СОДЕРЖАНИЕ СУБПОПУЛЯЦИЙ CD4⁺Т-КЛЕТОК В ПРОГНОЗЕ ЭФФЕКТИВНОСТИ БИОЛОГИЧЕСКОЙ ТЕРАПИИ ПСОРИАЗА У ДЕТЕЙ

Купцова Д.Г.[1], Радыгина Т.В.[1], Курбатова О.В.[1], Материкин А.И.[1], Епишев Р.В.[1], Опрятин Л.А.[1], Хотко А.А.[2], Мурашкин Н.Н.[1, 2, 3], Петричук С.В.[1]

[1] ФГАУ «Национальный медицинский исследовательский центр здоровья детей» Министерства здравоохранения РФ, Москва, Россия
[2] ФГБУ ДПО «Центральная государственная медицинская академия» Управления делами Президента РФ, Москва, Россия
[3] ФГАОУ ВО «Первый Московский государственный медицинский университет имени И.М. Сеченова» Министерства здравоохранения РФ (Сеченовский университет), Москва, Россия

Резюме. Псориаз – хроническое воспалительное заболевание кожи, характеризующееся повышенной пролиферацией эпидермальных клеток, нарушением кератинизации и воспалительной реакцией в дерме, обусловленной активацией Т-лимфоцитов и синтезом провоспалительных цитокинов. Патофизиология псориаза также связана со снижением противовоспалительных функций иммуносупрессивных клеток. В последнее время все чаще встречаются случаи развития резистентности к проводимой терапии биопрепаратами в детском возрасте, требующие отмены препарата или его замены. Цель исследования – оценить содержание субпопуляций Т-хелперов в прогнозе эффективности биологической терапии у детей с псориазом. Иммунофенотипирование популяций Т-хелперов периферической крови проводили у 110 детей с вульгарным псориазом до назначения биологической терапии, на 16-й и 52-й неделе лечения. Возраст детей составил от 6 до 18 лет. Тяжесть псориаза и эффективность терапии оценивали по индексу PASI, который изменялся от 0 до 68 баллов. Методом проточной цитометрии определяли содержание Т-хелперов, регуляторных Т-клеток (Treg), активированных Т-хелперов (Thact) и Th17-лимфоцитов. В группе пациентов с хорошим эффектом биологической терапии получено значимое снижение PASI, как на 16-й неделе терапии ($p = 0{,}000$), так и к году лечения ($p = 0{,}017$). У детей с псориазом, не зависимо от длительности и эффективности биопрепаратов, был увеличен процент Thact относительно нормативных значений. В группе 1 до назначения биологической терапии был увеличен процент Thact ($p = 0{,}005$) и Th17 ($p = 0{,}001$). Анализ

Адрес для переписки:
Купцова Дарья Геннадьевна
ФГАУ «Национальный медицинский исследовательский центр здоровья детей» Министерства здравоохранения РФ
119991, Россия, Москва, Ломоносовский пр., 2, стр. 1.
Тел.: 8 (499) 134-13-98.
Факс: 8 (499) 134-70-01.
E-mail: dg.kuptsova@gmail.com

Address for correspondence:
Daria G. Kuptsova
National Medical Research Center for Children's Health
2 Lomonosovsky Ave, Bldg 1
Moscow
119991 Russian Federation
Phone: +7 (499) 134-13-98.
Fax: +7 (499) 134-70-01.
E-mail: dg.kuptsova@gmail.com

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динамики содержания популяций Т-хелперов в течение года биологической терапии у детей с разной эффективностью лечения показал, что наиболее значимые изменения выявлены в содержании Th17 и Treg, а также их отношения Th17/Treg. ROC-анализ показал, что при отклонении Th17 выше 53%, Thact выше 181% и Th17/Treg выше 2,6 до назначения биопрепаратов в 75% случаев можно ожидать недостаточную эффективность терапии к году. К окончанию индукционного курса при отклонении Th17 выше 102% и отношении Th17/Treg выше 2,6 вероятность неэффективного лечения составляет уже 82%. В исследовании показана информативность оценки Thact до назначения биологической терапии, динамика Th17 к концу индукционного курса и Treg после 16 недель терапии в прогнозе эффективности ГИБП у детей с псориазом.

