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Case report of the dupilumab applying in atopic dermatitis child

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ABSTRACT

In recent years, there has been a clear trend towards an increase in the number of patients with severe atopic dermatitis. In most cases, patients are dissatisfied with the previous therapy, which requires hospital treatment to relieve acute manifestations of atopic dermatitis and the selection of pharmacological agents aimed at achieving long-term control under the of the disease symptoms

The article presents the features of the atopic dermatitis therapy of at the present stage, the experience of using the new biological drug dupilumab in a 7-year-old child.

***Keywords*:** T2 inflammation; atopic dermatitis; children; biological therapy; dupilumab

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Клинический случай применения препарата дупилумаб у ребёнка с атопическим дерматитом

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АННОТАЦИЯ

В последние годы отмечена чёткая тенденция к увеличению числа больных атопическим дерматитом тяжёлого течения. В большинстве случаев у пациентов отмечается неудовлетворённость предшествующей терапией, что требует стационарного лечения для купирования острых проявлений атопического дерматита и подбора фармакологических средств, направленных на достижение долгосрочного контроля над симптомами болезни. В статье представлены особенности терапии атопического дерматита на современном этапе, опыт использования нового биологического препарата дупилумаб у ребёнка 7 лет.

Ключевые слова: Т2-воспаление; атопический дерматит; детский возраст; биологическая терапия; дупилумаб

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Background

Atopic dermatitis (AtD) is a recurrent systemic chronic inflammatory skin disease associated with pruritus and worsened quality of life. The incidence of AtD ranges from 2% to 10% in adults and from 15% to 30% in children [1-3]. Multiple clinical observations indicate that there are different AtD phenotypes determining different effectiveness and different responses to standard treatment options associated with complex immunological mechanisms and a variety of causal factors [4-7].

Standard treatment for AtD includes a comprehensive approach involving elimination measures, hypoallergenic diet, emollients, topical corticosteroids, calcineurin inhibitors, antihistamines, and phototherapy. According to clinical guidelines, patients with severe AtD should receive systemic immunosuppressive

therapy. Such medications as cyclosporine A, azathioprine, methotrexate, etc., have a pronounced immunosuppressive or cytostatic effect that can suppress the proliferation of T-lymphocytes and the release of anti-inflammatory cytokines. The effect of immunosuppressive drugs is not direct so their long-term use may result in a number of adverse effects including an increase in blood creatinine levels and the development of hypertension. The available clinical data provides evidence of a high frequency of cases where patients refuse to continue taking these drugs because of gastrointestinal and neurological disorders: in particular, 38%, 41% and 56% of patients refused treatment with cyclosporine A, methotrexate and tacrolimus, respectively [8]. In this regard, the studies of effectiveness and safety of a number of biologics affecting certain targets, such as interleukin (IL) IL-1R, IL-2, IL-4, IL-5 receptor antagonists, tumor necrosis factor alpha (TNF-α) and their receptor inhibitors [9-14], are ongoing.

One of new methods of treatment for allergic disorders in children and adults is biologic therapy with monoclonal antibodies [15]. The introduction of this method of treatment into clinical practice was preceded by progress in understanding the cellular and molecular mechanisms of inflammation and immune response regulation in allergic skin diseases and lung disorders [16–18].

The mechanisms of immune response of Type 2 (T2) inflammation in different organs have been actively studied in recent years. In particular, asthma and AtD are disorders which development may be considered as a result of Type 2 inflammation. The main mediators of T2- inflammation are IL-4, IL-13, IL-5, IL-9 that are secreted and produced by CD4+ Th2-cells as well as Group 2 innate lymphoid cells (ILC2s) under the influence of various allergens/antigens, viruses, bacteria and toxins.

The leading role of IL-4 and IL-13 in the development of Type 2 mediated inflammation may be associated with the activation of IL-4 and IL-13 receptor signaling pathways, T- and B-lymphocytes, mast cells, eosinophils and macrophages activity and the production of IgE antibodies, followed by the release of histamine, leukotrienes, prostaglandins, eotaxin, eicosanoids, and chemokines [19, 20].It is also known that IL-5 acts on the activation and survival of eosinophils, IL-9 increases the production of IgE antibodies and eosinophils. These cytokines can directly induce the production of cytokines by Th2 cells and ILC2s, and directly activate mast cells. Thymic stromal lymphopoietin activates Th0 and dendritic cells, and promotes B cell proliferation [21, 22].

