

Population of Th1/Th17 lymphocytes in the prognosis of the effectiveness of biological therapy in children with autoimmune diseases

SCO — краткое сообщение

<https://doi.org/10.53529/2500-1175-2025-4-101-104>


Svetlana V. Petrichuk, Tatyana V. Radigina, Daria G. Kuptsova, Olga V. Kurbatova, Matvey V. Konyashin, Andrey P. Fisenko

National Medical Research Center for Children's Health, Federal State Autonomous Institution of the Ministry of Health of the Russian Federation, Moscow, Lomonosovsky Prospect, Building 2, Building 1, Russian Federation

Keywords: children, autoimmune diseases, biological therapy, efficacy prognosis, Th17/Th1 lymphocytes

For citation: Petrichuk S.V., Radigina T.V., Kuptsova D.G., Kurbatova O.V., Konyashin M.V., Fisenko A.P. Population of Th1/Th17 lymphocytes in the prognosis of the effectiveness of biological therapy in children with autoimmune diseases. *Allergology and Immunology in Pediatrics*. 2025; 23 (4): 101–104. <https://doi.org/10.53529/2500-1175-2025-4-101-104>

Популяция Th17/Th1 лимфоцитов в прогнозе эффективности биологической терапии у детей с аутоиммунными заболеваниями

<https://doi.org/10.53529/2500-1175-2025-4-101-104>

Петричук С. В., Радыгина Д. Г., Купцова Д. Г., Курбатова О. В., Коняшин М. В., Фисенко А. П.

ФГАУ «Национальный медицинский исследовательский центр здоровья детей» Министерства здравоохранения РФ, 119991, г. Москва, Ломоносовский проспект, 2, с. 1, Россия

Ключевые слова: дети, аутоиммунные заболевания, биологическая терапия, прогноз эффективности, Th17/Th1 лимфоциты

Для цитирования: Петричук С.В., Радыгина Д.Г., Купцова Д.Г., Курбатова О.В., Коняшин М.В., Фисенко А.П. Популяция Th17/Th1 лимфоцитов в прогнозе эффективности биологической терапии у детей с аутоиммунными заболеваниями. *Аллергология и иммунология в педиатрии*. 2025; 23 (4): 101–104. <https://doi.org/10.53529/2500-1175-2025-4-101-104>

INTRODUCTION

The use of genetically engineered biological drugs (GEBD) in pediatric practice allows for the control of moderate and severe forms of autoimmune diseases, such as rheumatoid arthritis, inflammatory bowel disease (IBD), multiple sclerosis (MS), psoriasis (PS). Despite the proven effectiveness of biological therapy, a quarter of patients experience initial ineffectiveness of GEBD, and a third of patients experience a loss of effect after a year of therapy [1]. There is a need to search for peripheral blood biomarkers capable of predicting the effectiveness of GEBD.

Upon activation, naive CD4⁺ T cells differentiate into various populations of Th effector cells (Th1, Th2, Th17, Treg, Th9, Th22, follicular Th helpers) depending on the local cytokine environment. Th17 cells are of particular importance, playing a critical role in protecting the body from extracellular pathogens, as well as in the pathogenesis of autoimmune diseases. Being able to change their phenotype within their lineage, Th17 lymphocytes are highly plastic and can acquire the characteristics of effector

cells—Th1, Th2, T follicular helper (Tfh) cells—as well as regulatory T cells [2, 3]. In autoimmune diseases, redifferentiated Th17 lymphocytes more often form a population with a Th17/Th1 phenotype, combining the characteristics of both Th17 and Th1 lymphocytes and possessing high pro-inflammatory potential, as well as a unique ability to overcome histohematological barriers [3]. Classic Th17 lymphocytes are characterized by specific membrane markers, such as the lectin-like killer cell receptor CD161 and the chemokine receptor CCR6 (CD196), and are capable of producing the cytokines IL-17A, IL-17F, and IL-22. The Th17/Th1 population has the ability to produce an additional pro-inflammatory cytokine characteristic of the Th1 population, IFN γ , and has phenotypic features common to both Th17 and Th1 lines (CD4⁺CD161⁺CCR6⁺CXCR3⁺IL 17⁺IFN γ ⁺T cells). It has been shown that the plasticity of Th17 cell differentiation is characteristic of the progression of autoimmune diseases, and Th17/Th1 cells are more pathogenic due to increased levels of proinflammatory cytokines and a pronounced ability to proliferate.

In addition, the Th17/Th1 population is not inhibited by Treg cells compared to classical Th17 or Th1 lymphocytes [2]. Although Th17/Th1 cells are also found in healthy donors, interest in this population is due to a significant presence of these cells in inflammatory foci in multiple sclerosis [4], sarcoidosis [3], rheumatoid arthritis [2], and inflammatory bowel diseases [5]. It has also been shown that infiltrates of inflamed tissues account for up to half of the lymphocytes present there. Moreover, the process of redifferentiation of Th17 into Th1 is currently considered a promising direction for the treatment of autoimmune diseases [3].