Ключевые слова: дети, псориаз, биопрепараты, Т-хелперы, Th17, Treg

CONTENT OF CD4$^+$T CELL SUBPOPULATIONS IN PREDICTING THE EFFICACY OF BIOLOGICAL THERAPY FOR PSORIASIS IN CHILDREN

Kuptsova D.G.[a], Radigina T.V.[a], Kurbatova O.V.[a], Materikin A.I.[a], Epishev R.V.[a], Opryatin L.A.[a], Khotko A.A.[b], Murashkin N.N.[a, b, c], Petrichuk S.V.[a]

[a] *National Medical Research Center for Children's Health, Moscow, Russian Federation*
[b] *Central State Medical Academy of Department of Presidential Affairs, Moscow, Russian Federation*
[c] *I. Sechenov First Moscow State Medical University, Moscow, Russian Federation*

Abstract. Psoriasis is a chronic inflammatory skin disease characterized by increased proliferation of epidermal cells, impaired keratinization and an inflammatory reaction in dermis caused by activation of T lymphocytes and synthesis of pro-inflammatory cytokines. The pathophysiology of psoriasis is also associated with a decrease in anti-inflammatory functions of immunosuppressive cells. Recently, there are more cases of development of resistance to ongoing therapy with biologics in children, requiring cancellation of drug or its replacement. The aim of the study was to evaluate the content of T helper subpopulations in prognosis of effectiveness of biologics in children with psoriasis. Immunophenotyping of T helper populations was performed in 110 children with psoriasis vulgaris before appointment of biologics, at 16 and 52 weeks. Age of children ranged from 6 to 18 years. Severity of psoriasis and effectiveness of therapy were assessed by index PASI, which varied 0-68. Content of Tregs, Thact and Th17 was determined by flow cytometry. In group with a sufficient effect of biologics, a decrease in PASI was obtained, both at week 16 of therapy ($p = 0.000$) and by year of treatment, $p = 0.017$. In children with psoriasis, regardless of duration and effectiveness of biologics, percentage of Thact was increased relative to normal values. In group 1 before prescription of biologics was increased percentage of Thact ($p = 0.005$) and Th17 ($p = 0.001$). Analysis of dynamics of content of small populations of T helper during 1 year of use of biologics in children with different efficacy of therapy showed that significant changes were found in content of Th17 and Treg, as well as their Th17/Treg. ROC analysis showed that when Th17 deviation was above 53%, Thact above 181% and Th17/Treg above 2.6 before biologics were prescribed, insufficient efficacy of therapy could be expected in 75% of cases by year. By the end of induction course, with a Th17 deviation above 102% and a Th17/Treg above 2.6, probability of ineffective treatment was already 82%. The study shows the informative value of assessment of Thact before appointment of biologics, dynamics of Th17 by the end of induction course and Treg after 16 weeks of therapy in prognosis of effectiveness of biologics in children with psoriasis.

Keywords: children, psoriasis, biologics, T helpers, Th17, Treg

Introduction

Psoriasis is a systemic chronic inflammatory disease with an immunogenetic basis [3, 11]. Adaptive immune cells in psoriasis are activated by aberrant signaling of innate immune cells, and subsequently release inflammatory mediators that enhance psoriatic manifestations on the skin. The cellular link of the immune system is predominantly involved in the development and maintenance of inflammation in psoriasis [3, 14]. Clinically, psoriasis is characterized by well-defined red, scaly plaques, and histologically by increased proliferation of keratinocytes, dense skin inflammatory infiltrates and angiogenesis [7, 14].

A special role in psoriasis is assigned to Th17-lymphocytes (Th17) and cytotoxic T lymphocytes ($CD8^+$), since they largely produce cytokines of the interleukin (IL)-17 family, thereby stimulating the proliferation of keratinocytes [9, 13, 14]. It has been shown that in psoriasis, Th17 enhances the immune response of Th1 cells, mainly due to the production of IL-17A, which is responsible for the recruitment of neutrophils, activation of innate immunity cells, enhancement of B-cell functions and the release of pro-inflammatory cytokines [7, 9]. A high percentage of Th17 cells have been found in the circulating and affected skin of psoriasis patients and a direct correlation has been established between the number of Th17 cells and the PASI (Psoriasis Area and Severity Index) [8, 9, 13].