Five biologics have been recently developed targeting inhibition of Type 2 inflammation: monoclonal anti-IgE, anti-IL-5 and IL-5 receptor antibodies, as well as monoclonal anti-IL-4Rα receptor antibodies.Thus, omalizumab inhibits the binding of IgE antibodies to high-affinity IgE receptors (FcεRI) located on the surface of mast cells. The effect of mepolizumab and reslizumab is aimed at blocking IL-5, and that of benralizumab at the IL-5 receptor subunit. Dupilumab inhibits the effects of IL-4 and IL-13 by specifically binding to IL-4Ra, a common subunit of the IL-4 and IL-13 heterodimeric receptors [23, 24].

The actions of biologics are associated with blockade of certain classes of cytokines and signaling pathways which lead to a decrease in many markers of T2-inflammation, such as IgE, pro-inflammatory cytokines and chemokines (eotaxin; thymus and activation regulated chemokine), periostin, nitric oxide levels. The use of targeted biologics opens new horizons in the treatment of allergic diseases.

Dupilumab is of special interest for the treatment of moderate-to-severe AtD patients aged 6 years and older who demonstrate inadequate response to topical drugs, or patients for whom these drugs are not recommended, or patients with moderate-to-severe asthma aged 12 years or older with an eosinophilic phenotype, or patients with OCS-dependent asthma treated with systemic glucocorticoids [25, 26].

Dupilumab is a recombinant human monoclonal antibody (IgG4) that blocks IL-4 signaling through type I receptors (IL-4Ra/yc) and common IL-4 and IL-13 signaling through type II receptors (IL-4Ra/IL-13Ra).

To evaluate the effectiveness and safety of dupilumab in AtD, a 9-pont GRADE methodology (Grading of Recommendations Assessment, Development and Evaluation) has been used to determine critically important (7-9), important (4-6) and insignificant results (1-3). Critical results included statistically significant changes in SCORAD score (Severity Scoring of Atopic Dermatitis — assessment of the severity of AtD symptoms), EASI-50 and EASI-75 (Eczema Area and Severity Index score decrease by 50 and 70%, respectively), as well as on the scales of pruritus and frequency of adverse events (safety parameters) associated with the use of the drug. Important parameters included overall assessment by the investigators, the use of rescue drugs, pain, sleep disorders, symptoms of anxiety and depression, quality of life (QoL). The quality of the evidence for each result was assessed as high, moderate, low or very low [25, 26].The effectiveness and safety of dupilumab were confirmed by a decrease in the AtD severity, a decrease in the requirement for basic and symptomatic therapy, and improvement in the quality of life in adults, adolescents aged 12-17 years, and children aged 6-11 years.

The effectiveness and safety studies of dupilumab were started in Department of Allergology and Dietetics of FSBRI "Federal Research Center for Nutrition and Biotechnology" in September 2020. Currently, the drug is being used in 20 pediatric patients aged 6 to 17 years.

This article describes a case report of a 7-year-old with severe AtD resistant to conventional therapy.

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Clinical case

S., a girl aged 7 years (born in 2013), was admitted to Department of Allergology and Dietetics complaining of pronounced pruritus, involvement of large skin areas on the face, neck, torso, upper and lower extremities (Fig. 1–3).

History of the present illness, patient's life history. Family medical history has records of allergic rhinitis in the patient's father and her paternal aunt. The girl was born from her mother's third pregnancy, which was unremarkable and ended with spontaneous term delivery. Birth weight: 3880 g; length: 51 cm; Apgar score 8/9. Breastfeeding was initiated immediately after the delivery. Breastfeeding was stopped when the child was 2.5 years old. At the age of 3 months, having received a Malyutka formula in addition to breastmilk, the child developed first skin lesions on her face and torso. These lesions included areas of hyperemia, exudation and were accompanied by pronounced itching. Initiation of complementary feeding at the age of 6 months was accompanied by an increased number of skin lesions. The child was diagnosed with atopic dermatitis and was followed up by a pediatrician. Treatment included antihistamines and topical glucocorticoids. At the age of 1 year, the child had a Staphylococcus skin infection and was treated with antimicrobial drugs. At the age of 2.5 years, there was involvement of the upper and lower extremities and increased skin itching; the disease became severe and continuously recurrent. No allergist consultations were sought. The girl was followed up by a dermatologist at a local clinic; no outpatient allergy testing was conducted. Following a trip to Altai, there was a disease remission, which lasted for a year. In February 2020, the skin lesions became generalized with increased severity of pruritus and the development of sleep disorders. At the age of 5 years, the patient started having complaints of sneezing, itching, redness of the eyes, itchy nose and congestion. She was examined by an ENT specialist at a local clinic and was diagnosed with pollen disease and allergic rhinoconjunctivitis. Symptomatic therapy was initiated (antihistamines, nasal glucocorticoids) and resulted in a good response.

