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New opportunities of therapy of severe atopic dermatitis

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ABSTRACT

This article presents a case of the successful use of dupilumab in a 21-year-old patient with severe atopic dermatitis, concomitant bronchial asthma, and allergic rhinitis. The patient was observed in the allergological department of the Krasnoyarsk Clinical Regional Hospital for 2 years. The disease was characterized by constant skin symptoms, frequent exacerbations, resistance to standard therapy, including systemic glucocorticosteroids and immunosuppressors. Considering the above factors, targeted therapy was started with dupilumab, registered in the Russian Federation for use in atopic dermatitis resistant to standard therapy. Against the background of biological therapy (13 injections were carried out), a stable significant decrease in skin syndrome activity was achieved (SCORAD index decreased from 72 to 9 points), and the patient's quality of life significantly improved.

Keywords: atopic dermatitis; biological therapy; dupilumab; case report

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Новые возможности терапии тяжёлого атопического дерматита

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АННОТАЦИЯ

Представлен случай успешного применения препарата дупилумаб у 21-летнего пациента с тяжёлым атопическим дерматитом, сопутствующей бронхиальной астмой и аллергическим ринитом. Пациент наблюдался в аллергологическом отделении КГБУЗ «Красноярская краевая клиническая больница» в течение 2 лет. Заболевание характеризовалось постоянными кожными симптомами, частыми обострениями, устойчивостью к стандартной терапии, в том числе системными глюкокортикоидами и иммуносупрессивными препаратами. Учитывая вышеперечисленные факторы, было принято решение о начале таргетной терапии дупилумабом, зарегистрированным в Российской Федерации для применения при атопическом дерматите, резистентном к стандартному протоколу лечения. На фоне введения препарата (13 процедур) достигнуто стойкое значимое снижение активности кожного синдрома (снижение индекса SCORAD с 72 до 9 баллов) и значительное улучшение качества жизни пациента.

Ключевые слова: атопический дерматит; биологическая терапия; дупилумаб; клинический случай

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Background

Atopic dermatitis remains a complicated issue in allergology. The incidence of this disease is up to 20% in children and 2-8% in adults [1]. There has been a 2.1-fold increase in the incidence of atopic dermatitis over the past 16 years. Severe atopic dermatitis is not a life-threatening condition, however, it seriously affects the patients' quality of life [2]. Despite the development

of new therapeutic options for severe atopic dermatitis, long-term disease control cannot be achieved so far.

In recent years, special attention has been paid to the use of genetically engineered biologics, monoclonal antibodies that inhibit the key inflammatory cytokines and their receptors [3–5]. Due to their selective effects, biologics are not associated with adverse effects that are common for conventional drugs used in the treatment of allergic diseases (i.e. disorders of carbohydrate and mineral metabolism; atrophic skin changes; suppression of hematopoiesis; secondary immunodeficiency, etc.) — glucocorticoids and immunosuppressive agents.

Currently, only one genetically engineered biologic, dupilumab, is approved in the Russian Federation for the treatment of atopic dermatitis. It is approved as treatment for patients with moderate to severe atopic dermatitis with inadequate response to topical agents in patients over 6 years of age. The mechanism of action of dupilumab is the inhibition of interleukin (IL) 4 and 13-mediated signaling pathways by its specific binding to the IL-4Ra-a subunit, which is common for the IL-4 and IL-13 receptor complexes. IL-4 and IL-13 are known to be key cytokines of T2-mediated inflammatory response that is typical for atopic disorders. Multicenter clinical studies have demonstrated the effectiveness of dupilumab in the treatment of atopic dermatitis [6-8].

Case report

A 20-year-old male patient presented to Allergy Unit of RSBHI "Krasnoyarsk Regional Clinical Hospital" complaining of generalized itchy skin rash causing a sleep disorder, intermittent nasal obstruction, episodes of sneezing and rhinorrhea when contacting with animals (dogs, cats) and in the spring during the flowering of trees. There were also episodes of difficulty with breathing.