The pathophysiology of psoriasis is not only related to the activation of pro-inflammatory reactions, but also to a decrease in the anti-inflammatory functions of immunosuppressive cells [10, 11]. It has been shown that regulatory T cells (Treg), regulatory B cells and myeloid-derived suppressor cells (MDSCs) do not perform their classical homeostatic functions in psoriasis [8, 10, 11]. It is known that Tregs are able to suppress the activation and proliferation of effector cells through the production of TGF-β and IL-10 [5, 12]. An increase in Th17 content and a decrease in the proportion of Treg in the peripheral blood of patients with psoriasis lead to an imbalance of Th17/Treg, which correlates with the severity of the disease [7, 8, 9, 13].

Over the past decade, the use of biologics in children with psoriasis has shown its effectiveness, persistent long-term remission and significantly improved the quality of life of patients [2, 15]. The targeting effect of genetically engineered biological drugs (GEBD) is based on a blockade of the main pro-inflammatory cytokines of disease pathogenesis, such as tumor necrosis factor-alpha (TNFα), IL-17, IL-12 and IL-23 [2, 15]. However, in recent years, there are more and more cases of resistance to biologic therapy in children, requiring withdrawal or replacement of the drug [1, 4, 6]. Factors in the loss of response to GEBD therapy in patients with psoriasis include a high body mass index, a burdened family history and the production of antibodies to biologics [1, 2, 4, 6]. Nevertheless, there is a lack of information and guidelines on the tactics of switching biologics, and a complete lack of clear laboratory markers for predicting the efficacy of GEBD in children with psoriasis.

The aim of the study was to evaluate the content of $CD4^+$ cell subpopulations (Thact, Th17, Treg) in predicting the effectiveness of biologics in children with psoriasis.

Materials and methods

In 110 children with psoriasis vulgaris, peripheral blood T helper subpopulations were examined before biological therapy, at weeks 16 and 52 of therapy with adalimumab, etanercept and ustekinumab. The effectiveness of therapy was assessed by achieving "PASI 75" or more by the year of therapy: group 1 included children with insufficient effect of biologics ("IE", less than PASI 75, n = 52), group 2 – children with good effect of biologics ("PASI 75" and more, n = 58). The age of the examined children ranged from 6 to 18 years. The children of groups 1 and 2 did not differ in age: 12.3 (7.8-16.4) years versus 12.5 (8.8-15.3) years, p = 0.821. Inclusion criteria in the study: the age of children from 6-18 years old, established diagnosis of psoriasis vulgaris, compliance with the frequency and dose of administration GEBD. Exclusion criteria: other forms of psoriasis in children, age over 18, inability to obtain a blood sample. The severity of psoriasis was assessed by the PASI, which varied from 0 to 68 (Me 14.0 (9.0-19.9)). The study complied with the ethical principles of the Declaration of Helsinki (WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects, 2013) and was approved by the local ethical committee National Medical Research Center for Children's Health of the Russian Ministry of Health (protocol No. 2 of 14.02.2020).

Immunophenotyping of peripheral blood lymphocyte populations was performed by flow cytometry using monoclonal antibodies from the "Beckman Coulter" (USA). Sample preparation involved incubating 100 μL of whole blood with 10 μL of fluorochrome-labelled monoclonal antibodies for 20 minutes in the dark. For lysis of erythrocytes was used BD FACS™ Lysing Solution (BD Biosciences, USA), with incubation time in the dark at room temperature not exceeding 10-12 minutes. The samples obtained were recorded on flow cytometer the Novocyte (ACEA Biosciences, USA). The following populations were determined by the sequential gating method: $CD3^+CD4^+$ (T helpers), $CD4^+CD127^{low}CD25^{high}$ (Treg), $CD4^+CD25^+CD127^{high}$ (activated T helpers – Thact) and $CD3^+CD4^+CD161^+$ (Th17). Statistical analysis was performed using Statistica 10.0 (StatSoft,

USA) and ROC analysis using SPSS 16.0 (SPSS: An IBM Company, USA). Descriptive statistics of the number of cells are presented in the form of a median (lower – upper quartiles) – Me ($Q_{0.25}$-$Q_{0.75}$). The non-parametric Mann–Whitney test considered differences between independent groups; differences were considered significant at $p < 0.05$. The study included children of different ages; in this regard, in order to assess changes in the lymphocyte population, the deviation of individual indicators from the age norm level was calculated according to the formula:

$X_n = (X_{min}\text{-}X) / 0{,}01*(X_{max} - X_{min})$,

X_n, value of the individual index normalized to the age norm; X, value of the studied index; X_{max}, upper limit of the age norm; X_{min}, lower limit of the age norm. The range of age norm was taken as 100%.

