematous papules and plaques. Eruptions are registered more often in the primiparous in trimester III of pregnancy and resolve on days 7–10 after childbirth. Eruptions are mainly localized in the region of abdomen, hips and buttocks, and often in the stretch-mark area.

Autoimmune progesterone dermatitis is characterized by polymorphic eruptions, often urticarial, that recur monthly cyclically during the luteal phase of the menstrual cycle and resolve spontaneously during menstruation. The disease exacerbation can be noted with the use of oral contraceptives containing progesterone.

Reticular erythematous mucinosis is a rare disease characterized by the appearance of erythematous patches, nodules and plaques, and urticarial-like patches and papules. This condition is often registered in middle-aged women.

Systemic lupus erythematosus is accompanied by urticarial and urticarial-like eruptions, especially in the active phase of the disease. CSU may be one of the first symptoms of systemic lupus erythematosus and precedes its manifestation by 10 years.

Autoinflammatory diseases include cryopyrin-associated syndromes which represent a group of rare congenital autoinflammatory diseases, including familial cold autoinflammatory syndrome/familial cold urticaria, Muckle–Wells syndrome (MWS), and chronic infantile onset neurologic cutaneous articular/neonatal onset multisystem inflammatory disease (CINCA/NOMID). These syndromes are characterized by an early onset, usually in the first year of life, recurrent or persistent fever, urticarial or urticarial-like rash, a wide range of joint lesions from arthralgias to recurrent and persistent arthritis in severe cases, and (for MWS and CINCA/NOMID) damage to the central and peripheral nervous systems. The most frequent complication is amyloidosis, which develops as a result of chronic inflammation and which often causes the death of patients.

Schnitzler's syndrome is characterized by the recurrent urticarial skin eruptions in combination with monoclonal gammopathy associated with clinical and biological signs of inflammation and the risk of developing AA amyloidosis and lymphoproliferative diseases. The manifestations of systemic inflammation in this disease also include recurrent fever, pain in bones and muscles, arthralgia/arthritis, lymphadenopathy, hepato- or splenomegaly, and increased levels of acute-phase markers (ESR, C-reactive protein, and SAA).

Mast cell monoclonal activation syndrome is characterized by symptoms caused by the release of mast cell mediators, including recurrent anaphylactic episodes with hypotension and fainting that occurs for no apparent reason (idiopathic anaphylaxis) or after being stung by Hymenoptera. The diagnosis is confirmed by the serial determination of blood tryptase levels and bone marrow biopsy with immunohistochemical and molecular genetic studies. In these patients, the diagnostic criteria for systemic mastocytosis are inapplicable.

Table. Assessment of urticaria activity (UAS7) for 7 days [8].

Score	Degree of manifestations	
	Blisters	Itching
0	No	No
1	Mild (<20 blisters / 24 h)	Mild (present but not bothersome)
2	Moderate (20–50 blisters / 24 h)	Moderate (bothersome, but does not affect daytime activity and sleep)
3	Intense (>50 blisters / 24 h, or large confluent blisters)	Intense (severe itching, quite bothersome, disrupting daytime activity and sleep)

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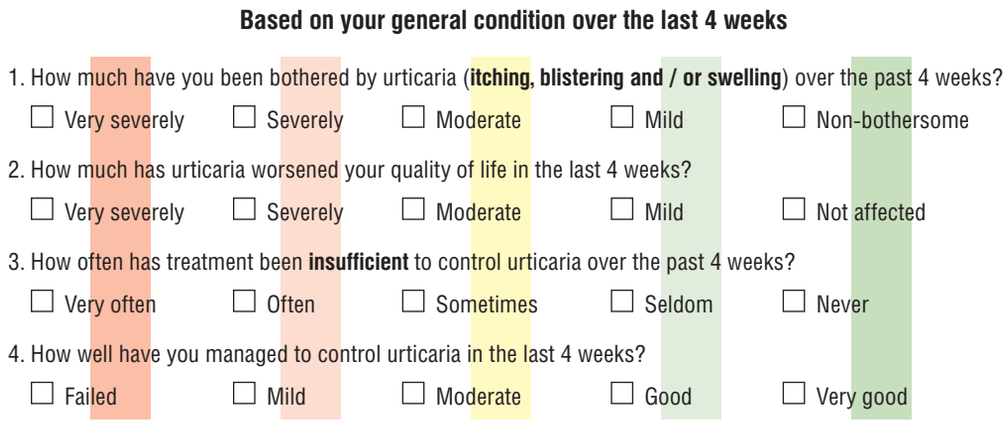

Fig. 4. Determination of urticaria symptom control (UCT-test) [29].