The analysis of medical history and pediatric health records showed that the first signs of atopic dermatitis had developed during infancy with episodic involvement of large skin areas. Starting from the age of 3 years, the symptoms became mild (the skin lesions were mainly located in the area of elbow joints) and increased after consumption of large amounts of citruses or sweet dishes. At the age of 3 years, the patient started experiencing symptoms of rhinitis, conjunctivitis, difficulties with breathing when contacting with animals (a cat, a dog, or a rabbit). At the same age, the patient was diagnosed with asthma. Episodes of suffocation were rare; the patient did not receive basic asthma treatment and used salbutamol on demand. At the age of 4 years, the patient started experiencing symptoms of hay fever (rhinitis, conjunctivitis). The patient was followed up by a pediatric allergist who diagnosed sensitization to pollen (birch, wormwood) and epidermal (cat, dog, rabbit) allergens. There were signs of cross-reactivity when eating peas or almond (itching and throat discomfort) and drug intolerance (cefotaxime and penicillin caused an itchy skin rash). The patient did not have a family history of atopic diseases, nor had he any signs of infestations. The patient received therapy with antihistamines and cromones, and used short-acting beta-agonists on demand. At the age of 7 years, the patient received two courses of the allergy medicine Ruzam, which resulted in some improvement: signs of atopic dermatitis and hay fever became minimal in the spring; the patient stopped having episodes of suffocation and did not require therapy with short-acting bronchodilators. He was considered to have steady asthma remission. During the adolescence, the patient noted the development of pronounced skin manifestations in the hands, elbows and popliteal regions. Therapy with emollients and topical steroids resulted in a moderate improvement.

At the age of 18, the patient's atopic dermatitis became significantly more severe with involvement of large areas of the skin: in addition to the hands, elbows and popliteal regions, skin lesions also spread to his face, ears, neck, scalp, trunk, buttocks, thighs, and the dorsal surface of the feet. In October 2018 and November 2019, due to the exacerbation of the disease, the patient received inpatient treatment in a Clinic of Dermatology and Venereal Diseases using systemic and topical glucocorticoids, antihistamines, emollients, which resulted in incomplete brief improvement. In December 2019, due to a disease exacerbation, the patient was hospitalized to Department of Allergy of Krasnoyarsk Regional Clinical Hospital.

Results of physical examination, laboratory tests, investigations and allergy tests

On admission: erythematous squamous skin lesions on the back, abdomen, chest, shoulders, forearms, buttocks, thighs; the skin in these areas appears thickened, the skin markings are increased in some areas; the eyelids, forehead, and cheeks demonstrate a slight hyperpigmentation, hyperemia, and peeling. There is an increase in the skin markings, mild hyperemia and excoriations on the dorsal surface of the feet. SCORing of Atopic Dermatitis (SCORAD) index = 72 points, which corresponds to severe atopic dermatitis.

The peripheral lymph nodes are not enlarged. Signs of nasal obstruction. Auscultation reveals vesicular breath sounds without any rhonchi. Respiratory rate is 16 breaths per minute; blood oxygen saturation (SaO_2) 98%. Clear heart sounds, no murmurs, regular rhythm; HR = 79 bpm; BP 105/75 mm Hg.

Abdominal palpation is painless and unremarkable.

Laboratory tests showed an increased eosinophil count in the peripheral blood (12.9%; 780 cells/μL) and an increased total IgE level (482 IU/mL).

X-ray examination of the paranasal sinuses showed no abnormalities; chest X-ray exam revealed no pulmonary lesions, normal structure of the roots of the lungs and bronchovascular markings; no midline shift; well-defined and smooth contour of the diaphragm and no signs of pleural effusion.

Spirometry Baseline parameters: Forced Vital Capacity (FVC) 93.5%; Forced Expiratory Volume in first

second (FEV1) 88.8%, FEV_1/FVC 80.8%. 20 min after the use of salbutamol 400 μg: FVC 93.6%, FEV1 90.1%, FEV1/FVC 81.9%. Conclusion: pulmonary ventilation parameters are within the normal range. The bronchodilator test result is negative; FEV1 increase after the use of salbutamol 400 μg is 1.5%.

Allergy testing ImmunoCAP test confirmed the sensitization to allergens of birch, pollen of a mixture of herbs, cat and dog hair, and hazelnuts.

Treatment

The patient received a course of treatment with topical and systemic glucocorticoids (prednisolone 60 mg IV), antihistamines (loratadine 10 mg/day), and emollients. Due to weak response to therapy, such therapeutic options as a calcineurin inhibitor (tacrolimus) and immunosuppressive medications (cyclosporin 200 mg/day) were also used and produced an incomplete improvement. SCORAD index at the time of discharge was 15.3. Recommended outpatient therapy included topical therapy with mometasone furoate, tacrolimus, cyclosporin at a dose of 100 mg twice daily (daily dosage = 200 mg) with an allergist consultation once a month for the assessment of treatment response and treatment adjustment if necessary. One month after the discharge from the hospital, the cyclosporin dose was reduced to 150 mg/day, and 2 months after the discharge it was decreased to 100 mg/day.

