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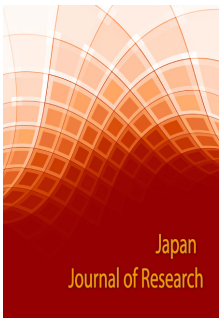

A New Treatment Strategy For Children With Congenital Ichthyosis Based on Immunopathogenesis

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Abstract

Congenital ichthyosis (CI) is a clinico-genetic heterogeneous disease and belongs to the group of severe genodermatoses. Characteristic clinical symptoms of the disease are erythroderma and peeling, itching, hyperkeratosis, gross structural and functional disorders of the epidermal barrier, functions of other organs and systems. Patients have an extremely low quality of life due to changes in appearance, discomfort and persistent symptoms of the disease. There are no effective methods of treating ichthyosis now. Scientists all over the world are developing new methods of treatment. Our research group set a task to find new methods of treating children with CI. We carried out scientific work to study immunopathogenetic mechanisms in patients with CI.

The aim of the study was to examine the cell-mediated immunity state in patients with CI via assessment of the pattern of lymphocyte subpopulations in peripheral blood.

Methods:*The research was conducted to study the content of the main and small lymphocyte subpopulations in 86 patients with established diagnosis of CI aged from 1 month to 18 years. The diagnosis was made according to the clinical data and the results of molecular genetic testing. Comparative analysis of blood immunological indicators in children with CI and in patients with other immunemediated chronic dermatoses: atopic dermatitis (AD; n = 68) and psoriasis vulgaris (Ps; n = 55). The level of T lymphocytes,T helpers (Th), cytotoxic T lymphocytes (Tc), B lymphocytes, NK cells, Treg-cells (Treg), activated T helpers (Thact), Th17 lymphocytes in peripheral blood was evaluated via flow cytometry using monoclonal antibodies. Statistical analysis was performed via Statistica 10.0. Differences between the groups were assessed via Mann-Whitney non-parametric test, differences were considered significant atp < 0.05.*

Results: *A significant increase in the content of activated T-helpers in peripheral blood was revealed in patients with CI and Ps compared with those of children with AD ($p < 0.001$). And also in children with CI, there was an increased content of B-lymphocytes, Treg- and T17- lymphocytes. The obtained results opened up the possibility for us to use drugs for immunobiological targeted therapy of Ps in a new treatment strategy for children with CI. We performed targeted immunosuppressive therapy in children from the CI group who had increased activation and proliferation of CD4+ lymphocytes. In a short time after initiation of therapy, there was a significant decrease in erythroderma and itching, and an improvement in the quality of life of patients and their families.*

Conclusion: *Immunological dysregulation in children with CI is presented in the form of pathological activation of Th-lymphocytes, as a result of terminal differentiation of naive CD4+ cells towards switching to Thact, Treg, Th17- lymphocytes. A comparative analysis of immunological parameters in children with CI, Ps and AD demonstrated comparable results of Thact immunophenotypes in patients in CI and Ps groups. A new strategy in therapy in children with CI based on immunopathogenesis has demonstrated its therapeutic effectiveness in real clinical practice.*

Introduction

Congenital ichthyosis occurs as a result of genetic defects in more than 50 genes and has more than 60 clinical subtypes [1-3]. The phenotypic heterogeneity of ichthyosis is the result of pathological molecular interactions associated with impaired function of proteins encoded by defective genes [4]. The latter lead to impaired metabolism, assembly, transport of intercellular lipids and terminal differentiation of keratinocytes [5, 6]. As a result, the structural stability and integrity of the stratum corneum are disrupted and gross violations of the structure and function of the skin barrier are formed, transepidermal water loss (TEWL) increases.

For a long time, the treatment of patients with CI was only symptomatic - daily skin care, the appointment of systemic drugs to reduce itching and erythroderma, including oral

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antihistamines, corticosteroids, systemic retinoids, intravenous immunoglobulins, in severe forms - cytostatics. However, the therapeutic response from such treatments is insignificant, temporary and unstable, and the quality of life of patients and their families remains extremely low [2,7,8].