Objective: to evaluate the informative value of determining the Th17/Th1 lymphocyte population in predicting the effectiveness of biological therapy in children with autoimmune diseases.

MATERIALS AND METHODS

A total of 263 children aged 3 to 18 years with autoimmune diseases undergoing pathogenetic therapy and receiving treatment at the Federal State Budgetary Institution “National Medical Research Center for Children’s Health” of the Ministry of Health of Russia were examined, including 113 children with inflammatory bowel diseases (Crohn’s disease (CD), $n = 74$; ulcerative colitis (UC), $n = 39$), 68 children with multiple sclerosis (MS), and 82 children with psoriatic arthritis (PA). The activity of the inflammatory process was assessed in children with IBD using the PCDIA index for CD and the PUCAI index for UC, in children with PA using the PASI (Psoriasis Area and Severity Index) and BSA (Body Surface Area) indices, and in patients with MS using the presence of demyelination foci on MRI. Patients were examined prior to the initiation of biological therapy (in patients with IBD — anti-TNF therapy with infliximab (IFX) and adalimumab (ADA), in patients with PA — therapy with ADA and ustekinumab (UST), in patients with MS — therapy with interferon $\beta 1\alpha$ (IFN $\beta 1\alpha$); the clinical effect of therapy was assessed after one year. The examination was performed in accordance with ethical standards and approved by the local ethics committee of the Federal State Budgetary Institution “National Medical Research Center for Children’s Health” of the Ministry of Health of Russia.

Immunophenotyping of blood lymphocytes was performed using flow cytometry (Novocyte, ACEA Biosciences, USA). The following monoclonal an-

tibodies conjugated with fluorochromes were used: CD4-FITC, CD127-PE, CD25-PC7, CD161-PE, CD3-PC5, CD196(CCR6)-PE-Cy7, CD183(CXCR3)-APC. To isolate populations of regulatory T cells (Treg; $CD4^+CD25^{high}CD127^{low}$), Th17 lymphocytes ($CD4^+CD161^+CD3^+$) and Th17/Th1 lymphocytes ($CD4^+CD3^+CD161^+CD196^+CD183^+$) a stepwise gating strategy was used. The percentage of Treg, Th17, and Th1/Th17 cells from $CD4^+$ T lymphocytes was evaluated. The percentage of Treg, Th17, and Th1/Th17 cells from $CD4^+$ T lymphocytes was evaluated. Statistical data processing was performed using Statistica 16.0 (StatSoft, USA). ROC analysis was performed using IBM SPSS Statistics 27. The data are presented in the following format: median (lower and upper quartiles) — Med ($Q_{0,25}$; $Q_{0,75}$). The Mann-Whitney nonparametric test was used to assess the statistical significance of the differences; differences were considered significant at $p < 0.05$.

RESULTS AND DISCUSSION

The analysis revealed that the content of proinflammatory Th17/Th1 cells in the circulation of the studied sample of patients with autoimmune pathology varied from 3 to 45% of $CD4^+$ T cells. It was found that the content of this population before the appointment of biological therapy in children with IBD, MS, and PS correlated with the effectiveness of treatment by the year of therapy. In all pathological conditions, patients with insufficiently effective (IE) treatment by the end of the year of therapy were characterized by a significantly higher content of the Th1/Th17 cell population compared to patients with effective treatment. The Th1/Th17 cell content in patients with IBD in the IE group was 19.0 [12.7; 24.4]% versus 12.6 [8.5; 16.5]% in the group of children with effective therapy ($p < 0.001$); for patients with MS: 14.5 [11.3; 21.9]% versus 11.1 [10.1; 13.6]% ($p = 0.007$); for patients with PD: 12.8 [10.9; 14.4] vs. 7.1 [5.0; 9.6] ($p < 0.001$). It was found that patients with IBD and MS did not differ in terms of Th17/Th1 cell content in either the NE group or the effective therapy group, while patients with PS had lower values in both groups ($p < 0.001$). The ROC analysis showed good quality of the “IE-effectiveness” status separation model for patients with IBD AUC = 0.809 (0.72–0.84) and for patients with MS AUC = 0.783 (0.67–0.90), and excellent quality of the model for patients with PS AUC = 0.931 (0.86–0.99). At the same time, the cutoff point at the minimum differ-

ence between sensitivity and specificity coefficients was: for VZV — 15.6%, for RS — 12.8%, for patients with PS — 9.9% of CD4⁺ T cells. It is interesting to note that our results are consistent with those of Quirant-Sánchez B. et al [4], who, using Kaplan-Meier survival analysis in patients with MS, showed that patients with a Th1Th17_{CM} cell content (CD4⁺C-CR7⁺CD45RA⁻CCR6⁺CXCR3⁺) less than 11.48% had an 88% recurrence-free survival rate, while those with Th1Th17_{CM} greater than 11.48% had a recurrence-free survival rate of only 50% ($p = 0.013$). Furthermore, it has been demonstrated that, regardless of the drug (dimethylfumarate, fingolimod), an increased percentage of Th1Th17_{CM} lymphocytes before treatment can be a prognostic biomarker for MS relapses or MRI activity during the first 12 months of therapy [4].

