

РОЛЬ КЛЕТОК-СУПРЕССОРОВ МИЕЛОИДНОГО ПРОИСХОЖДЕНИЯ В ПРОГНОЗЕ ЭФФЕКТИВНОСТИ ГЕННО-ИНЖЕНЕРНЫХ БИОЛОГИЧЕСКИХ ПРЕПАРАТОВ У ДЕТЕЙ С ПСОРИАЗОМ

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Резюме. Псориаз – хроническое воспалительное заболевание кожи характеризуется повышенной пролиферацией эпидермальных клеток, нарушением кератинизации и воспалительной реакцией в дерме, обусловленной активацией Т-лимфоцитов и синтезом провоспалительных цитокинов. Патология псориаза связана не только с активацией провоспалительных реакций, а также со снижением противовоспалительных функций иммуносупрессорных клеток. Известно, что Treg, Vreg и клетки-супрессоры миелоидного происхождения (MDSCs) не выполняют свои классические гомеостатические функции при псориазе. В последние годы все чаще встречаются случаи развития резистентности к проводимой терапии генно-инженерными биологическими препаратами (ГИБП) в детском возрасте, требующие замены или отмены препарата. Цель исследования состояла в оценке содержания субпопуляций MDSCs и их функциональной активности в периферической крови у детей с псориазом при разной эффективности ГИБП. Обследовано 110 детей с вульгарным псориазом до назначения биологической терапии, на 16-й и 52-й неделях терапии адалимумабом, этанерцептом и устикинумабом, в возрасте от 6 до 18 лет. Группу сравнения – 34 здоровых ребенка, сопоставимых по возрасту. Эффективность терапии оценивали по достижению PASI 75 к году терапии. Методом многоцветной проточной цитометрии проводили оценку содержания MDSCs и их субпопуляций, и активности аргиназы-1. Установлено увеличение содержания MDSCs у детей с псориазом относительно группы сравнения ($p = 0,000$). Анализ эффективности биологической терапии у детей с псориазом,

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по индексу PASI, показал достоверное снижение тяжести заболевания в группе пациентов с хорошим эффектом, как на 16 неделе терапии ($p = 0,000$), так и к году лечения ГИБП ($p = 0,017$). У детей с псориазом при разной эффективности и длительности биологической терапии выявлена разная динамика содержания MDSCs. В группе пациентов с хорошим эффектом биологической терапии, как до начала лечения, так и к 52-й неделе терапии, выше процент общей популяции MDSCs ($p < 0,01$). У детей с псориазом выявлено увеличение иммуносупрессивной функций MDSCs по активности аргиназы-1 относительно группы сравнения (Me 3,2 (3,0-3,4) MFI против Me 2,7 (2,6-2,9) MFI; $p = 0,000$). Активность аргиназы-1 у пациентов с псориазом в стадии регресса заболевания (PASI < 10) достоверно увеличена относительно детей в прогрессирующей стадии псориаза (PASI \geq 10; $p = 0,001$). Таким образом, содержание MDSCs и их супрессорная активность MDSCs у детей с псориазом информативна в прогнозе эффективности терапии ГИБП. Ускользание эффекта биологической терапии после индукционного курса сопровождается снижением количества MDSCs и их функциональной активности.

Ключевые слова: MDSCs, аргиназа-1, дети, псориаз, биопрепараты, проточная цитометрия