Innovative technologies have opened up new opportunities in the field of medicine, offering new methods of diagnosis and treatment for patients with severe, uncontrolled diseases. Next generation sequencing, (NGS) and complete genome sequencing (WGS) made it possible to identify genetic defects in CI and reveal the molecular mechanisms associated with them[4,9].

Recent studies have shown that the clinical symptoms of the disease (intense itching, diffuse erythroderma, generalized peeling, dry skin) are also caused by immune inflammation in the skin structure [10,11]. Structural disorders activate subpopulations of Thelper -lymphocytes in the skin. As a result of cellular activation, there is an increased expression of inflammatory mediators, cytokines, chemokines, activation of new signaling pathways, inducing increased expression of a number of proinflammatory cytokines. This triggers a cascade of immune inflammation in patients with CI and other chronic immuno-compromised skin diseases [12,13]. As a result of continuous immune-mediated inflammation, the condition of patients is rapidly deteriorating, their quality of life and their family decreases.

The study of the immune mechanisms of Atopic dermatitis and Psoriasis allowed scientists to identify the immunopathogenesis of diseases and develop new therapies. The role of Th1, Th2, Th17, Th22 lymphocyte subpopulations in the immunopathogenesis of Ps has been proven [14,15], the dominant immunological Th2 phenotype in patients with AD [16,17]. This allowed scientists to develop new therapies using targeted immunobiological drugs: tumor necrosis factor alpha (TNF) inhibitors, IL-12/IL-23 inhibitor, Anti IL-17-A and others, for the treatment of patients with Ps[18-20], Anti IL-4/IL-13 and others, for the treatment of patients with AD [17,21,22]. Currently, the list of drugs for immunobiological therapy is expanding [23,24].

By analogy, we decided to investigate cellular immunity in children with CI, Ps and AD, and conduct a comparative analysis.

The purpose of the study

Identification of the features of immunological dysfunction in children with congenital ichthyosis, based on the study of cellular immunity for the development of new therapies

Materials and methods

The study included 86 children (group 1) with different forms of CI aged from 1 month to 18 years, as well as 68 children with severe AD (group 2) and 55 patients with Ps (group 3) - SCORAD > 50 for children with AD and PASI ≥ 12 for children with Ps. All groups were comparable in age. The preliminary clinical diagnosis of CI was established by dermatologists of the Research Institute of Pediatric Dermatology. The final clinical and genetic subtype of the disease was determined after conducting molecular genetic studies using the NGS method. The group with CI included patients with the following forms of the disease: Congenital ichthyosiform erythroderma (CIE, n = 13), Netherton syndrome (NS, n = 17), Lamellar ichthyosis (LI, n = 17), Keratinopathic ichthyosis (KPI, n = 15), Vulgar ichthyosis (VI, n = 11) and other orphan forms of CI (n = 13). All patients underwent immunophenotyping of lymphocytes.

Immunophenotyping of lymphocytes was performed by flow cytometry on a cytofluorimeter Novocyte (ACEA Biosciences, USA) using monoclonal antibodies (Beckman Coulter, USA). In the CD45+ region, the content of major and small subpopulations of lymphocytes in peripheral blood was determined: T-lymphocytes (CD3+); T-helper cells (CD3+CD4+/Th); cytotoxic T-lymphocytes (CD3+CD8+/Tc); B-lymphocytes (CD3-CD19+); NK cells (CD3–CD16+CD56+); regulatory T cells (CD4+CD25highCD127low/Treg); activated T-helper cells (CD4+CD25+CD127high/Thact);Th17 -lymphocytes (CD3+CD4+CD161+/Th17).

