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Clinical Observations Of Alopecia Areata Associated with Ige -Dependent and Ige -Independent Atopic Dermatitis in the Dynamics of Anticytokine Therapy

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Abstract:

Depending on atopic sensitization, IgE -dependent and IgE -independent variants of atopic dermatitis are isolated, which also differ in their immunological profile and activation of cytokines belonging to different types of T-cell immune response. For the treatment of severe forms of atopic dermatitis, the drug dupilumab is used, which selectively blocks the main T2 type cytokines, IL-4 and IL-13. Of particular clinical interest is the association between atopic dermatitis and alopecia areata. The article describes clinical observations of two patients treated with dupilumab who have IgE-dependent and IgE-independent atopic dermatitis and concomitant alopecia areata. In a patient with IgE-dependent atopic dermatitis and a universal form of alopecia areata, treatment with dupilumab showed a pronounced positive effect on not only on the clinical

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manifestations of atopic diseases, but also on alopecia areata in the form of regrowth of eyelashes, eyebrows and partial regrowth of hair on the head. In atopic dermatitis, which is regarded as IgE-independent, the therapeutic result of dupilumab is characterized by moderately positive dynamics of atopic rashes and negative dynamics of alopecia areata in the form of progression of the disease from subtotal to total form with partial hair loss on the body. The use of anti-cytokine therapy, given its impact on the immunological profile, in combined immune-mediated pathology, requires an assessment of the endotypes of associated heterogeneous diseases. This will make it possible to personalize pathogenetic treatment by targeting the general molecular mechanisms of pathological processes.

1. Introduction

Recent advances in molecular genetic research allows for considering atopic dermatitis (AD) as a heterogeneous disease characterized by several endotypes. Since IgE-mediated mechanisms do not determine the mandatory development of AD, there are external "extrinsic" and internal "intrinsic" types of AD. [1] New types of systemic therapy for AD are represented by targeted drugs, such as dupilumab , a monoclonal antibody that blocks the receptors of key cytokines of allergic inflammation IL -4/ IL -13, and selective inhibitors of the JAK - STAT intracellular system, which mediates the signaling of the main inflammatory cytokines. AD is associated with a number of other immune diseases, one of which is alopecia areata (AA). [2,3] Since the immune mechanisms of AA and AD are multidirectional, there are currently enough clinical observations in which dupilumab therapy in the treatment of AD in patients with concomitant AA also has a positive effect on the course of AA, contributing to hair restoration. even in severe, long-term forms of AA. [4,5] At the same time, clinical cases are described when the treatment of AD dupilumab worsened the course of AA, leading to total alopecia. [6, 7] The possibility of the existence of endotypes not only of AD, but also of AA, characterized by different profiles of key inflammatory cytokines, is allowed. At the same time, the molecular endotype of AA associated with AD, may depend on the endotype of the accompanying AD, in particular, on its external or internal variant. [8, 9] The successful use of Janus kinase (JAK) inhibitors in the treatment of both AD and AA is due to the fact that the JAK - STAT system is involved in the signaling of a wide range of cytokines, including IL -4, IL - 5, IL -13, IL -15, IFN - g, which are related to Th 2 and Th 1 types of immune response. [10,11]

This article presents clinical observations of the features of the course of AA in patients with intrinsic and extrinsic types of AD during the use of systemic anticytokine therapy with dupilumab.