In March 2020, the girl was admitted to the hospital, where for the first time she underwent a clinical and immunological examination which revealed an increase in the level of specific IgE antibodies to allergens of birch, meadow grasses, cow's milk protein, egg (yolk and protein), peas, pork, lamb, carrot. The total IgE level was 7,864 IU/mL (reference range <100), the peripheral blood eosinophil count was 15.8%, the absolute amount was 0.79×10^9/L. The results of testing for parasitic infections were negative. Prescribed treatment (strict and long-term dairy-free diet, ketotifen, topical and systemic glucocorticoids (dexamethasone) for 7 days, methylprednisolone aceponate, betametasone + gentamycin + clotrimazole, hydrocortisone, and a skin care agent [dexpanthenol]) did not result in a significant response. Treatment discontinuation resulted in an AtD exacerbation. The child's mother refused to start a course of systemic therapy with cyclosporin.

For decision-making regarding the feasibility of biologics targeted therapy, the patient was referred to Department of Allergology and Dietetics of FSBRI "Federal Research Center for Nutrition and Biotechnology".

The results of physical examination, laboratory tests and investigations on admission to Department of Allergology and Dietetics of FSBRI "Federal Research Center for Nutrition and Biotechnology".

Physical examination results. At the time of examination, the patient's condition was severe because of the primary disease. The patient's well-being was impaired

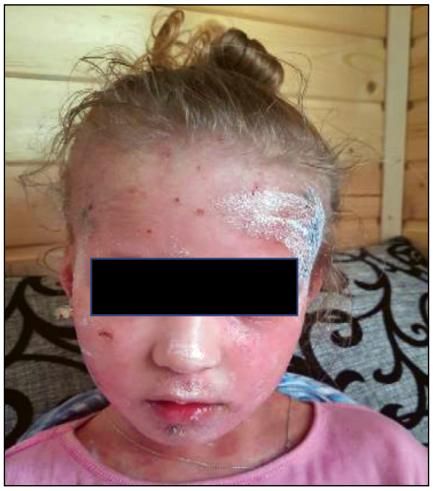

Fig. 1. Patient's S facial skin., 7 years old, before treatment: intense hyperemia, pronounced dryness of the skin, multiple papular rashes, crusts, excoriation.

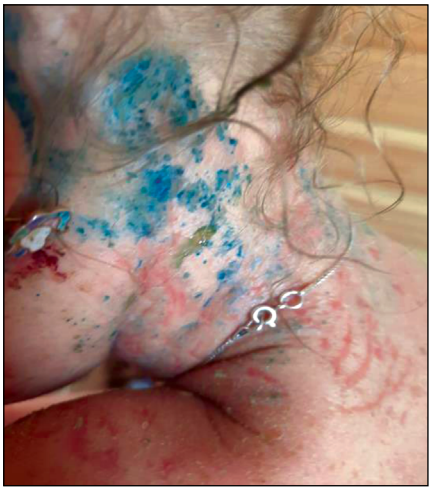

Fig. 2. Patient's S neck skin., 7 years old, before treatment: intense hyperemia, pronounced dryness of the skin, multiple papular rashes, crusts, excoriation.

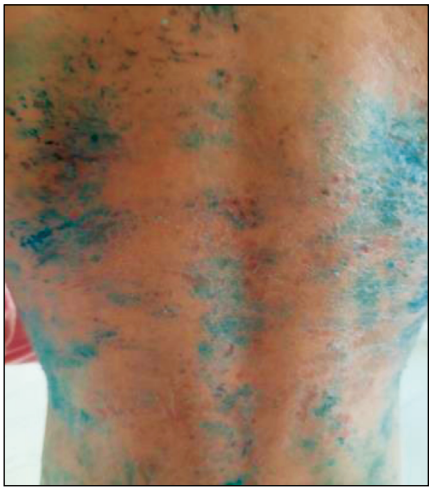

Fig. 3. Patient's S skin of the back., 7 years old, before treatment: intense hyperemia, pronounced dryness of the skin, multiple papular rashes, crusts, excoriation.

because of significant pruritus and sleep disorder. Body weight 19 kg, height 114 cm, body mass index 14.6; Z-score = 0.55 kg/m^2. There is skin hyperemia and multiple erythematous-squamous skin rash on the skin of the torso, areas of lichenification on the extensor areas of the upper and lower extremities, hemorrhagic crusts, multiple excoriations. Blood pressure 110/65 mm Hg; nasal obstruction. Auscultation reveals rough breath sounds without any rhonchi. Respiratory rate = 20 breaths per minute; oxygen saturation (SpO_2) 97%. Heart sounds are rhythmic, no murmurs, heart rate is 65 bpm; abdominal palpation is painless and unremarkable. SCORAD score = 60 points.