Note: Patients from groups 2 and 3 were shown immunobiological therapy according to existing protocols and clinical recommendations, taking into account the severe, uncontrolled course of their chronic dermatoses. An immunological study in patients was conducted before the start of immunobiological therapy.

Sequencing method – Next generation sequencing, (NGS)

Statistical processing method - using the program "Statistica 10.0". Descriptive statistics are presented in the format: median (lower and upper quartiles) – Me (Q0,25-Q0,75).

Deviations from the level of the age norm were calculated using the formula: Xn = (Xmin-X) / 0.01*(Xmax - Xmin), where Xn is the value of an individual indicator normalized to the age norm; X is the value of the studied indicator; Xmax is the upper limit of the age norm; Xmin is the lower limit of the age norm.

The range of deviations from the age norm was 0-100%.

The nonparametric Mann–Whitney criterion was used to assess the significance of differences between the indicators in the groups. The difference was considered statistically significant at $p < 0.05$.

Results

At the first stage of the study, the composition of cellular immunity in children with CI was evaluated.

The study of the content of the main populations of lymphocytes in the blood of children with CI (Figure 1).

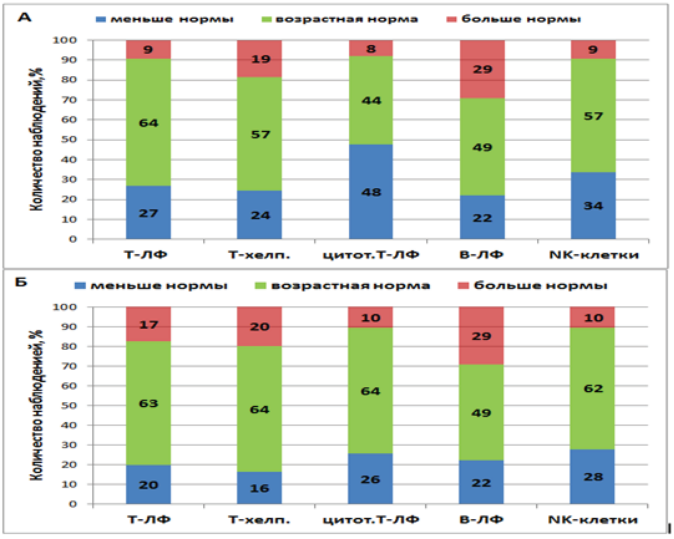


Figure 1. *Distribution of patients by relative (А) and absolute (Б) levels of major lymphocyte populations in the group of children with Congenital ichthyosis*

Revealed:

- 27 % have a decrease in T- lymphocytes
- 24 % have a decrease in Th lymphocytes
- 50 % have a decrease in Tc lymphocytes
- 1/3 of patients have an increased content of B lymphocytes
- 35 % have a decrease in NK cells

The study of indicators of small subpopulations of Th-lymphocytes revealed an increased content of the three small subpopulations studied by us: Activated Thact? Treg and Th17-lymphocytes in children with CI (Figure 2).

Revealed:

- In 90% of patients, an increase in Thac lymphocytes exceeding the age norm 2-4 times.
- 50% have an increase in Th17 lymphocytes
- 62% have an increase in Treg lymphocytes