Results and discussion

Analysis of the efficacy of biologics in children with psoriasis, as measured by index the PASI, showed a significant and significant reduction in disease severity in the group of patients with good effect of GEBD (PASI 75), both at 16 weeks of therapy (PASI decreased from 20.1 (14-31) to 11.3 (7-15), $p = 0.000$), and by year of treatment – PASI decreased to 6.1 (1.5-9.9), $p = 0.017$. However, in the group of children with insufficient effect of biological therapy (group 1), the decrease in the PASI index was less pronounced and by the year of treatment of biologics PASI exceeded 10 points (16 weeks – 16.2 (15-21), 52 weeks of GEBD – 10.9 (4.9-22). It is worth noting that the groups of children with different efficacy of biologics before the appointment of therapy according to the PASI index did not differ ($p = 0.631$), but by the 16th week of therapy, a significant difference was revealed between the groups according to PASI ($p = 0.000$), which persisted by the year of treatment ($p = 0.002$).

An assessment of the content lymphocyte population showed that children with psoriasis, irrespective of the duration and effectiveness of therapy GEBD, had an increased percentage of Thact relative to the normal values (over 100; Table 1). In patients of group 1, the percentage of Thact ($p = 0.005$) and Th17 ($p = 0.001$) was significantly increased before the appointment of therapy, relative to the indicators of group 2 (Table 1, Figure 1).

At the end of the biological therapy induction course (16 weeks), children with psoriasis in group 1, as before the start of therapy, had a higher Th17 content than in group 2 (Table 1, Figure 1). The assessment of content Th17 by the year of biological therapy treatment in patients with insufficient effect also showed a significant increase in the content of this population relative to the indicators of group 2 ($p = 0.003$; Figure 1, Table 1).

Analysis of content Treg in children with psoriasis showed that regardless of the effectiveness of biological therapy both before treatment and at the end of

TABLE 1. CONTENT OF Thact, Th17, Treg POPULATIONS IN CHILDREN WITH PSORIASIS AT DIFFERENT EFFECTIVENESS OF BIOLOGICAL THERAPY (% DEVIATION FROM AGE-SPECIFIC NORM)

Population	Duration of therapy, week	Group 1 Insufficient effect (IE, n = 52)	Group 2 PASI 75 (n = 58)	p
Thact, % CD4	0	225.2 (183.3-264.1)	164.3 (114.3-235.9)	0.005
	16	181.3 (149.1-211.7)	202.3 (101.6-269.0)	0.956
	52	198 (125.0-246.9)	156.1 (79.7-169.0)	0.279
Treg, % CD4	0	31.8 (-12-82)	70.8 (4.5-136.0)	0.116
	16	66.2 (7.58-125.00)	67.5 (48.0-131.8)	0.359
	52	-18.4 (-68.2-19.6)	90.1 (16.0-159.1)	0.008
Th17, % CD4	0	73.5 (51.5-135.9)	25.2 (-5.9-54.4)	0.001
	16	161.1 (109.1-177.2)	33.7 (-5.6-83.8)	0.000
	52	117.4 (72-215)	41.7 (-1.5-56.5)	0.003

Note. p, differences between independent groups by Mann–Whitney test; $p < 0.05$.