Correlation analysis did not reveal any significant relationships between the Th17/Th1 population content and patient age or disease duration. A significant direct relationship was found between the content of dual Th17/Th1 cells and Th17 lymphocytes (CD4⁺CD161⁺CD3⁺) for all the studied pathologies: the regression equation for patients with IBD was: $Y = -2.1 + 0.69 \times X$ ($R = 0.83$; $p < 0.001$), for patients with MS: $Y = 1.3 + 0.54 \times X$ ($R = 0.82$; $p < 0.001$), for patients with PS: $Y = 2.5 + 0.38 \times X$ ($R = 0.73$; $p < 0.001$), where X is the content of Th17 lympho-

cytes, and Y is the content of Th17/Th1 cells, R is the correlation coefficient. The obtained regression coefficients show that the Th17/Th1 population accounts for approximately 69% of Th17 lymphocytes in patients with IBD, about 54% in patients with MS, and about 38% in patients with PS. No correlation was found between the content of Th17/Th1 cells and Treg in all the pathologies studied. We have previously shown that an increased content of Th17 lymphocytes, as well as an increase in the Th17/Treg ratio, is a prognostic marker of the loss of the effect of biological therapy in these pathologies [6–8]. It was shown that the Th17/Th1 cell population studied in this work using the approach of assessing CCR6/CXCR3 coexpression consists of two populations: Th17.1 (IL-17/IFN γ) and ex-Th17 (IFN γ) [9]. The ex-Th17 (IFN γ) population is considered to be the most autoaggressive and requires further study in autoimmune diseases.

CONCLUSION

The Th17/Th1 ratio varies depending on the pathology, with the highest ratios found in children with inflammatory bowel disease. Th17/Th1 thresholds have been identified for children with IBD, MS, and PS, allowing for the prediction of the response to biological therapy.

REFERENCES

1. Chanchlani N., Lin S., Bewshea C., Hamilton B., Thomas A., Smith R., Roberts C., Bishara M., Nice R., Lees C.W., Sebastian S., Irving P.M., Russell R.K., McDonald T.J., Goodhand J.R., Ahmad T., Kennedy N.A.; PANTS Consortium. Mechanisms and management of loss of response to anti-TNF therapy for patients with Crohn's disease: 3-year data from the prospective, multicentre PANTS cohort study. *Lancet Gastroenterol Hepatol*. 2024; 9 (6): 521–538. [https://doi.org/10.1016/S2468-1253\(24\)00044-X](https://doi.org/10.1016/S2468-1253(24)00044-X).
2. Yang P., Qian F.Y., Zhang M.F., et al. Th17 cell pathogenicity and plasticity in rheumatoid arthritis. *J Leukoc Biol*. 2019; 106 (6): 1233–1240. <https://doi.org/10.1002/JLB.4RU0619-197R>.
3. Kuklina E.M., Glebezdina N.S. Markers of Th1 polarized Th17 cells (literature review). *Acta biomedica scientifica*. 2023; 8 (3): 55–62. <https://doi.org/10.29413/ABS.2023-8.3.5>. (In Russ.)
4. Quirant-Sánchez B., Presas-Rodriguez S., Mansilla M.J., et al. Th1Th17_{CM} Lymphocyte Subpopulation as a Predictive Biomarker of Disease Activity in Multiple Sclerosis Patients under Dimethyl Fumarate or Fingolimod Treatment. *Mediators Inflamm*. 2019; 2019: 8147803. Published 2019 Jun 26. <https://doi.org/10.1155/2019/8147803>.
5. Cao H., Diao J., Liu H., Liu S., Liu J., Yuan J., Lin J. The Pathogenicity and Synergistic Action of Th1 and Th17 Cells in Inflammatory Bowel Diseases. *Inflamm Bowel Dis*. 2023 May 2; 29 (5): 818–829. <https://doi.org/10.1093/ibd/izac199>. PMID: 36166586.
6. Petrichuk S.V., Miroshkina L.V., Semikina E.L., Toptygina A.P., Potapov A.S., Tsimbalova E.G., Radygina T.V. Indicators of the lymphocyte subsets as efficiency predictors of therapy with inhibitors of TNF α in children with inflammatory bowel disease. *Medical Immunology (Russia) / Meditsinskaya Immunologiya*. 2018; 20 (5): 721–730. <https://doi.org/10.15789/1563-0625-2018-5-721-730>. (In Russ.)
7. Radygina T.V., Kuptsova D.G., Kurbatova O.V., Petrichuk S.V., Semikina E.L., Fisenko A.P., Abdullaeva L.M., Bursagova B.I. Features of parameters of cellular immune depending on the activity of foci of demyelination in children with multiple sclerosis.