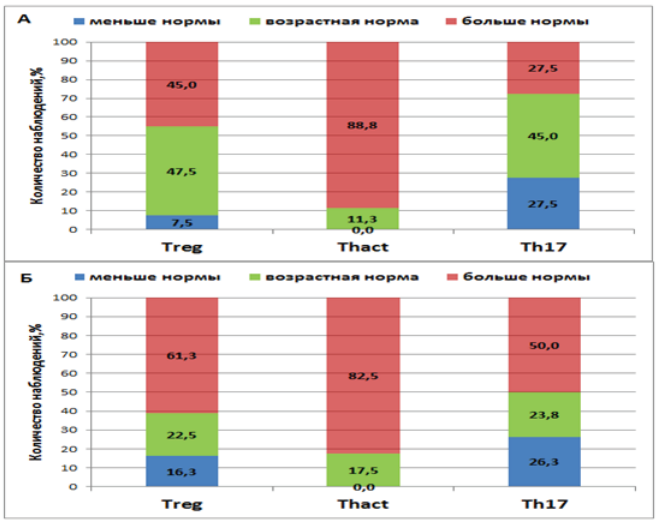


***Figure 2**. Distribution of patients by relative (A) and absolute (Б) levels of minor CD4+ populations of T lymphocytes in the group of children with Congenital ichthyosis*

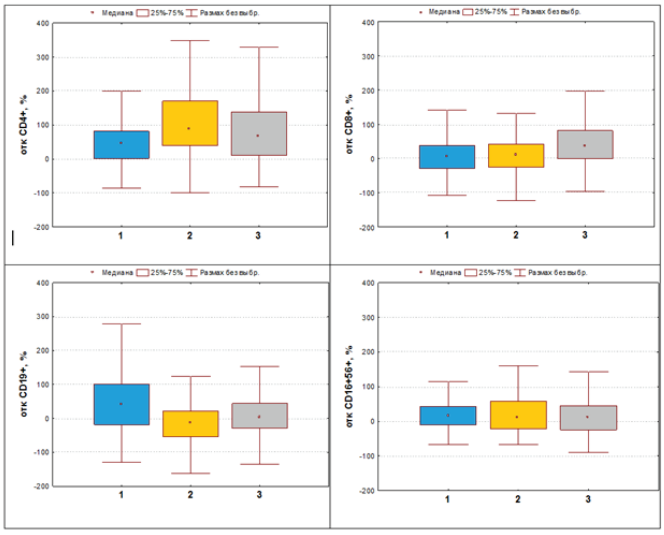


***Figure 3**. Levels of major T-cell populations (% of deviations from the age reference) in the groups of Congenital ichthyosis (1), Atopic dermatitis (2), and Psoriasis (3)Note. The dotted line shows the reference range (0–100%).*

At the second stage, we conducted a comparative analysis of the main populations of lymphocytes in the peripheral blood of patients with CI, AD and Ps (Figure 3).

Revealed:

- Statistically significant decrease in the relative content of T-lymphocytes in children with CI compared with children with AD ($p<0.001$) and Ps ($p<0.001$).
- Statistically significant decrease in the content of Th-lymphocytes in children with CI relative to those in children with AD ($p<0.001$)
- Statistically significant increased content Tc- lymphocytes in children with Ps relative to the indicators in children with AD and CI ($p<0.001$).
- Statistically significant increased content of B-lymphocytes in children with CI relative to the indicators in children with AD and Ps ($p<0.001$).
- NK content was lower in the group of children with CI, however, there was a significant difference in no groups have been identified.

The results of a comparative analysis of the content of small subpopulations of CD4+ lymphocytes (Thact, Treg, Th17 lymphocytes) in the peripheral blood of children in three study groups are shown in Figure 4.

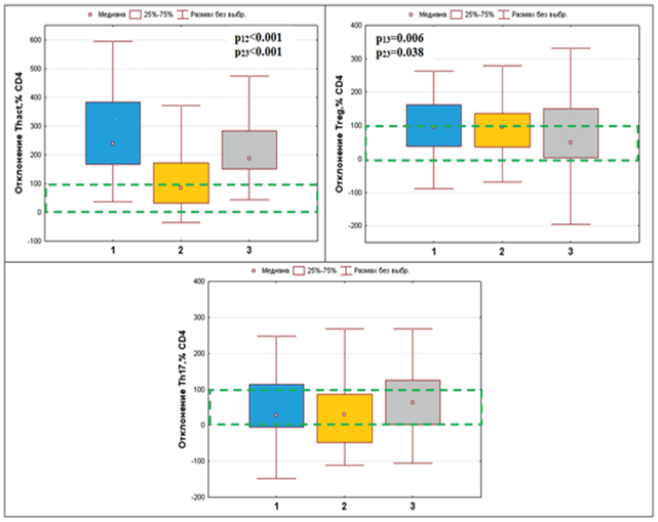


***Figure 4**. Levels of minor subpopulations of CD4+ T-cells (Thact, Treg, Th17) in peripheral blood of children with Congenital ichthyosis (1), Atopic dermatitis (2), and Psoriasis (3)*
Note. The dotted line shows the reference range (0–100%).