ROLE OF MYELOID-DERIVED SUPPRESSOR CELLS IN PREDICTION OF THE EFFECTIVENESS OF BIOLOGICS IN CHILDREN WITH PSORIASIS

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Abstract. Psoriasis is a chronic inflammatory skin disease characterized by increased proliferation of epidermal cells, impaired keratinization, and an inflammatory reaction in the dermis due to activation of T-lymphocytes and synthesis of proinflammatory cytokines. Pathophysiology of psoriasis is associated not only with activation of proinflammatory reactions, but also with decreased anti-inflammatory functions of immunosuppressive cells. It is known that Treg, Breg and MDSCs do not perform their classical homeostatic functions in psoriasis. In recent years, there have been more and more cases of developing resistance to ongoing therapy with genetically engineered biological drugs (GEBD) in childhood, requiring replacement or discontinuation of the drug. The aim of our work was to estimate the content of MDSCs subpopulations and their functional activity in the peripheral blood of children with psoriasis at different effectiveness of biotherapeutic drugs. We examined 110 children with psoriasis vulgaris before the appointment of biologics, at 16 and 52 weeks of therapy with adalimumab, etanercept and ustikinumab, aged 6 to 18 years. Comparison group consisted of 34 healthy children. The effectiveness of therapy was assessed by the achievement of PASI 75 by one year of therapy. Contents of myeloid-derived suppressor cells (MDSCs) and their subpopulations, and the activity of arginase-1 were assessed by multicolor flow cytometry. An increased content of MDSCs was found in children with psoriasis against the comparison group ($p = 0.000$). Analysis of the effectiveness of biologics in children with psoriasis, according to PASI, showed a significant reduction in disease severity in the group of patients with good effect, both at week 16 of therapy ($p = 0.000$) and by one year ($p = 0.017$). In the group of patients with good effect of biological therapy, percentage of total MDSCs population was higher, both before start of treatment and by 52nd week of therapy ($p < 0.01$). Children with psoriasis showed increased immunosuppressive function of MDSCs by arginase-1 activity versus the comparison group ($p = 0.000$). The arginase-1 activity in patients with psoriasis at the stage of disease regression (PASI < 10) was significantly increased relative to children in progressive stage of psoriasis (PASI \geq 10; $p = 0.001$). Thus, the content of MDSCs and their suppressive activity in children with psoriasis is an informative efficiency predictor of the biological drugs. Fading of biotherapy effect after the induction course is accompanied by decreased number of MDSCs and their functional activity.

Keywords: myeloid-derived suppressor cells, arginase-1, children, psoriasis, biologics, flow cytometry

Introduction

Psoriasis is a chronic inflammatory skin disease with hereditary predisposition and is characterized by increased proliferation of epidermal cells, impaired keratinization, and an inflammatory response in the dermis due to activation of T lymphocytes and synthesis of proinflammatory cytokines [1, 6]. The pathophysiology of psoriasis is related not only to the activation of proinflammatory reactions, but also to a decrease in the anti-inflammatory functions of immunosuppressor cells. In particular, it has been shown that regulatory T cells, regulatory B cells, and myeloid-derived suppressor cells (MDSCs) do not perform their classical homeostatic functions in psoriasis [9, 10].

MDSCs are a population of immature myeloid cells with an immune regulatory role [3, 11]. MDSCs originate from common myeloid precursors in the bone marrow and under normal conditions differentiate into endothelial cells, macrophages, dendritic cells, or neutrophils [8]. However, under inflammatory conditions, aberrant resistant myelopoiesis can lead to the accumulation of immature myeloid cells. Increased growth factors (GM-CSF and VEGF) and cytokines (TNF α , IFN γ , IL-1 β , IL-6 and TGF β) are known to accelerate the expansion of MDSCs in the bone marrow and lead to the accumulation of these cells in the periphery [2, 13]. MDSCs possess surface markers of myeloid cells and have no specific markers characteristic of lymphocytes, dendritic cells, natural killer cells, and macrophages [13, 14]. MDSCs express CD11b⁺ and CD33⁺ myeloid cell markers, but are negative for HLA-DR antigens and linear specific antigens (Lin) such as CD3, CD19, and CD56 [7]. Two main subpopulations of MDSCs are currently characterized: monocytic (M-MDSCs) and granulocytic (G-MDSCs) [4, 13].

MDSCs exhibit suppressor activity against innate and adaptive immune cells using different immunosuppression mechanisms [4, 13, 14]. One of the mechanisms by which MDSCs develop immunosuppression is the depletion of nutrients for T cells, in particular arginine stores. MDSCs produce the enzyme arginase-1, which degrades arginine and also causes damage to the α -chain of the TCR, thus blocking activation and proliferation T cells [2, 4, 13]. MDSCs modulate the immune response in a variety of diseases, including numerous types of cancer, inflammatory bowel disease, trauma, burns, infections, and transplants [2, 3, 11, 13]. Previously, we showed that children with psoriasis have increased levels of MDSCs relative to healthy children [6]. Also, adult patients with psoriasis have been shown to have increased MDSCs in peripheral blood compared to

healthy controls, which is associated with the severity and duration of the disease [2, 3, 8, 15].