Allergy testing. There was an increase in the serum levels of allergen-specific IgE antibodies to the allergens of apple (63.8 IU/mL), pear (10.4 IU/mL), plum (1.78 IU/mL), lamb (2.09 IU/mL), chicken egg (1.525), buckwheat (0.385), cat (27 IU/mL), nFel d 1 (125 IU/mL at a norm of 0-0.35) and pollen allergens (Table 1).

The patient was found to have low blood levels of vitamin D (25-hydroxy vitamin D) - 21.35 ng/mL (reference range 30-100).

The results of testing for infestations (IgM and IgG to Toxacara canis, Ascaris, Giardia lamblia) and herpes infections (Epstein-Barr virus, Cytomegalovirus, herpes virus type 5, herpes simplex types 1 and 2) were negative.

Complete blood count, metabolic panel and urinalysis results were unremarkable.

The results of thyroid function tests (free T3, free T4, thyroid stimulating hormone), tests for thyroid peroxidase and thyroglobulin antibodies results were within the normal ranges.

Investigations. Abdominal and renal ultrasonography did not reveal any structural abnormalities. Thyroid ultrasound showed signs of thyroid enlargement and signs of autoimmune thyroiditis. The patient was examined by an endocrinologist and was diagnosed with grade 1 endemic goiter, euthyroidism. Vitamin D deficiency.

Clinical diagnosis: Atopic dermatitis, extensive, severe, continuously recurrent state of disease, resistant to conventional therapy. Hay fever: allergic rhinitis, allergic conjunctivitis, remission. Sensitization to the allergens of pollen of trees, grass and weeds. Food allergy. Grade 1 endemic goiter, euthyroidism. Vitamin D deficiency.

Taking into account inadequate response to AtD continuous treatment with antihistamines cetirizine, Suprastin, topical glucocorticoids (methylprednisolone aceponate, betamethasone + gentamicin + clotrimazole, hydrocortisone) and severe, persistent, continuously recurrent state of disease, the decision was made to initiate targeted biologic therapy with dupilumab at the starting dose of 600 mg (two 300 mg injections) followed by administration of 300 mg every 4 weeks.

Dupilumab treatment outcomes. Two weeks after the first injection, the patient noticed a significant improvement of her well-being regarding reduced itch intensity and sleep improvement. Treatment resulted in a significant improvement of AtD-related clinical symptoms. SCORAD score was 27 points after 4 weeks of treatment.

2.5 months after the treatment initiation, the severity of the patient's pruritus significantly decreased and she started having better sleep. SCORAD score was 16 points (see Fig. 4).

No AtD exacerbations were observed during a three-month course of dupilumab administration. The child continued following a hypoallergenic diet and using skin care products (dexpanthenol). Her nasal obstruction became less severe. Topical glucocorticoids (mometasone furoate) that had been used for the treatment of seasonal allergic rhinitis were discontinued. It is planned to continue dupilumab treatment at a dose of 300 mg SC once every 4 weeks for a long period of time.

No dupilumab-related adverse events have been observed.

Dupilumab treatment resulted in changes in complete blood count and serum immunoglobulin E, A, M and G level changes (see Table 2, 3). Total IgE serum level decreased (from 6,948 to 1,965 IU/mL).

Thus, the use of dupilumab resulted in a significant improvement in the skin condition and a decrease in

Table 1. Study of specific IgE antibodies to pollen allergens

Test	Parameter, IU/mL	
	Result	Reference range
Screening for herbal allergens No.1: Dactylis glomerata, Festuca pratensis, perennial rye grass, Phleum pratense, Poa pratensis.	36.2	0–0.35
Screening for indoor allergens: dust (*D. Pteronyssinus*, *D. Farinae*), cockroach	0.112	0–0.35
Screening for herbal allergens: Ambrosia elatior, Artemisia vulgaris, Leucanthemum, dandelion, European goldenrod	2.91	0–0.35
Screening for late-flowering trees allergens: Acer negundo, Betula verrucosa, oak, Fagus grandifolia, walnut	0.284	0–0.35
Screening of allergens of early-flowering trees: Alnus incana, hazel, elm, willow, poplar	51.3	0–0.35