Revealed:

- A statistically significant increased content of Thact-lymphocytes in children with CI, relative to the group of children with AD ($p<0.001$).
- A statistically significant increased content of Thact-lymphocytes in children with Ps, relative to the ratio of children with AD ($p<0.001$). There was no significant difference in the content of Thact- lymphocytes in children with CI and Ps.
- Increased content of Treg and Th17- lymphocytes in children with CI and Ps to the ratio of children with AD. There was no significant difference in the content of Th17- lymphocytes in the groups of children with CI and Ps.

Discussion

The analysis of the content of major and small populations of lymphocytes in children with CI allowed us to identify changes in cellular immunity and immunological features in patients. A comparative analysis of immunological parameters in the blood of patients with CI with other immuno-mediated chronic skin diseases: AD,Ps, demonstrated both their similarity and significant differences between the groups (Figures 3 and 4). The study of the content of small subpopulations of T-helpers in the peripheral blood of children with CI showed an increase in the absolute content of activated T-helpers in 90% of patients (Figure 2). At the same time, in some children, Thact indicators were very high, exceeding the upper limit of age norms by 3-4 times. An increased content of Treg and Th17-lymphocytes was also found in children with CI. At the same time, there was a significant decrease in the relative content of Th- lymphocytes in children with CI relative to those in patients with AD.

Indicators of the content of Tc lymphocytes in the groups with AD and CI turned out to be comparable, but lower than in patients with Ps (Figure 3). Also, in children with CI, a significant increase in the content of B-lymphocytes was revealed relative to patients with AD and Ps, while in 49% of patients the result was in the age range of the norm. It has been shown that B-lymphocyte dysfunction is of particular importance in the pathogenesis of the most severe forms of CI, such as Netherton syndrome [25]. In all three groups, the content of NK cells was below normal or tended to the lower limit of the returnable norms (Figure 3) [26].

The increased content of small subpopulations of Th-lymphocytes with a normal or reduced value of the total number of T-helpers allowed us to conclude that the basis of the immunopathogenesis of CI is the dysfunction of Th-lymphocytes due to a violation of the terminal differentiation of naive CD4+ T lymphocytes towards the proliferation of Thact, Treg, Th17 subpopulations of lymphocytes (Fig.4).

The results obtained are comparable with the data of the world literature, as in the works of A. Malik et al. [11], A. Paller et al. [10]. They revealed increased expression of IL17-A in the blood and skin of patients with CI and Ps, also showed similarities in immunological dysfunction in the two diseases. The authors also demonstrated a significant correlation between the severity of ichthyosis and the expression of IL-17A in the blood ($r = 0.57$, $p < 0.03$). Using the IASI-E scale (erythema ichthyosis severity index) and TEWL, a direct relationship was shown between the severity of clinical symptoms (impaired skin barrier function, erythroderma) and laboratory immunological parameters in blood and skin in patients with CI and Ps. Based on the data obtained, the authors propose the repurposing of drugs for immunopathogenetic targeted therapy of Ps for the treatment of patients with CI. Immunopathogenetic therapy was performed using IL-12/IL-23 inhibitors (ustekinumab) and IL-17A (secukinumab) [27-29]. A year later, against the background of biological therapy, a decrease in skin erythema, peeling, and a decrease in TEWL indicators were noted. The results obtained show the role of Th-lymphocyte activation and cytokine expression of Th signaling pathways in the development of immunopathogenesis and clinical symptoms of CI.