Clinical case 1

A 14-year-old girl with the following diagnoses: atopic dermatitis, moderate course; allergic rhinoconjunctivitis year-round; bronchial asthma, controlled, moderate course; polyvalent sensitization (birch, house dust mites, cat epithelium, nuts, wheat); alopecia areata, universal form. The patient developed atopic dermatitis at the age of 2 months, at the age of 4 she was diagnosed with allergic rhinoconjunctivitis, at the age of 10 - bronchial asthma. For the first time, hair loss was noted at the age of 5 in the form of a single focus in the occipital region, which arose after antibiotic therapy of bronchitis and overgrown on its own within two months. After several repeated recurrences of focal hair loss, at the age of 6, the course of AA acquired a progressive character in the form of multiple foci, increasing in size, which led to complete loss of hair on the scalp by the age of 7. By the age of 8, there was also hair loss in the area of the eyebrows and on the skin of the trunk, as well as a pronounced thinning of the eyelashes. Against the background of local therapy, including topical corticosteroids and hair growth-stimulating drugs, a short remission was observed in the form of focal regrowth of hair on the head, which fell out within 2-3 months. At the age of 11, cyclosporine therapy was carried out due to the severe course of AD. During the treatment, there was a positive dynamic of both skin manifestations and AA in the form of a complete restoration of eyelashes, eyebrows, and vellus hair on the body and partial regrowth of hair on the skin of the scalp. But, after 4 months of therapy, a pronounced exacerbation of AA was observed, manifested by total hair loss on the face and head. The clinical effect of cyclosporine on AD was also short-lived.

In March 2022, at the age of 13, the girl was initiated on anti-cytokine therapy with dupilumab due to severe AD and concomitant respiratory allergies at a dose of 600 mg subcutaneously every 14 days for 3 months, followed by a dose reduction to 300 mg every 14 days. Concomitant therapy included: montelukast 5 mg 1

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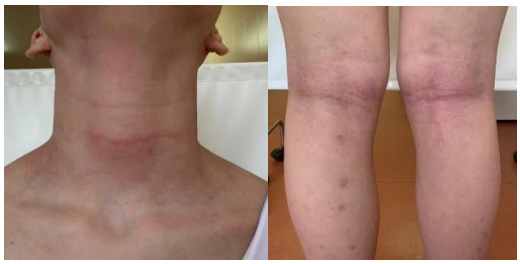
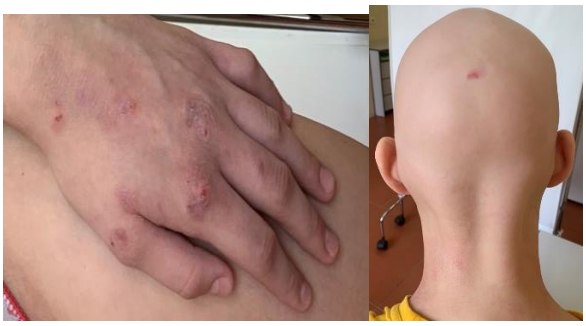
time per day (for 3 months), budesonide + formaterol 4.5/160 mcg 1 dose 1 time per day (for 1 month), cetirizine 10 mg 1 time per day (1 month), externally topical GCS, and emollients. Lab reports pre-treatment: (from October 2021): IgE total> 5000 IU / ml (normal 0-150), eosinophilia up to 22% (normal 0-5), decrease in serum iron level to 7.1 µmol / l (norm 9.3 - 23.6), a decrease in the level of ferritin to 13.1 ng / ml (norm 15-300); other indicators are within normal limits.

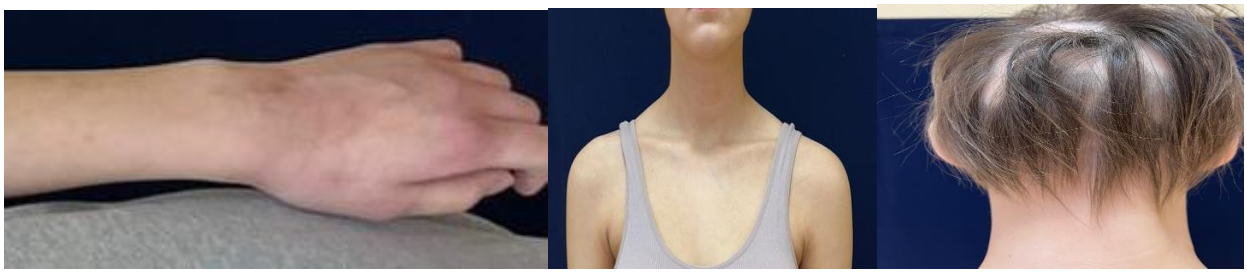
After 6 months of treatment with dupilumab, the girl showed good results, manifested by almost complete cleansing of the skin, remission of bronchial asthma, regrowth of eyelashes, eyebrows, and partial regrowth of hair on the head.