Despite the combination therapy used, no steady improvement was observed, and there were persistent recurrences of atopic dermatitis. In September 2020, the patient was admitted to Allergy Unit again with severe manifestations of dermatitis (SCORAD = 64), debilitating pruritus and a sleep disorder. Taking into account the severe course of the disease, frequent exacerbations (4 exacerbations in 2020), the lack of a stable effect from conventional therapy and immunosuppressive drugs, frequent use of systemic glucocorticoids, concomitant allergic rhinitis and asthma (in remission), it was decided to use the genetically engineered drug dupilumab. As recommended in the prescribing information, the initial dose was 600 mg (two 300 mg SC injections) followed by 300 mg SC once every two weeks. No adverse drug reactions were observed.

Outcome and follow-up results

While on therapy with dupilumab (a total of 13 injections), there was clear improvement (significant regression of skin lesion and pruritus, as well as sleep normalization). SCORAD index by the 13th dosing was 9 points (see Fig. 1).

During the entire follow-up period, the patient did not have any exacerbations of allergic rhinitis or signs of nasal obstruction, and experienced no shortness of breath. The treatment was considered to be effective and was continued.

With regard to biomarkers of T2-mediated inflammation, we evaluated the peripheral blood eosinophil count before each drug dosing and the total IgE level before the drug dosing and after 8th dosing (for technical reasons). During dupilumab therapy, the eosinophil count increased reaching its peak by the 4th dosing, and then started decreasing reaching 71% of the baseline value by the 13th dosing (without reaching the normal range) (see Fig. 2). Baseline total IgE level was 482 IU/mL, and decreased to 458 IU/mL after the 8th dupilumab dosing.

Discussion

Classical manifestations of the atopic march include signs of atopic dermatitis with subsequent development of food allergy, allergic rhinitis and, finally, asthma. These disorders are due to a persistent T2-mediated immune response, the laboratory manifestations of which include peripheral blood eosinophilia and increased total immunoglobulin E level (IgE) [9]. To date, there is evidence of concomitant development of skin manifestations and airway obstruction in some patients.

In our case report, the patient demonstrated classical features of T2-dysfunction that started from the skin involvement and early development of allergic rhinitis