The presence of angioedema in CSU patients, especially an isolated one, and an atypical clinical presentation necessitate the differential diagnostics with hereditary or acquired angioedema [8].

From a diagnostic point of view, CSU in most cases is considered by doctors as a diagnosis by ruling out, which explains its long-term establishment [27, 30]. In this regard, the extended diagnostics to identify the causes of CU and differential diagnostic search should be expedient and reasonable [4, 8].

Principles of therapeutic management of patients with urticaria

Professor E.S. Fedenko spoke about the current principles of managing CU patients and the algorithm of therapy, focusing on the need to achieve the main goal of therapy which is the complete control of disease symptoms. The main principles of patient management are the elimination and removal of causes/triggers, pharmacotherapy, induction of tolerance, and regular self-monitoring of the condition by the patients [4, 8].

The contemporary algorithm of pharmacotherapy assumes the staged management of CU patients, in particular the CSU patients (Fig. 5) [4, 8].

The first line of therapy is the administration of a standard dose of nsH_1-AH. Almost 60% of CSU patients continuously experience the symptoms despite treatment with second-generation H_1-AH at standard doses [31]. If the effect is not achieved or insufficient within 2–4 weeks or earlier, subject to intolerance of symptoms, the dose of second-generation H_1-AH, which is the second line of therapy, is proposed to be increased up to fourfold. Notably, the increase in the dose of nsH_1-AH up to fourfold is a treatment not upon indications but with proven efficacy and safety [4, 8]. However, almost 40% of CSU patients experience no additional effect from the increased dose of H_1-AH and continually suffer from symptoms [31].

In the case of ineffective second line therapy for 2–4 weeks or earlier, if the symptoms are intolerable, the treatment with omalizumab (third-line therapy) is recommended [8, 4, 32]. In accordance with modern algorithms, the treatment with omalizumab is recommended for 6 months before changing to the fourth line of CU therapy in the case of ineffectiveness or earlier administration if the symptoms are intolerable. Patients who are torpid to the treatment with omalizumab will receive the fourth line therapy. Clinical studies have shown the efficacy of cyclosporine in the treatment of CSU, but this treatment is not conducted in accordance with indications (registration through a medical commission is required). The constant monitoring of blood pressure, kidney function, and the blood level of cyclosporine is necessary to prevent possible complications. A short-term course for the treatment of urticaria exacerbation with glucocorticosteroids (GCS) is possible at any treatment stage. The long-term treatment with GCS should be avoided [4, 8].

Immunobiological therapy

As part of the expert discussion, Professors O.M. Kurbacheva and O.G. Elisyutina, MD, PhD discussed the theoretical justification and practical use of immunobiological drugs in allergology in general and directly for the treatment of CU. Biological therapy in allergology is used actively to treat the severe forms of atopic bronchial asthma and atopic dermatitis. In 2014, the officially approved therapy for chronic idiopathic (spontaneous) urticaria with omalizumab was initiated. In the current European consensus document EAACI/GA2LEN/EDF/WAO for the definition, classification, diagnostics, and treatment of urticaria, omalizumab is the only biological drug recommended for use in cases of the ineffectiveness of nsH_1-AH [4].

Role of omalizumab in the treatment of patients with urticaria

Omalizumab, a recombinant DNA derivative, is a humanized IgG1-kappa monoclonal antibody that binds selectively to free human IgE to prevent IgE from binding to FcεRI[4]. The main mechanisms of omalizumab action

[4] Guidelines for medical use of the Ksolar® medicinal product (LP-004376 dated July 17, 2017, amendment No. 4 dated October 23, 2020.