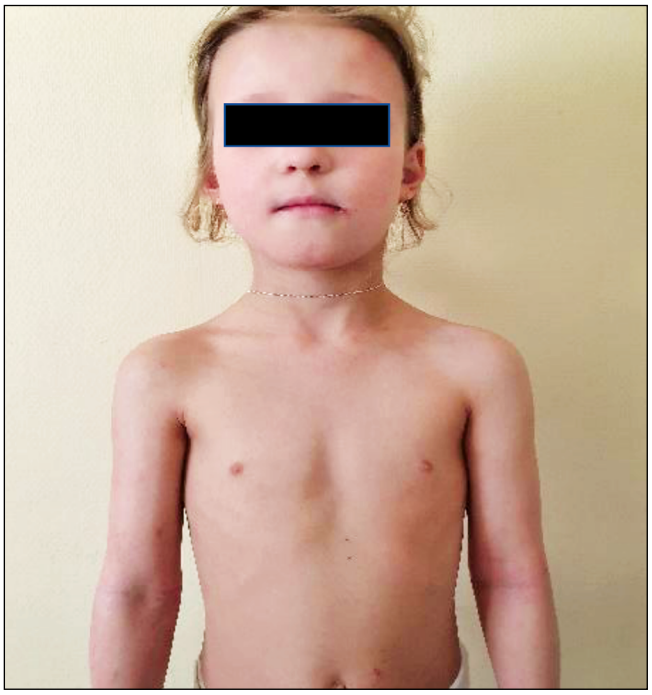

Fig. 4. Patient's S skin of the trunk., 7 years old, after the 3rd injection of dupilumab: the intensity of hyperemia, the severity of dry skin, peeling, the number of papular rashes, excoriation significantly decreased.

skin itch in a child with severe AtD. At first, the patient demonstrated an increase in her eosinophil count (both absolute and relative); however, this parameter was within the normal range (10.2% / 0.7 x 10^9/L) after the 4th injection.

Discussion

This case report demonstrates the effectiveness of the new biologic dupilumab in a 7-year-old child suffering from severe continuously recurrent AtD resistant to standard therapy. Three-month treatment with dupilumab allowed to achieve control over the AtD symptoms, prevent the development of serious corticosteroid-related adverse reactions and significantly improve the quality of life of the patient and her parents.

Conclusion

Thus, the analysis of published literature data and the results of the conducted studies shows that it is important to ensure an individual approach to AtD treatment that takes into account the specifics of the disease course, its severity, and response to therapy. Determination of relevant specific biomarkers of AtD is a promising field of research as it will allow to select patients who need therapy with certain drugs.

Table 2. Complete blood count results before and after 1st and 3rd dupilumab injections

Parameter	Reference range	Before treatment	After the first injection	After the third injection
Hemoglobin, g/L	114–147	129.1	124	118
Red blood cells, 10^{12}/L	4.09–5.33	4.927	4.793	4.577
Hematocrit, %	35–43	40.87	39.85	37.24
WBC, 10^9/L	3.9–11.5	7.54	6.72	6.71
Neutrophils, %/10^9	38–60/1.1–5.8	45.2/3.4	38.4/2.6	32.8/2.2
Lymphocytes, %/10^9	33–50/0.9–5.0	32.5/2.5	35.9/2.4	37.9/2.5
Monocytes, %/10^9	5–12.5/0.37–1.26	7.6/0.6	7.6/0.5	6.4/0.4
Eosinophils, %/10^9	0–5/0.02–0.65	14.3/1.1	17.5/1.2	21.8/1.5
Platelets, 10^9/L	175–436	371.9	390	334.8/7.86
Erythrocyte sedimentation rate, mm/h	2–20	5	8	2

Table 3. Immunoglobulin E, A, M, G levels in serum before and after the 1st and 3rd dupilumab injections

Parameter	Reference range	Before treatment	After the first injection	After the third injection
Total IgE, IU/mL	0–100	6948	5010	1965
IgM, g/L	0.34–2.5	1.15	1.25	0.97
IgG, g/L	6.8–16.5	10.45	11.19	9.58
IgA, g/L	0.7–4.06	2.21	2.22	1.85

The study of dupilumab effectiveness and safety and clinical experience gained with this drug in pediatric patients with AtD give us certain hopes in achieving disease control. Dupilumab is crucial for the treatment of severe AtD since the drug allows to reduce the number of medications used and to improve patients' quality of life.

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Authors' contribution. V.A. Revyakina — concept and design of the study, writing the text; I.A. Larkova, E.D. Kuvshinova, V.A. Mukhortykh, K.S. Melnikova — collection and processing of the material; V.A. Mukhortykh — editing by. All authors made a significant contribution to the development of the concept, preparation of the article, read and approved the final version before publication.

Consent for publication. Written consent for publication of relevant medical information and photos within the manuscript was obtained from the patient's parents.

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