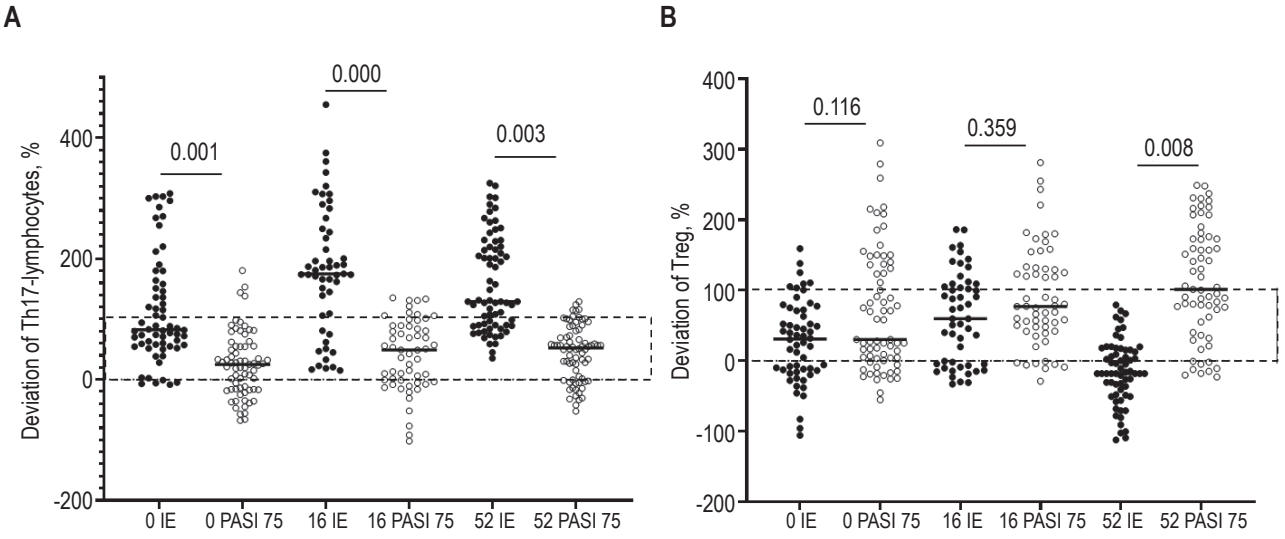

Figure 1. Deviation of the relative numbers of Th17 (A) and Treg (B) with insufficient effect (IE) and achievement of PASI 75 in children with psoriasis before, at 16 and 52 weeks of biological therapy

Note. The range of age norm was taken as 100%.

the induction course (16 weeks), the percentage of Treg in the groups was in the range of normal values (Figure 1, Table 1). However, by the year of treatment with biologics in group 1, a significant decrease in the percentage of Treg ($p = 0.008$) was obtained relative to the indicators of group 2 ($p = 0.008$), while in the group with insufficient effect of biologics, the percentage of Treg was lower than the normal values (Figure 1).

Assessment of the dynamics of T helper populations in children with psoriasis with insufficient effect of biological therapy revealed a significant increase in Th17 by 16 weeks of therapy ($p_{0-16} = 0.046$), which persisted to a year of therapy and was higher than normal values. Analysis of the dynamics of content Treg in this group showed a significant decrease in the population by year of therapy ($p_{0-52} = 0.047$, $p_{16-52} = 0.006$).