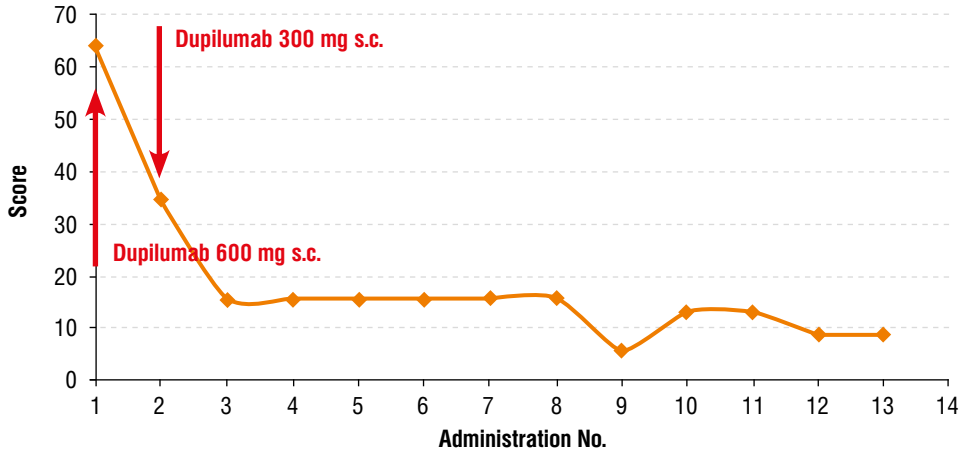

Fig. 1. Disease activity (SCORAD) against background of dupilumab use

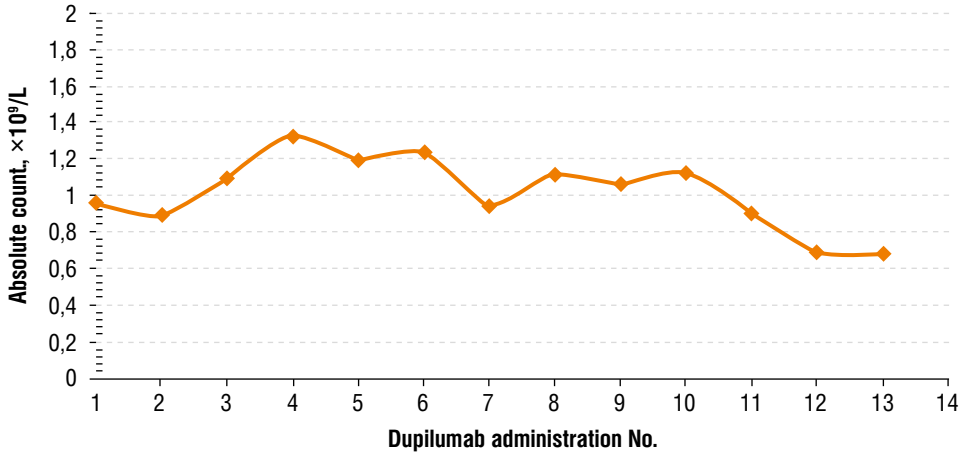

Fig. 2. Number of eosinophils in peripheral blood against background of dupilumab preparation application

and asthma. Despite the use of adequate therapy for associated allergic disorders and the patient's compliance with the recommendations on hypoallergenic lifestyle and diet, it was not possible to achieve stable control over his symptoms. Frequent recurrences of atopic dermatitis, starting from adolescence, with generalization of the skin process, accompanied by pronounced sleep disorders and a decrease in physical activity, required long-term use of not only topical, but also systemic glucocorticoids, and immunosuppressive drugs. Given the comorbidity of the disorder, the risks of asthma exacerbations in case of comorbid severe atopic dermatitis are increased. Due to the availability of the new genetically engineered drug dupilumab for the treatment of moderate to severe atopic dermatitis in patients over 6 years of age, a decision was made to use it in our patient as he had other T2-mediated allergic disorders (allergic rhinitis, atopic asthma) [6, 11, 12]. There was a significant clinical improvement even after first injections of dupilumab with no adverse drug reactions indicating a high effectiveness and safety of the drug.

Markers of T2 inflammation, the peripheral blood eosinophil count and total IgE concentration, were assessed in this case. In this case report, peripheral blood eosinophil counts were increasing while on therapy with dupilumab and reached a peak at Week 8 of treatment. They decreased later, which is consistent with the data of placebo-controlled clinical studies that also showed a transient increase in the blood eosinophil count, despite the positive clinical effect of dupilumab therapy in patients with atopic dermatitis. Studies with dupilumab in asthma patients have shown that the reduction in the severity of eosinophilic inflammation in the lungs occurs regardless of the blood eosinophil count (normal or increased), and is also associated with clinical improvement [3, 12]. A temporary increase in the blood eosinophil count may be related to the dupilumab-induced inhibition of eosinophil migration to the tissue by suppressing IL-4 and IL-13-mediated production of eotaxins and vascular cell adhesion molecule 1 (VCAM-1), while the drug does not affect the production or release of eosinophils from the bone marrow [13].

The comparison of the total IgE levels at baseline and after 16 weeks of treatment in our patient demonstrates that this parameter tended to decrease; however, its further monitoring is necessary, since it was previously shown that the decrease in total IgE, unlike other biomarkers of T2 inflammation (e.g. periostin, pro-inflammatory cytokines and thymus and activation-regulated chemokine, TARC), although slower, is by more than 70% at Week 52 of treatment, which is associated with impaired B-cell proliferation and IgE secretion as a result of IL-4 binding impairment caused by dupilumab [11, 14].

Thus, the availability of genetically engineered biologics for the treatment of atopic dermatitis expands the range of treatment options for patients with moderate to severe course of disease resistant to conventional treatment, and allows improving their quality of life, reducing the risk of adverse effects of systemic glucocorticoids and immunosuppressive medications [15, 16].

Conclusion

This case report is interesting as assessment of the response to treatment for atopic dermatitis concomitant with other allergic diseases. Based on our experience and the experience of other authors, we recommend considering targeted therapy in patients with severe atopic dermatitis with a weak response to conventional treatment regimens.

Increasing evidence related to the use of dupilumab will enable evaluation of its effectiveness in patients with atopic dermatitis and other T2-mediated allergic diseases.

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