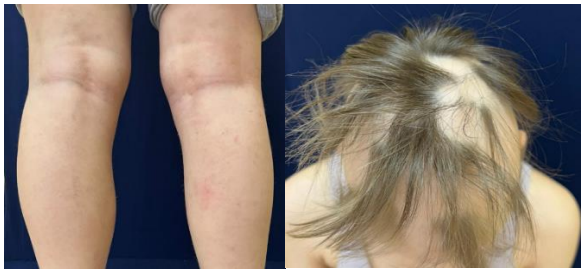
Considering the severity of the disease and severe comorbidity, anticytokine therapy with dupilumab was continued. During the treatment, remission of atopic diseases is maintained, and there are no relapses of AA.





Patient D., 14 years old, diagnosis: atopic dermatitis, moderate course; allergic rhinoconjunctivitis year-round; bronchial asthma, controlled, moderate course; alopecia areata, universal form. Pictures before the start of Genetically Engineered Biologic Drugs (GEBD) with dupilumab





Patient D., 14 years old, after 10 months of therapy with dupilumab

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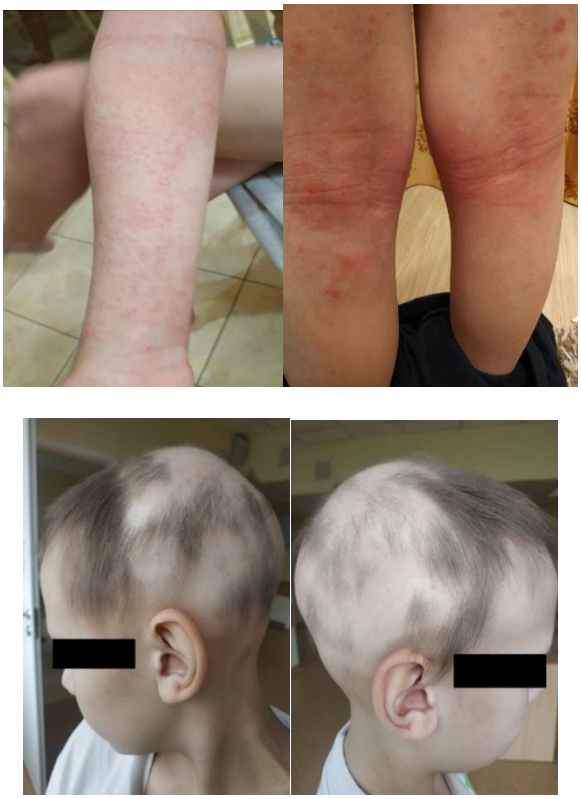
Clinical case 2

An 11-year-old boy is observed with the following diagnoses: atopic dermatitis, common form, severe course, stage of incomplete drug remission; total alopecia. Rashes on the skin in a child from 2 months of age, the last 2 years, there has been deterioration in the course of the skin process, frequent addition of a bacterial infection. External treatment with topical corticosteroids and antibacterial drugs, the use of antihistamines were ineffective. At the age of 4, the child experienced attacks of suffocation and difficulty in nasal breathing, was diagnosed with obstructive bronchitis, a preliminary diagnosis was bronchial asthma, allergic rhinitis. During therapy with antihistamines and inhaled corticosteroids, respiratory symptoms stopped without subsequent relapses. At the age of 7 years, for the first time, an alopecia focus appeared on the skin of the occipital part of the head, which developed despite external therapy for 4 months. Later, several more episodes of exacerbation of AA were noted in the form of foci of hair loss on the head.