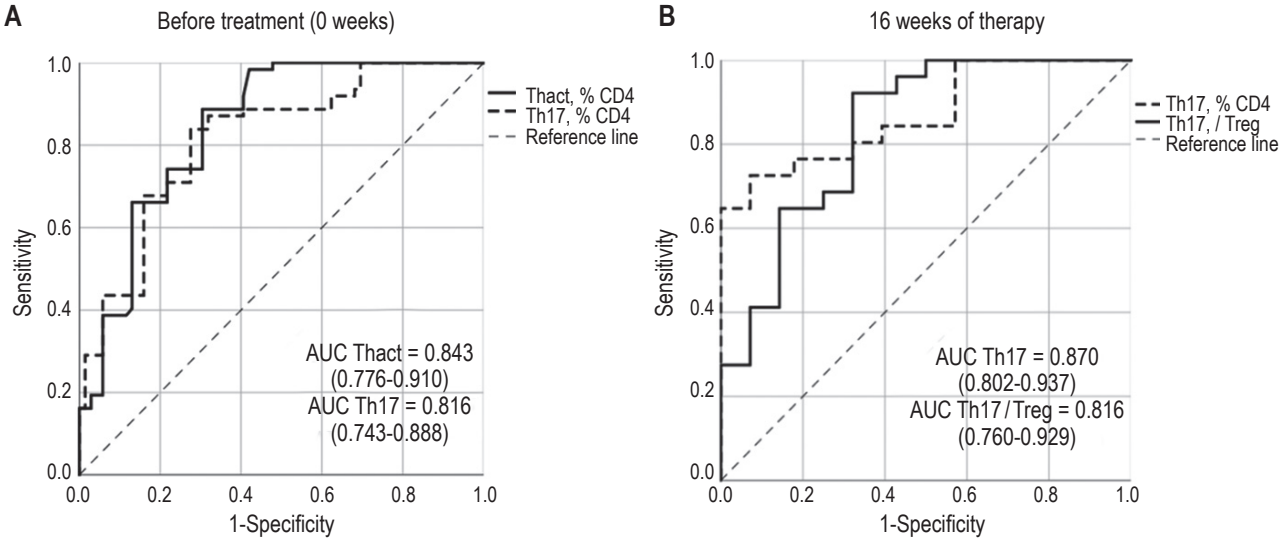

Figure 2. ROC-analysis of deviation of Th17, Thact in predicting efficacy of biological therapy in children with psoriasis before prescription (A) and Th17, ratio Th17/Treg at 16 weeks of biological therapy (B)

Note. AUC, area under curve.

Analysis of the Th17/Treg ratio in children with psoriasis at different effectiveness of biological therapy showed that the Th17/Treg ratio was significantly increased in the group of children with insufficient effect of biologics before therapy and during the year relative to group 2 (week 0: 3.0 (2.6-3.6) *vs* 1.6 (1.2-2.5), p = 0.001; week 52: 3.9 (2.6-4.3) *vs* 1.7 (1.2-2.3), p = 0.000).

The performed ROC analysis showed an excellent separating model for the "PASI 75 – insufficient effect" states for Th17, Thact and Th17/Treg ratio before the appointment of biological therapy and for Th17, Th17/Treg at 16 week of biologics (AUC > 0.8; Figure 2). The calculation of threshold values of indicators with the coincidence of sensitivity (Se) and specificity (Sp) showed that with a deviation of Th17 above 53%, Thact above 181% and Th17/Treg above 2.6 before the appointment of biologics in 75% of cases, insufficient effectiveness of biological therapy can be expected by the year. ROC analysis of the immunological parameters at 16 weeks showed that with a Th17 deviation above 102% and a Th17/Treg ratio above 2.6, there is already an 82% chance of ineffective treatment (Figure 2).

Conclusion

Thus, this analysis allowed us to identify the most informative $CD4^+$ cell counts in predicting and evaluating the effectiveness of biologics in children with psoriasis. Analysis of the dynamics of small populations T helper during year of biologics in children with different efficacy of therapy showed that the most significant changes were detected in the content of Th17 and Treg populations and their ratio (Th17/Treg), which is consistent with the results in adult patients with psoriasis [5, 7, 8, 13]. The study demonstrates the information value of content Thact estimation before biological therapy, the dynamics of Th17 by the end of induction course and the dynamics of content Treg after 16 weeks of biological therapy in prognosis of biologics efficacy in children with psoriasis.

References

1. Curmin R., Guillo S., de Rycke Y., Bachelez H., Beylot-Barry M., Beneton N., Chosidow O., Dupuy A., Joly P., Jullien D., Richard M.A., Viguier M., Sbidian E., Paul C., Mahé E., Tubach F.; PSOBIOTEQ Study GroupSwitches between biologics in patients with moderate-to-severe psoriasis: results from the French cohort PSOBIOTEQ. *J. Eur. Acad. Dermatol. Venereol., 2022, Vol. 36, no. 11, pp. 2101-2112.*

2. Duarte A., Mebrahtu T., Goncalves P.S., Harden M., Murphy R., Palmer S., Woolacott N., Rodgers M., Rothery C. Adalimumab, etanercept and ustekinumab for treating plaque psoriasis in children and young people: systematic review and economic evaluation. *Health Technol. Assess., 2017, Vol. 21, no. 64, pp. 1-244.*

3. Georgescu S.R., Tampa M., Caruntu C., Sarbu M.I., Mitran C.I., Mitran M.I., Matei C., Constantin C., Neagu M. Advances in understanding the immunological pathways in psoriasis. *Int. J. Mol. Sci., 2019, Vol. 20, no. 3, 739.* doi: 10.3390/ijms20030739.