are the decrease in the level of free IgE and downregulation of FcεRI expression on mast cells and basophils [33–35]. The FcεRI levels decrease as a result of the degradation of free FcεRI, which us not bound to IgE, and the cancellation of IgE binding to FcεRI+ or FcεRII+ (CD23) cells (B cells, dendritic cells, eosinophils, and monocytes) [34, 36]. In one phase III study, the therapy with omalizumab led to a similar response in patients, regardless of the urticaria activity index [37]. Within 24 h after the administration of omalizumab, the control of urticaria was noted in 28% of patients (decrease in UAS7 ⩾ 90%) [38]. Evidently, this rate of symptom control can be achieved due to the capability of omalizumab to accelerate the dissociation of the IgE–FcεRI complex on the mast cell surface. In the range of physiological concentrations, omalizumab can accelerate the dissociation of the already formed IgE–FcεRI complex on the surface of mast cells and basophils, in addition to its capability to bind free IgE, which leads to the disruption of the IgE-mediated signaling cascade [38, 39]. Reduction of the release of mediators from mast cells is the next mechanism of action of omalizumab [33, 40–42]. Omalizumab can also induce eosinophil apoptosis [43].

The results of phase II clinical trials (X-CIUSITE and MYSTIQUE) proved the therapeutic efficacy of anti-IgE therapy in CSU patients and demonstrated for the first time the efficacy and safety of omalizumab in comparison with placebo [44, 45].

The results of the phase III clinical trial programs ASTERIA I, II, and GLACIAL were fundamental in the approval of omalizumab by the Food and Drug Administration and the European Medicines Agency for the treatment of CSU resistant to therapy with H_1-receptor blockers in patients aged 12 years and older and served as the basis for the registration of the drug for this indication in Russia [37, 46, 47]. In 2015, a meta-analysis of seven randomized, double-blind, placebo-controlled studies evaluating the efficacy and safety of omalizumab, which included 1312 CSU patients, was conducted and published. This meta-analysis provided high-quality evidence for the efficacy and safety of omalizumab in these patients and recommended a treatment dose of 300 mg every 4 weeks. The frequency and type of adverse events were similar in the treatment with omalizumab and with placebo [48]. According to the results of a meta-analysis of studies of real clinical practice (67 observational studies of omalizumab therapy in adolescents and adults with CSU) published in 2019, reliable and clinically significant changes in the activity index (severity) of urticaria were obtained per week according to the UAS7 scale (−25.6; 95% confidence interval (CI): −28.2 to −23.0; $p < 0.001$). The overall complete and partial response to omalizumab therapy was approximately 90% (72.2% of patients achieved 0 points on UAS7; 95% CI: 66.1–78.3, $p < 0.001$; 45 studies, 1158 patients). Omalizumab improved the quality of life of CSU patients assessed by the CU Quality of Life Questionnaire (−42.3; −18.9 to −65.8; $p < 0.001$; 70 patients). The incidence of adverse events was 4% (95% CI: 1.0–7.0, $p < 0.001$; 47 studies, 1314 patients). The efficacy and safety of omalizumab in