Our study of cellular immunity in patients with CI revealed the features of immunological disorders in the form of dominant immunological activation of T helper cells and proliferation of Thact, Treg and Th17- lymphocytes. The results of the study and comparative analysis in groups of children with CI, AD, and Ps showed similarity of immunological profiles in patients with CI and Ps. A correlation was found between Thact and symptoms such as erythroderma and itching. To determine the correlation, we used the VIIS (Visual Ichthyosis Severity Index) methodology for visual assessment of ichthyosis severity [30], a 10-point numerological itch scale [31]. They also assessed the quality of life of children according to the CDLQI (Dermatological Quality of Life Index for Children) questionnaire [31], and DLQI (Dermatological Quality of Life Index) for adolescents over 15 years old [31]. We performed immunopathogenetic therapy in some patients with CI. The following is a clinical example of therapy for a teenager with Netherton syndrome.

The clinical case - The boy - 12 years old

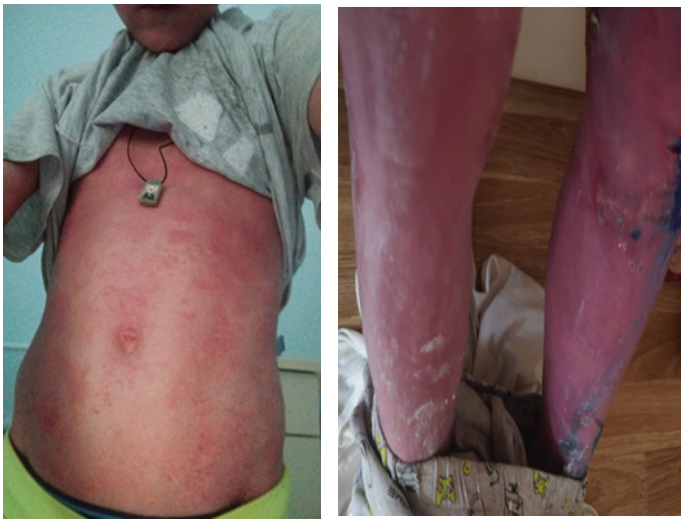
Until the age of 9, the boy was observed by a dermatologist and an allergist-immunologist with a diagnosis of AD. The course of the disease is without remission, with severe exacerbations, which often required the administration of systemic corticosteroids. Increased sensitization to epidermal allergens and meadow grass pollen was detected. A high level of total IgE was detected - 39720 units /ml and eosinophilia in the blood - 650 cel/µl. The allergist prescribed elimination therapy, drug symptomatic therapy. Despite the high commitment to therapy on the part of the parents, the boy's condition remained severe, the course of AD was uncontrolled, with severe exacerbations. Generalized erythroderma, intense itching, and a decrease in the quality of life of the teenager and his family were observed.

We carried out molecular diagnostics In our center using the WGS method. It was revealed 2 pathogenic nucleotide variants in the SPINK5 gene: chr5:147481003A>T and chr5:147496015G>T in a heterozygous state.

We have established the final diagnosis: Netherton syndrome.

The study of cellular immunity revealed an increased content of Thact- lymphocytes, Th17, Th2- lymphocytes.

At the first stage, immunobiological therapy with a monoclonal antibody was prescribed: Anti-IL-4/IL-13- Dupilumab, 300 mg 1 time per month.