4. Golhen K., Winskill C., Theiler M., Buettcher M., Yeh Y.-H., Zhang N., Welzel T., Pfister M. Understanding efficacy-safety balance of biologics in moderate-to-severe pediatric psoriasis. *Front. Med. (Lausanne), 2022, Vol. 9, 944208.* doi:10.3389/fmed.2022.944208.

5. Grover P., Goel P.N., Greene M.I. Regulatory T cells: Regulation of identity and function. *Front. Immunol, 2021, Vol. 12, 750542.* doi:10.3389/fimmu.2021.750542.

6. Hong J.J., Hadeler E.K., Mosca M.L., Brownstone N.D., Bhutani T., Liao W.J. TNF-alpha inhibitors and ustekinumab for the treatment of psoriasis: therapeutic utility in the era of IL-17 and IL-23 inhibitors. *J. Psoriasis Psoriatic Arthritis, 2022, Vol. 7, no. 2, pp. 79-92.*

7. Kim J., Moreno A., Krueger J.G. The imbalance between Type 17 T-cells and regulatory immune cell subsets in psoriasis vulgaris. *Front. Immunol., 2022, Vol. 13, 1005115.* doi:10.3389/fimmu.2022.1005115.

8. Kuptsova D., Radygina T., Murashkin N., Petrichuk S.V. Indicators of cellular immunity and suppressor cells of myeloid origin in children with psoriasis. *Immunopathology, Allergology, Infectology, 2020, no. 3, pp. 55-65.* (In Russ.)

9. Li B., Huang L., Lv P., Li X., Liu G., Chen Y., Wang Z., Qian X., Shen Y., Li Y., Fang W. The role of Th17 cells in psoriasis. *Immunol. Res., 2020, Vol. 68, no. 5, pp. 296-309.*

10. Mizumaki K., Horii M., Kano M., Komuro A., Matsushita T. Suppression of IL-23-mediated psoriasis-like inflammation by regulatory B cells. *Sci. Rep., 2021, Vol. 11, no. 1, pp. 1-13.*

11. Nussbaum L., Chen Y.L., Ogg G.S. Role of regulatory T cells in psoriasis pathogenesis and treatment. *Br. J. Dermatol., 2021, Vol. 184, no. 1, pp. 14-24.*

12. Orsmond A., Bereza-Malcolm L., Lynch T., March L., Xue M. Skin barrier dysregulation in psoriasis. *Int. J. Mol. Sci., 2021, Vol. 22, no. 19, 10841.* doi: 10.3390/ijms221910841.

13. Shi Y., Chen Z., Zhao Z., Yu Y., Fan H., Xu X., Bu X., Gu J. IL-21 Induces an imbalance of Th17/Treg cells in moderate-to-severe plaque psoriasis patients. *Front. Immunol., 2019, Vol. 10, 1865.* doi: 10.3389/fimmu.2019.01865.

14. Vičić M., Kaštelan M., Brajac I., Sotošek V., Massari L.P. Current concepts of psoriasis immunopathogenesis. *Int. J. Mol. Sci., 2021, Vol. 22, no. 21, 11574.* doi: 10.3390/ijms222111574.

15. Yiu Z.Z.N., Mason K.J., Hampton P.J., Reynolds N.J., Smith C.H., Lunt M., Griffiths C.E.M., Warren R.B.; BADBIR Study GroupDrug survival of adalimumab, ustekinumab and secukinumab in patients with psoriasis: a prospective cohort study from the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR). *Br. J. Dermatol., 2020, Vol. 183, no. 2, pp. 294-302.*

Авторы:

Купцова Д.Г. *— младший научный сотрудник, врач клинической лабораторной диагностики лаборатории экспериментальной иммунологии и вирусологии ФГАУ «Национальный медицинский исследовательский центр здоровья детей» Министерства здравоохранения РФ, Москва, Россия*

Радыгина Т.В. *— к.м.н., старший научный сотрудник лаборатории экспериментальной иммунологии и вирусологии ФГАУ «Национальный медицинский исследовательский центр здоровья детей» Министерства здравоохранения РФ, Москва, Россия*