To treat psoriasis in children, algorithms for external and systemic therapy have been developed based on physical examination and clinical evaluation of characteristic signs and changes in the patient's skin. In cases of moderate or severe disease, as well as in the ineffectiveness of previously used therapy, the prescription of genetically engineered biological drugs (GEBD) is indicated [1, 10]. The targeting effect of biologics is based on the blockade of the main proinflammatory cytokines involved in the pathogenesis of psoriasis, such as TNF α , IL-17, IL-12 and IL-23 [1, 3, 10]. To achieve a sustained remission on biologics requires long-term treatment, which, unfortunately, does not guarantee the preservation of the effect in the case of drug withdrawal. One of the factors of loss of response to GEBD therapy is the production of antibodies to biological drugs, and monitoring their level is recognized as a necessary criterion for controlling the ongoing treatment [5]. In recent years, there have been more and more cases of development of resistance to the ongoing therapy of GEBD in children, requiring replacement or withdrawal of the drug [5, 12]. In this connection, the search for informative immunological criteria of effectiveness of biologics for psoriasis, as well as the identification of factors that lead to a decrease or absence of the effect of GEBD in patients with psoriasis, remains relevant.

The aim of the study was to evaluate the content of MDSCs subpopulations and their functional activity in peripheral blood in children with psoriasis at different efficacy of GEBD.

Materials and methods

The study included 110 children with vulgar psoriasis who were treated with HIBP at the Department of Dermatology with the Laser Surgery Group of the Federal State Institution "Scientific and Research Center of Children's Health" of the Ministry of Health of Russia. The patients were examined before biological therapy, at weeks 16 and 52 of therapy with adalimumab, etanercept and ustekinumab. Inclusion criteria in the study: age of children 6-18 years old, established diagnosis of psoriasis vulgaris, compliance with the multiplicity and dose of GEBD administration. Exclusion criteria: other forms of psoriasis in children, age over 18 years, 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 effectiveness of therapy was assessed by achieving PASI 75 by one year of therapy: group 1

included children with an insufficient effect of GEBD (“IE”, less than PASI 75, n = 52), group 2 included children with a good effect (“PASI 75” or more, n = 58). The children examined ranged in age from 6 to 18 years, children in 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. 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).

The content of MDSCs subpopulations was determined by stepwise gating according to a previously described algorithm [6], using multicolor flow cytometry: including the isolation of the “lymphoid-monocytic” region, the isolation of a population of cells that do not carry linear lymphocytic markers CD3, CD19, CD56 with PE fluorochrome and are negative for HLA-DR – FITC, the isolation of a double positive population for CD11b markers – APC-Cy7 and CD33 – PE-Cy7, division of the subpopulation of MDSCs by expression of CD14 – PerCP and CD15 – APC (Beckman Coulter, Sony Biotechnology, USA). The MDSCs were phenotyped as monocytic (M-MDSCs) with the phenotype CD11b⁺CD14⁺CD33⁺HLA-DR^{-/low}, granulocytic subpopulation (G-MDSCs) as CD11b⁺CD15⁺CD33⁺HLA-DR^{-/low} and population cells negative CD14 and CD15 (M⁻G⁻-MDSCs) with the phenotype CD11b⁺CD33⁺HLA-DR^{-/low}CD14⁻CD15⁻.

The immunosuppressive ability of the MDSCs population was assessed by the activity of the

intracellular enzyme arginase-1 in 40 children with psoriasis and 32 children in the comparison group. Sample preparation included isolation of peripheral blood mononuclear cells from patients. To the isolated cell suspension (100 μL), 10 μL of monoclonal antibodies were added according to the following panel: CD3, CD19, CD56, HLA-DR – FITC (cocktail), CD11b – APC-Cy7 and CD33 – PE-Cy7. Permeabilization cells was performed using the BD Cytotfix/Cytoperm kit (USA) according to the manufacturer’s instructions. After permeabilization of the cells, 10 μl of arginase-1 with fluorochrome PE was added and incubated for 20 min in a dark place. The sample was recorded on a Novocyte flow cytometer (ACEA Biosciences, USA). The activity of arginase-1 enzyme was determined by mean fluorescence intensity – MFI.

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.