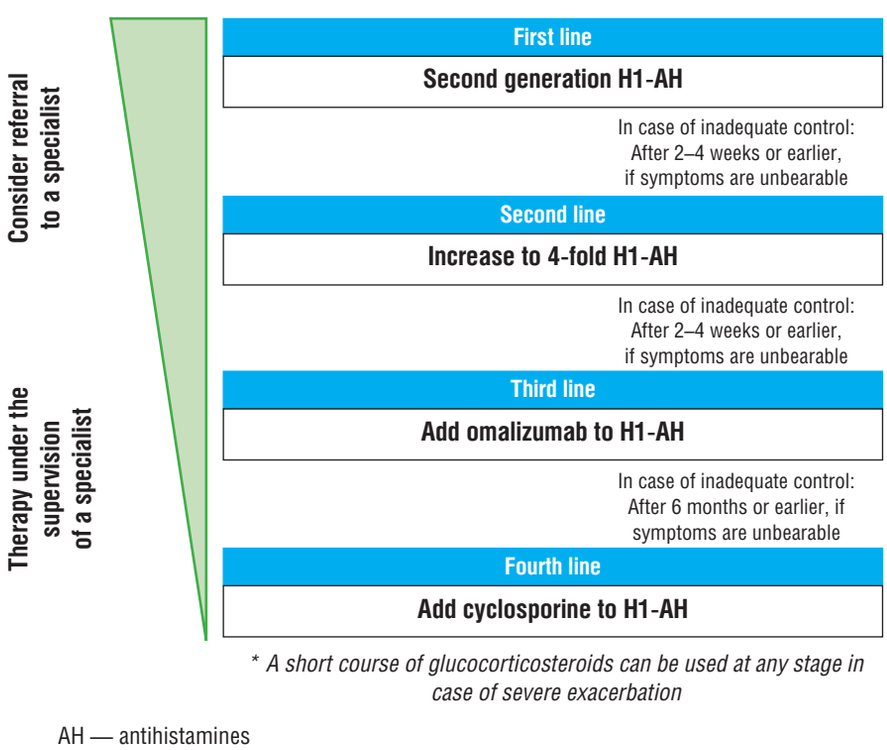

Fig. 5. Algorithm for drug treatment of patients with chronic urticaria [4].

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the treatment of CSU under conditions of daily clinical practice have been demonstrated, and they correspond to or exceed the results obtained in randomized clinical trials [49].

The characteristics of the clinical response to omalizumab include the response rate (early if up to 4 weeks inclusive; late if 5 to 24 weeks). In this regard, the recommended starting duration of omalizumab therapy is 6 months. Thus, if omalizumab treatment is discontinued early, potential responses to the drug may be missed [4, 50]. According to our own data, 88.8% of patients achieved the effect after the first injection of omalizumab (data obtained as a result of medical practice, provided by I.V. Danilycheva, Chief Researcher, Department of Allergology, Institute of Immunology). The optimal duration of omalizumab therapy has not been established. Experts recommend the assessment of the patient's condition every 3 months. Rapid withdrawal of the drug can lead to the loss of control and recurrence of CSU. According to the XTEND-CIU study, the long-term therapy with omalizumab for 48 weeks led to a significantly stable improvement in the quality of life of patients, as assessed by the Dermatology Index of Quality of Life. Compared with other randomized clinical trials, high percentages of well-controlled patients (73%) and patients with total control of CSU were observed based on their UAS7 0 (52%) at week 24 of therapy, with maintenance of a controlled course at week 48 of treatment [51].

A certain group of factors indicate the need for long-term treatment with omalizumab; these factors include concomitant angioedema, concomitant inducible urticaria, the lack of complete control of CSU symptoms after 6 months of starting therapy, a high initial score (28–42) on the UAS7 scale, and slow response to starting therapy [4, 52]. Omalizumab therapy improves the quality of life of patients with CSU and concomitant angioedema significantly due to a significant and clinically meaningful decrease in their amount and activity (severity) compared with the placebo group. This effect was demonstrated in a multicenter, randomized, placebo-controlled X-ACT study with a 28-week treatment period with omalizumab [53]. The aspects of the management of patients with CSU and concomitant angioedemas, including those with the clinical phenotype of CSU manifested only by isolated angioedemas, were presented in the speech by E.A. Latysheva, MD, PhD.

Currently, an evidence indicates the possibility of increasing the therapeutic dose of omalizumab to 450 or 600 mg for the treatment of CSU in the case of insufficient clinical response to the standard dose of the drug. A review of data from real-life clinical trials highlights the evidence that the increase in the dose of omalizumab is associated with a complete response rate in 60% of CSU patients with insufficient response to the standard dose of the drug. This approach may be a safe and effective strategy for the use of omalizumab in a single cohort of patients [54].

The issue of therapy discontinuation due to the achievement of disease remission is relevant. No protocols have been approved for omalizumab withdrawal. Approaches have been proposed to consider to the simultaneous complete withdrawal of the drug; such approaches include the increase in the interval of omalizumab administration, reduction of the dose of omalizumab, and increase in the interval of drug administration [55]. No generally accepted definition exists for CSU remission. Patients who have no symptoms of CSU (UAS7 0 points), provided that they have not taken any medications for more than 6 months, can be referred to as the group of patients with complete remission [56].