A B

Figure 5*. Patient's skin condition before therapy (A). Develop similar to Pustular psoriasis skin condition(B).*

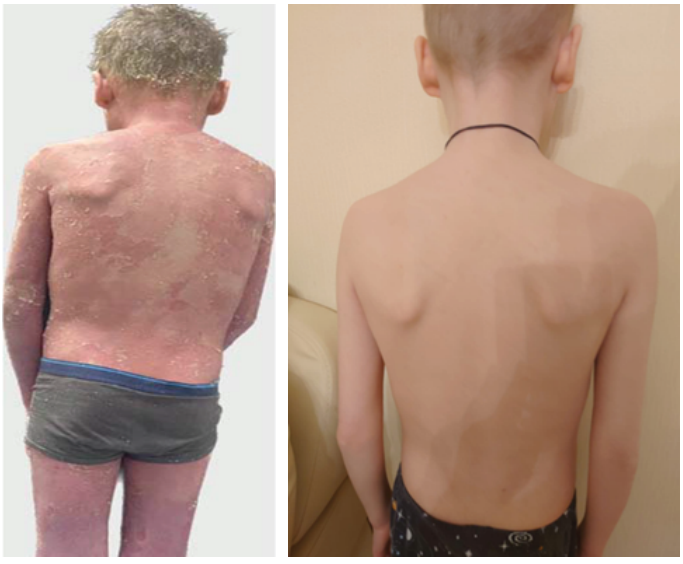
At the beginning of therapy, an improvement in the condition of the skin and itching was obtained. After 6 months of therapy, it worsened again, with the development of pustular psoriasis of a similar condition (Figure 5).

We prescribed intravenous immunoglobulins (IVIG), Methotrexate. After stabilization of the condition, targeted immunopathogenetic therapy aimed at IL-17A with the cytokine drug Secukinumab (anti–IL-17A) 150 mg 1 time per month was initiated. A therapeutic response was obtained - a decrease in erythroderma, itching. However, allergens, especially pollen and household allergens, significantly worsened control. For this reason, it was decided to add the drug Dupilumab (anti IL-4 /anti IL-13) 300 mg n / a 1 time per month.

We could successfully carry out immunobiological therapy only against the background of constant replacement therapy with intravenous immunoglobulins. Currently, the teenager is receiving a combination therapy of Anti-IL-17A and Anti IL-4/ IL-13, IVIG with a pronounced positive effect (Figure 6)

A detailed description of this clinical case is published by us in the article [34].

We performed immunobiological therapy in 10 children with NS with a good therapeutic response. The results allowed us to conclude that biological drugs aimed at the Th17, Th2 cytokine profile show their effectiveness in NS.



A B

Figure 6*. The skin condition of a teenager before (A) and after therapy(B).*

Currently, the scientific experience of using immunobiological targeted therapy in children with other severe forms of CI is expanding[35]. We are considering biological drugs: Infliximab (anti TNF-alpha), Secukinumab (anti IL-17A), Ixekizumab (anti IL-17A), Ustekinumab (inhibitor IL-12/anti IL-23), Dupilumab (anti IL-4/anti IL-13), Specolimab (anti IL-36), Janus kinase inhibitors, anti TSLP in a new therapeutic strategy for the treatment of children with different forms of CI.

A deep understanding of the pathogenetic mechanisms of CI, new knowledge about the immunopathogenesis of the disease will help scientists develop new therapeutic approaches.

Conclusion

The study of cellular immunity in children with CI revealed a dominant immunological profile of pathological activation of Th- lymphocytes, a violation of the terminal differentiation of naive CD4+ T- lymphocytes towards Thact, Treg and Th17 -lymphocytes.

The study of immunological parameters in children with CI, psoriasis and AD demonstrated comparable results in patients with CI and Ps.

A deep understanding of the pathogenetic mechanisms of CI and new knowledge about the immunopathogenesis of the disease will help us develop new therapeutic approaches. Targeted immunobiological drugs targeting cytokines of the Th17, Th2 signaling pathways have shown therapeutic efficacy in children with Netherton syndrome.

The results of new research and the exchange of experiences will help create new treatment protocols for children with CI, provide a personalized approach to the treatment of patients with such a serious illness, aimed at therapeutic success and improving the quality of life of patients and their families.

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Disclosure of interest

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