Results and discussion

Assessment of the MDSCs population in children with psoriasis showed a significant increase in this population relative to the comparison group (Table 1). The increase in the relative amount of the MDSCs population is mainly due to the monocytic MDSCs subpopulation (M-MDSCs). A significant increase in both the absolute and relative numbers of M-MDSCs,

TABLE 1. RELATIVE AND ABSOLUTE NUMBER OF MDSCS AND THEIR SUBPOPULATIONS IN CHILDREN WITH PSORIASIS AND IN THE COMPARISON GROUP

Population cells		Psoriasis (n = 110)	Comparison group (n = 32)	p
MDSCs	cells/μL	75 (48-114)	41 (25-53)	0.000
	% PBMCs	2.7 (1.6-3.9)	1.4 (0.9-1.7)	0.000
M-MDSCs	cells/μL	10 (4-26)	3 (1-8)	0.000
	% MDSCs	14.5 (5.7-29.1)	9.7 (6.6-16.1)	0.006
G-MDSCs	cells/μL	15 (6-32)	8 (4-16)	0.001
	% MDSCs	21.0 (10.9-36)	25.2 (12.6-43.8)	0.339
M ⁻ G ⁻ -MDSCs	cells/μL	39 (25-58)	21 (9-35)	0.000
	% MDSCs	54.7 (38.9-70.1)	66.3 (43.2-77.2)	0.032

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

as well as in the absolute numbers of G-MDSCs and M-G-MDSCs, with a decrease in the relative number of nondifferentiated MDSCs (M-G-MDSCs), relative to those in the comparison group, was found for children with psoriasis (Table 1).

Analysis of the effectiveness of biologics in children with psoriasis, according to the PASI index, showed a significant and significant reduction in the severity of the disease in the patient group when PASI 75, both at 16 weeks of therapy (from 20.1 (14.0-31.0) to 11.3 (7.0-15.0), $p = 0.000$), and by one year of GEBD treatment – 6.1 (1.5-9.9), $p = 0.017$. In the group of children with insufficient effect of biologics the decrease of PASI index was less pronounced and by one year of therapy PASI was higher than 10 points (16 weeks – 16.2 (15.0-21.0), 52 weeks of GEBD – 10.9 (4.9-22.0)). Before prescription of biological therapy, groups 1 and 2 did not differ in terms of PASI index ($p = 0.631$), but starting from week 16 of therapy, PASI index in the group of patients with good effect was significantly lower than in the group with poor effect.

Analysis of the content of MDSCs subpopulations at different efficacy of GIBP in children with psoriasis showed that the percentage of total MDSCs population was significantly reduced in the group of patients with insufficient effect of biologics, both before treatment started and by 52 weeks of therapy relative to group 2 (Figure 1).

In children with psoriasis, different dynamics in the content of MDSCs subpopulations were revealed with

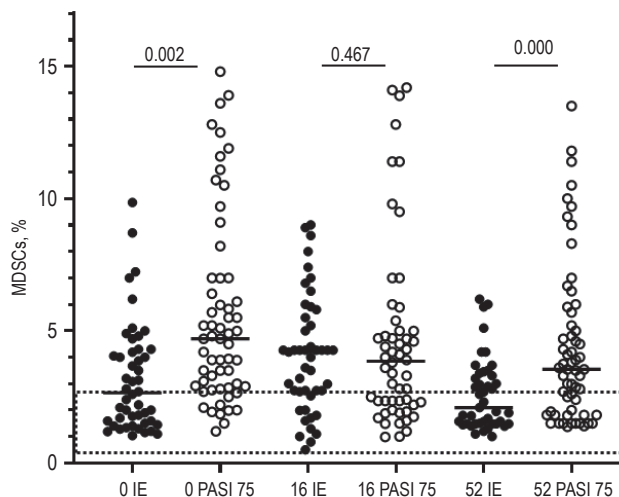


Figure 1. Relative number of MDSCs at insufficient effect (IE) and reaching PASI 75 (PASI 75) in children with psoriasis at 0, 16, 52 weeks of biological therapy

Note. The dotted line indicates the range of the comparison group.

different efficacy and duration of biologics: at the time of incubation course of GEBD therapy, a significantly lower percentage of M-MDSCs was obtained in group 1 compared to group 2 ($p = 0.041$). By one year of GEBD therapy, a significant increase in the granulocyte subpopulation of G-MDSCs ($p = 0.003$) with a decrease in the number of undifferentiated M-G-MDSCs was obtained in the group with a good effect ($p = 0.000$; Table 2).