Topical issues of safety of genetically engineered biological therapy were highlighted in the report of E.V. Kozhinova, Ph.D. The lecturer presented information on the aspects of a detailed assessment of the safety of genetically engineered biological therapy at the preclinical and all stages of clinical trials and post-registration use of the drug. She emphasized the prospects for mandatory full submission of information on the safety of biological products in publicly available Internet sources for medical practitioners. Omalizumab has been proven safe in randomized clinical trials and in real-life clinical practice. The cumulative experience of using omalizumab in patients with atopic bronchial asthma and chronic spontaneous and induced urticaria is more than 1,300,000 patient years [57].

During the educational event, I.V. Danilycheva, Ph.D. touched upon the topic of new frontiers in CU therapy. Over the past several years, a significant number of articles have been published, focusing on the development of new approaches and molecules aimed at regulating the release of mediators from effector cells in CU. Experts and researchers focus on the membrane receptors expressed by mast cells and basophils and intracellular signaling molecules [13].

Possible effects on the mast cell include the following:

1. Suppression of signals of activation and proliferation of mast cells.

Suppression of signals of activation and proliferation of mast cells can be achieved by blocking the effect on FcεRI, thymic stromal lymphopoietin receptors, KIT (stem cell factor), IL-4 and IL-5, C5a, MRGPRX2, and chemoattractant molecule homologous to the receptors expressed by Th2 lymphocytes [58]. Clinical trials are currently being performed to evaluate the efficacy and safety of the ligelizumab molecule (ClinicalTrials.gov). The second-generation monoclonal anti-IgE antibody, ligelizumab (QGE031), can bind with high affinity to the Cε3 domain of free IgE. Compared with omalizumab, ligelizumab has 40–50 times greater affinity for IgE *in vitro* and demonstrates 6–9 times more suppression of allergen-induced skin prick tests. This action provides a stronger and more prolonged binding of free IgE than omalizumab [59]. Ligelizumab demonstrates preferential inhibition of IgE binding to FcεRI but is less effective in

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inhibiting IgE:CD23 (FcεRII) interactions compared with omalizumab [60].

2. Inhibition/suppression of intracellular signals of activation and degranulation of mast cells.

The inhibition/suppression of intracellular signals of activation and degranulation of mast cells can be mediated by blocking Bruton tyrosine kinase (BTK) and spleen tyrosine kinase. BTK is associated with the activation of the B-cell antigen receptor (BCR). Therefore, the inhibition of BCR can lead to a decrease in the secretion or production of antibodies, including IgE, by plasma cells. In addition, BTK is present in mast cells. As part of a phase II clinical study, the efficacy and safety of remibrutinib molecule (LOU064), a highly selective covalent inhibitor of BTK, is being studied in CSU patients. Remibrutinib can penetrate into the mast cell and bind to BTK, suppressing the downstream cascade of signals from FcεRI and leading to the activation and release of mediators, including histamine, cytokines, and chemokines [61].

3. Inhibition of mast cells by binding to inhibitory receptors.

Siglec-8, CD200R, and CD300 receptors can be targets for this effect. Siglec-8 is expressed on eosinophils, mast cells, and to a lesser extent, basophils. Siglec-8 is also an inhibitory immunoregulatory receptor. The binding of this receptor induces eosinophil apoptosis. In mast cells, Siglec-8 binding does not induce apoptosis but inhibits FcεRIα-mediated calcium entry and the release of prostaglandin D2 and histamine [62, 63]. A therapeutic monoclonal antibody that is targeted at Siglec-8, antolimab (AK002), has been developed. Currently, a phase IIa study of this promising drug on patients with symptomatic dermographism and cholinergic urticaria is being completed.

A number of molecules that act on the main pathways for mast cell activation are in various phases of clinical trials (ClinicalTrials.gov**)**. Although not all potential molecules are approved for the treatment of CU patients, several will be able to solve the problem of treating this difficult category of patients.

Practical Experience

The main part of the educational program was devoted to the presentation of clinical cases of patients from the points of view of the differential diagnostics of CSU and disease therapy. Experts (Latysheva E.A., MD, PhD, I.V. Danilycheva, Ph.D., K.S. Pavlova, Ph.D., O.G. Elisyutina, MD, PhD, and Nazarova E.V., Ph.D.) demonstrated and analyzed clinical cases from their own practice, along with young employees of the Institute of Immunology (I.V. Dorofeeva, A.V. Primak, and I.A. Manto) who presented clinical demonstrations concerning the differential diagnostics and therapy of patients with CSU and urticarial vasculitis, an autoinflammatory disease, and with spontaneous histaminergic or hereditary angioedema.