Курбатова О.В. *— к.м.н., старший научный сотрудник лаборатории экспериментальной иммунологии и вирусологии ФГАУ «Национальный медицинский исследовательский центр здоровья детей» Министерства здравоохранения РФ, Москва, Россия*

Материкин А.И. *— к.м.н., врач-дерматовенеролог отделения дерматологии с группой лазерной хирургии ФГАУ «Национальный медицинский исследовательский центр здоровья детей» Министерства здравоохранения РФ, Москва, Россия*

Епишев Р.В. *— к.м.н., врач-дерматовенеролог отделения дерматологии с группой лазерной хирургии ФГАУ «Национальный медицинский исследовательский центр здоровья детей» Министерства здравоохранения РФ, Москва, Россия*

Authors:

Kuptsova D.G., *Junior Research Associate, Clinical Laboratory Physician, Laboratory of Experimental Immunology and Virology, National Medical Research Center for Children's Health, Moscow, Russian Federation*

Radygina T.V., *PhD (Medicine), Senior Research Associate, Laboratory of Experimental Immunology and Virology, National Medical Research Center for Children's Health, Moscow, Russian Federation*

Kurbatova O.V., *PhD (Medicine), Senior Research Associate, Laboratory of Experimental Immunology and Virology, National Medical Research Center for Children's Health, Moscow, Russian Federation*

Materikin A.I., *PhD (Medicine), Dermatovenerologist, Department of Dermatology with the Laser Surgery Group, National Medical Research Center for Children's Health, Moscow, Russian Federation*

Epishev R.V., *PhD (Medicine), Dermatovenerologist, Department of Dermatology with the Laser Surgery Group, National Medical Research Center for Children's Health, Moscow, Russian Federation*

Опрятин Л.А. *— врач-дерматовенеролог отделения дерматологии с группой лазерной хирургии ФГАУ «Национальный медицинский исследовательский центр здоровья детей» Министерства здравоохранения РФ, Москва, Россия*

Хотко А.А. *— к.м.н., доцент кафедры дерматовенерологии и косметологии ФГБУ ДПО «Центральная государственная медицинская академия» Управления делами Президента РФ, Москва, Россия*

Мурашкин Н.Н. *— д.м.н., руководитель НИИ детской дерматологии, заведующий отделением дерматологии с группой лазерной хирургии и заведующий лабораторией патологии кожи у детей отдела научных исследований в педиатрии ФГАУ «Национальный медицинский исследовательский центр здоровья детей» Министерства здравоохранения РФ; профессор кафедры дерматовенерологии и косметологии ФГБУ ДПО «Центральная государственная медицинская академия» Управления делами Президента РФ; профессор кафедры педиатрии и детской ревматологии ФГАОУ ВО «Первый Московский государственный медицинский университет имени И.М. Сеченова» Министерства здравоохранения РФ (Сеченовский университет), Москва, Россия*

Петричук С.В. *— д.б.н., профессор, главный научный сотрудник лаборатории экспериментальной иммунологии и вирусологии ФГАУ «Национальный медицинский исследовательский центр здоровья детей» Министерства здравоохранения РФ, Москва, Россия*

Opryatin L.A., *Dermatovenerologis, Department of Dermatology with the Laser Surgery Group, National Medical Research Center for Children's Health, Moscow, Russian Federation*

Khotko A.A., *PhD (Medicine), Associate Professor, Department of Dermatology and Cosmetology, Central State Medical Academy of Department of Presidential Affairs, Moscow, Russian Federation*

Murashkin N.N., *PhD, MD (Medicine), Professor, Head of the Research Institute of Pediatrics Dermatology, Dermatology Department with Laser Surgery Unit and Children's Skin Pathology Laboratory, National Medical Research Center for Children's Health; Professor, Department of Dermatovenereology and Cosmetology, Central State Medical Academy of Department of Presidential Affairs; Professor, Department of Pediatrics and Pediatric Rheumatology, I. Sechenov First Moscow State Medical University, Moscow, Russian Federation*

Petrichuk S.V., *PhD, MD (Biology), Professor, Chief Research Associate, Laboratory of Experimental Immunology and Virology, National Medical Research Center for Children's Health, Moscow, Russian Federation*

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