TABLE 2. CONTENT OF SUBPOPULATIONS OF MDSCs IN CHILDREN WITH PSORIASIS IN PERIPHERAL BLOOD WITH DIFFERENT EFFECTIVENESS OF BIOLOGICS

Population	Duration of therapy, week	Group 1 Insufficient effect (IE, n = 52)	Group 2 Achievement of PASI 75 (n = 58)	p
MDSCs, % PBMCs	0	2.0 (1.5-3.8)	3.2 (2.8-5.8)	0.002
	16	4.1 (2.5-5.1)	2.9 (2.1-4.7)	0.467
	52	1.4 (1.0-2.3)	3.6 (1.8-6.1)	0.000
M-MDSCs, % MDSCs	0	21 (7.4-40.6)	18.7 (16.3-33.9)	0.682
	16	12.9 (6.7-30.4)	24.8 (11.7-35.3)	0.041
	52	17.2 (3.1-36.2)	19.3 (1.3-32.1)	0.915
G-MDSCs, % MDSCs	0	24.2 (14.4-37.1)	29.3 (15.1-43.2)	0.347
	16	28.2 (11.6-42.8)	21.1 (15.0-36.8)	0.613
	52	10.4 (4.0-16.1)	19.8 (8.7-59.3)	0.003
M-G-MDSCs, % MD-SCs	0	42.1 (30.2-53.0)	43 (20.6-48.9)	0.400
	16	50.1 (31.4-58.8)	48.3 (25.7-65.6)	0.231
	52	59.7 (59.7-87.0)	48.7 (26.1-60.8)	0.000

ROC analysis for MDSCs and their subpopulations before and at week 16 of therapy revealed only an average (AUC < 0.7) and poor quality (AUC < 0.6) divisor model for the PASI 75 states and insufficient effect: AUC MDSCs 0 week – 0.677; AUC MDSCs 16 week – 0.543. Thus, children with psoriasis showed higher levels of MDSCs prior to therapy than those in the insufficient-effect group when the biologics had a good effect ($p = 0.002$). However, because of the wide variation in the indices, it is impossible to calculate a reliable cut-off level for predicting efficacy.

Assessment of the immunosuppressive function of MDSCs by intracellular arginase-1 enzyme activity showed a significant increase in enzyme activity in children with psoriasis relative to the comparison group (Me 3.2 (3.0-3.4) MFI versus Me 2.7 (2.6-2.9) MFI; $p = 0.000$).

A direct correlation between arginase-1 activity and the relative number of G-MDSCs ($r = 0.30$; $p = 0.022$), M-MDSCs ($r = 0.40$; $p = 0.002$) and inverse with M-G-MDSCs ($r = -0.54$; $p = 0.000$) was detected. No direct correlation of the enzyme activity with the age of children and the duration of psoriasis disease was detected. Analysis of arginase-1 activity in patients with psoriasis in the disease regression stage

(PASI < 10) and in the progressive stage of the disease (PASI ≥ 10) showed a significant increase in arginase-1 activity in the regression stage (Me 3.2 (3.16-3.57) MFI versus 2.98 (2.88-3.01) MFI; $p = 0.001$).

Conclusion

Children with psoriasis with a good effect of biologics showed higher levels of MDSCs before the start of therapy and during the year of therapy than those in the group of children with ineffectiveness. The activity of arginase-1 in MDSCs in children with psoriasis was significantly increased in comparison with the comparison group. A direct correlation between arginase-1 activity and the relative number of G-MDSCs, M-MDSCs, and an inverse correlation with M-G-MDSCs was detected. In children in the progressive stage of psoriasis (PASI > 10), arginase-1 enzyme activity is significantly lower than in the regressive stage of the disease. Thus, the content of MDSCs and their suppressor activity of MDSCs in children with psoriasis is informative in predicting the effectiveness of HDI therapy. The slippage of the effect of biological therapy after the induction course is accompanied by a decrease in the number of MDSCs and their functional activity.

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