The Head of GA²LEN UCARE Center and Chief Researcher, I.V. Danilycheva, Ph.D., presented her own experience on anti-IgE therapy for CSU patients to the audience. In particular, she demonstrated a developed approximate algorithm for the treatment of CSU with omalizumab. The initial course of therapy includes subcutaneous administration of 300 mg omalizumab once per 4 weeks for 6 months. After 3 months from the start of therapy, the condition is preliminary assessed (UAS7, control of additional therapy). For "fast complete responders," the reduction and withdrawal of the second-generation H_1-AH are possible. For those who took GCSs before the start of therapy with omalizumab, an attempt is made to reduce the dose and withdraw GCSs. For "fast incomplete responders," putative "late" responders, and "non-responders," an increased dose of the second-generation H_1-AH is insisted, and an attempt is made to reduce the dose and cancel GCS for those who took GCSs before the start of the omalizumab therapy. In the case of severe exacerbations of urticaria, short courses of GCS are recommended. If the symptoms are intolerable, or large doses of GCSs are required to stop the exacerbation, the patient should be transferred to the fourth line of therapy. These patients should be reexamined in accordance with an expanded scheme with a skin biopsy study to rule out urticarial vasculitis. After 6 months of therapy with omalizumab, the condition is re-assessed (UAS7, control of adjunctive therapy). For "complete responders" not taking adjunctive therapy, an increase in the interval until the appearance of eruptions, a dose reduction to 150 mg, or both is recommended. The interval duration is established empirically. The appearance of the first symptoms of urticaria is a signal to continue the therapy. The absence of eruptions within 6 months can be considered a remission of CSU. In the case of impossibility to implement a new scheme, experts recommend returning to the original scheme and continuing the treatment for another 6 months. For "incomplete responders," continued therapy with omalizumab and increased dose of H_1-AH are suggested. For "non-responders," a transfer to the stage 4 of therapy is proposed. Further, every 3–6 months, the condition should be monitored in accordance with a similar scheme. The duration of omalizumab therapy is not determined and is determined by the clinical situation (I.V. Danilycheva, own data).

During the event, the audience had the opportunity to ask questions and share their own experiences. The online training program developed showed the effectiveness of this style of material presentation to the interested listeners who became active participants in the event, answered the test questions perfectly, and gave positive responses.

Conclusion

During the program, trainees had the opportunity to ask questions and share their own experiences. The experience of conducting this training program demonstrated the effectiveness of this style of presenting the material

to interested trainees who became active participants in the program, answered the test questions perfectly, and gave positive responses.

Additional information

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AUTHORS INFO

Corresponding author
Inna V. Danilycheva, MD, Cand. Sci. (Med.),
address: 24, Kashirskoye shosse, Moscow, 115522, Russia; ORCID: http://orcid.org/0000-0002-8279-2173;
eLibrary SPIN: 4547-3948; e-mail: ivdanilycheva@mail.ru

Natalia I. Ilyina, MD, Dr. Sci. (Med.), Professor;
ORCID: https://orcid.org/0000-0002-3556-969X;
eLibrary SPIN: 6715-5650; e-mail: instimmun@yandex.ru

Irina V. Dorofeeva, MD;
ORCID: https://orcid.org/0000-0002-4423-1797;
e-mail: idorofeeva1@gmail.com

Olga G. Elisyutina, MD, Dr. Sci. (Med.);
ORCID: https://orcid.org/0000-0002-4609-2591;
eLibrary SPIN: 9567-1894; e-mail: el-olga@yandex.ru

Oksana M. Kurbacheva, MD, Dr. Sci. (Med.), Professor;
ORCID: http://orcid.org/0000-0003-3250-0694;
eLibrary SPIN: 5698-6436; e-mail:kurbacheva@gmail.com

Elena A. Latysheva, MD, Dr. Sci. (Med.);
ORCID: http://orcid.org/0000-0002-1606-205X;
eLibrary SPIN: 2063-7973; e-mail: ealat@mail.ru