Due to the severe course of AD , (exacerbations more than 5 times a year, from the age of 10), the child receives anticytokine therapy with dupilumab at a dose of 300 mg subcutaneously once every 14 days, concomitant therapy - topical basic drugs for the treatment of AD . Therapy with dupilumab was started for the subtotal form of AA in the form of confluent lesions on the scalp. AA was treated with topical corticosteroids (clobetasol ointment). propionate 0.05%, external non-specific stimulating drugs. Lab reports showed: IgE total - 57.2 IU / ml (normal 0-150), sIgE: wormwood pollen 2.08+ Me / ml (class 2; norm <0.35), cat epithelium - 0.99+ IU / ml (1 class), tree pollen, house dust mites, fungi, epithelium of a dog, horse - no sensitization was detected. Other general clinical laboratory parameters are within reference values. During the treatment, the skin exacerbations decreased in number and severity. Rashes are represented by papular, erythematous-squamous elements on the skin of the flexor surfaces of the elbow and knee joints, small foci of lichenification persist, dryness, and moderate periodic itching. After 2 months of therapy with dupilumab, the boy experienced an exacerbation of AA in the form of total hair loss on the scalp and hair thinning in androgen-dependent areas of the body. There is still no hair on the head.



Patient V., 11 years old. Diagnosis: atopic dermatitis, common form, moderate course; alopecia areata, focal form. Pictures before the start of Genetically Engineered Biologic Drugs (GEBD) with dupilumab.

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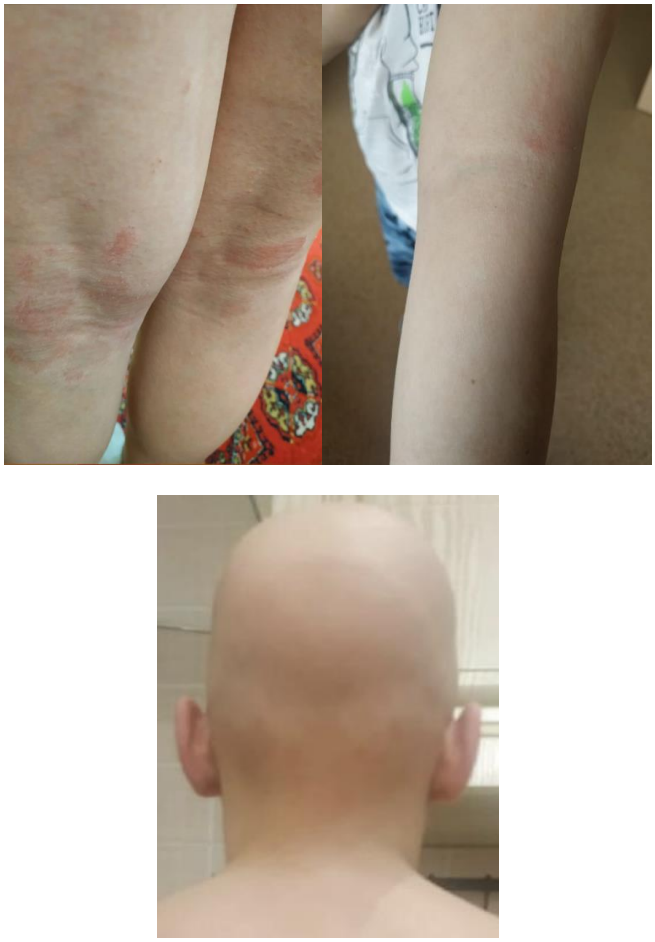

Patient V., 11 years old, 6 months after the start of Genetically Engineered Biologic Drugs (GEBD) with dupilumab

All patients received treatment at the Dermatovenerological Department of the Russian Children's Clinical Hospital of the Federal State Autonomous Educational Institution of Higher Education of the Russian National Research Medical University. N. I. Pirogov. The legal representatives of the patients signed an informed voluntary consent to photographic documentation and the opportunity to use images and clinical and laboratory data for scientific purposes, including in publications.