ОБ АВТОРАХ

Автор, ответственный за переписку:
Данилычева Инна Владимировна, к.м.н.;
адрес: Россия, 115522, Москва, Каширское шоссе, д. 24; ORCID: http://orcid.org/0000-0002-8279-2173;
eLibrary SPIN: 4547-3948; e-mail: ivdanilycheva@mail.ru

Соавторы:
Ильина Наталия Ивановна, д.м.н., профессор;
ORCID: https://orcid.org/0000-0002-3556-969X;
eLibrary SPIN: 6715-5650; e-mail: instimmun@yandex.ru

Дорофеева Ирина Владимировна;
ORCID: https://orcid.org/0000-0002-4423-1797;
e-mail: idorofeeva1@gmail.com

Елисютина Ольга Гурьевна, д.м.н.;
ORCID: https://orcid.org/0000-0002-4609-2591;
eLibrary SPIN: 9567-1894; e-mail: el-olga@yandex.ru

Курбачева Оксана Михайловна, д.м.н., профессор;
ORCID: http://orcid.org/0000-0003-3250-0694;
eLibrary SPIN: 5698-6436; e-mail:kurbacheva@gmail.com

Латышева Елена Александровна, д.м.н.;
ORCID: http://orcid.org/0000-0002-1606-205X;
eLibrary SPIN: 2063-7973; e-mail: ealat@mail.ru

DOI: https://doi.org/10.36691/RJA1425

Loliana S. Litvin, MD, Cand. Sci. (Med.);
ORCID: http://orcid.org/0000-0002-2229-1078;
eLibrary SPIN: 6105-1370; e-mail: loliana.litvin@novartis.com

Irina A. Manto, MD, Cand. Sci. (Med.);
ORCID: http://orcid.org/0000-0001-6432-394X;
eLibrary SPIN: 7944-5159; e-mail: irina.manto@yandex.ru

Evgeniya V. Nazarova, MD, Cand. Sci. (Med.);
ORCID: http://orcid.org/0000-0003-0380-6205;
eLibrary SPIN: 4788-7407; e-mail: evallergo@yandex.ru

Ksenia S. Pavlova, MD, Cand. Sci. (Med.);
ORCID: http://orcid.org/0000-0002-4164-4094;
eLibrary SPIN: 7593-0838; e-mail: ksenimedical@gmail.com

Anastasia S. Primak; MD;
ORCID: http://orcid.org/0000-0003-1309-5101;
e-mail: soulcreek.94@mail.ru

Elena S. Fedenko, MD, Dr. Sci. (Med.), Professor;
ORCID: https://orcid.org/0000-0003-3358-5087;
eLibrary SPIN: 5012-7242; e-mail: efedks@gmail.com

Rosalia V. Schubelko, MD, Cand. Sci. (Med.);
ORCID: https://orcid.org/0000-0001-6993-9831;
eLibrary SPIN: 4553-3234; e-mail: spapharia@gmail.com

Литвин Лолиана Стефановна, к.м.н.;
ORCID: http://orcid.org/0000-0002-2229-1078;
eLibrary SPIN: 6105-1370; e-mail: loliana.litvin@novartis.com

Манто Ирина Александровна, к.м.н.;
ORCID: http://orcid.org/0000-0001-6432-394X;
eLibrary SPIN:7944-5159; e-mail: irina.manto@yandex.ru

Назарова Евгения Валерьевна, к.м.н.;
ORCID: http://orcid.org/0000-0003-0380-6205;
eLibrary SPIN: 4788-7407; e-mail: evallergo@yandex.ru

Павлова Ксения Сергеевна, к.м.н.;
ORCID: http://orcid.org/0000-0002-4164-4094;
eLibrary SPIN: 7593-0838; e-mail: ksenimedical@gmail.com

Примак Анастасия Станиславовна;
ORCID: http://orcid.org/0000-0003-1309-5101;
e-mail: soulcreek.94@mail.ru

Феденко Елена Сергеевна, д.м.н., профессор;
ORCID: https://orcid.org/0000-0003-3358-5087;
eLibrary SPIN: 5012-7242; e-mail: efedks@gmail.com

Щубелко Розалия Васильевна, к.м.н.;
ORCID: https://orcid.org/0000-0001-6993-9831;
eLibrary SPIN: 4553-3234; e-mail: spapharia@gmail.com