2. Discussion

IgE -independent or internal (" intrinsic ") pathogenetic type of AD is characterized by an average prevalence of 20–22.8% with a predominance among females and a tendency to a later onset of the disease, with no obvious seasonality of exacerbations. At the same time, there are no obvious differences in the clinical manifestations of IgE -independent from IgE -dependent variants of AD. [12, 13] Differences between endotypes AD is predominantly concerned with immunological features and the profile of key cytokines that are involved in the initiation and maintenance of inflammation. It has been shown that in the "internal" AD subtype, along with the activation of Th 2 cells, there is an additional activation of Th 1, Th 22 and Th 17/ Th 23 lymphocytes and related cytokines. [14]

The study of the profile of cytokines in combined diseases of AD and AA was carried out in single studies. Kageyama R., Ito T. _ et al. (2021) [15] evaluated the expression of Th1 and Th2 cytokines in patients with AA without concomitant AD , as well as in patients with AA in combination with "internal" and "external" types of AD . According to the results of the study, in all patients with AA, regardless of the presence of atopy, there was an increase in the level of T h 1 cells (CD 8+ IFN -Y), however, in patients with AA and concomitant AD, certain "distortions" of the immunological profile were observed. Thus, when the "internal" type of AD and AA were combined, an

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increased expression of Th1 cells was determined (CD 4+ IFN -Y), while the "external" type of AD in AA was characterized by a ~~pronounced~~ predominance of the Th 2 cytokine profile (CD 4+ IL -4, CD 4+ IL -13) both in the blood serum and in the perifollicular infiltrate. It has been shown that the level of cells producing IFN - Y inversely correlates with the level of IgE.

It is assumed that the use of the Th 2 cytokine blocker dupilumab causes a shift in the immunological profile, including in AA foci, from Th 2 to T h 1. By blocking Th 2 cytokines in IgE -dependent AD, we can also obtain a good therapeutic effect in in relation to concomitant AA, since these two diseases, when combined, have the same basic cytokine profile. Conversely, dupilumab therapy for the "intrinsic" type of AD in patients with AA may adversely affect the course of AA, since it will further increase the bias of cytokine pathways towards the Th 1 profile.

Analyzing the presented clinical observations, it can be concluded that in the first case, AD in the patient belongs to the IgE -dependent variant, which is confirmed by a high level of total IgE (> 5000 IU / ml), eosinophilia, polyvalent sensitization and a combination with respiratory atopic diseases. Blocking key cytokines of atopic inflammation with dupilumab had a positive effect not only on the course of atopic diseases but also on hair restoration.

In the second clinical observation, characterizing AD on the basis of IgE -mediated mechanisms, it cannot be unequivocally stated that in this case, it is an IgE - independent variant since the child's history has indications of respiratory symptoms and a low degree of sensitization to wormwood and cat epithelium was revealed. However, such data as normal levels of total IgE and eosinophils in the blood serum, and the absence of clinical manifestations of respiratory allergies, testify more to the presence of an "internal" or IgE -independent variant of AD in the patient, which is immunologically characterized by additional activation of Th 1 immune mechanisms. Dupilumab therapy, by shifting the immune response towards the Th 1 profile, could affect the course of associated AA and provoke an exacerbation and progression of the disease to a total form. Of course, the possibility of spontaneous exacerbation of AA cannot be ruled out. Considering the incomplete clinical response to AD and worsening of AA during dupilumab therapy, it seems appropriate to replace the anti-cytokine drug dupilumab with JAK inhibitors.

3. Conclusions

Having a certain choice of target immunosuppressive therapy for AD, one should take into account not only the immunological profile of AD, but also comorbidity with other immune-mediated diseases. Our clinical observations confirm that the use of the Th2 cytokine blocker dupilumab in AD has a different therapeutic effect on the course of concomitant AA, which may be associated with AD subtypes depending on IgE sensitization. With the association of AD and AA, it seems relevant to determine the endotypes of these diseases in order to indivisualise pathogenetic therapy that has a positive effect on both pathological processes.

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