- Medical Immunology (Russia) / Meditsinskaya Immunologiya. 2023; 25 (5): 1019–1026. <https://doi.org/10.15789/1563-0625-FOP-2777>. (In Russ.)
8. Kuptsova D.G., Radigina T.V., Kurbatova O.V., Materikin A.I., Epishev R.V., Opryatin L.A., Khotko A.A., Murashkin N.N., Petrichuk S.V. Content of CD4+T cell populations in predicting the efficacy of biological therapy for psoriasis in children. Medical Immunology (Russia) / Meditsinskaya Immunologiya. 2023; 25 (5): 1071–1078. <https://doi.org/10.15789/1563-0625-COC-2704>. (In Russ.)
9. Kuklina E.M., Glebezdina N.S. Identification of Th1-polarized Th17 cells: solving the problem. Medical Immunology (Russia) / Meditsinskaya Immunologiya. 2023; 25 (4): 731–734. <https://doi.org/10.15789/1563-0625-IOT-2770>. (In Russ.)

ЛИТЕРАТУРА

1. Chanchlani N., Lin S., Bewshea C., Hamilton B., Thomas A., Smith R., Roberts C., Bishara M., Nice R., Lees C.W., Sebastian S., Irving P.M., Russell R.K., McDonald T.J., Goodhand J.R., Ahmad T., Kennedy N.A.; PANTS Consortium. Mechanisms and management of loss of response to anti-TNF therapy for patients with Crohn's disease: 3-year data from the prospective, multicentre PANTS cohort study. *Lancet Gastroenterol Hepatol*. 2024; 9 (6): 521–538. [https://doi.org/10.1016/S2468-1253\(24\)00044-X](https://doi.org/10.1016/S2468-1253(24)00044-X).
2. Yang P., Qian F.Y., Zhang M.F., et al. Th17 cell pathogenicity and plasticity in rheumatoid arthritis. *J Leukoc Biol*. 2019; 106 (6): 1233–1240. <https://doi.org/10.1002/JLB.4RU0619-197R>.
3. Куклина Е.М., Глебездина Н.С. Маркеры Th1-поляризованных клеток Th17 (обзор литературы). *Acta Biomedica Scientifica*. 2023; 8 (3): 55–62. <https://doi.org/10.29413/ABS.2023-8.3.5>.
4. Quirant-Sánchez B., Presas-Rodríguez S., Mansilla M.J., et al. Th1Th17_{CM} Lymphocyte Subpopulation as a Predictive Biomarker of Disease Activity in Multiple Sclerosis Patients under Dimethyl Fumarate or Fingolimod Treatment. *Mediators Inflamm*. 2019; 2019: 8147803. Published 2019 Jun 26. <https://doi.org/10.1155/2019/8147803>.
5. Cao H., Diao J., Liu H., Liu S., Liu J., Yuan J., Lin J. The Pathogenicity and Synergistic Action of Th1 and Th17 Cells in Inflammatory Bowel Diseases. *Inflamm Bowel Dis*. 2023 May 2; 29 (5): 818–829. <https://doi.org/10.1093/ibd/izac199>. PMID: 36166586.
6. Петричук С.В., Мирошкина Л.В., Семикина Е.Л., Топтыгина А.П., Потапов А.С., Цимбалова Е.Г., Радыгина Т.В. Показатели популяционного состава лимфоцитов как предикторы эффективности терапии ингибитором TNF α у детей с воспалительными заболеваниями кишечника. *Медицинская иммунология*. 2018; 20 (5): 721–730. <https://doi.org/10.15789/1563-0625-2018-5-721-730>.
7. Радыгина Т.В., Купцова Д.Г., Курбатова О.В., Петричук С.В., Семикина Е.Л., Фисенко А.П., Абдуллаева Л.М., Бурсагова Б.И. Особенности показателей клеточного иммунитета в зависимости от активности очагов демиелинизации у детей с рассеянным склерозом. *Медицинская иммунология*. 2023; 25 (5): 1019–1026. <https://doi.org/10.15789/1563-0625-FOP-2777>.
8. Купцова Д.Г., Радыгина Т.В., Курбатова О.В., Материкин А.И., Епишев Р.В., Опрятин Л.А., Хотко А.А., Мурашкин Н.Н., Петричук С.В. Содержание субпопуляций CD4+Т-клеток в прогнозе эффективности биологической терапии псориаза у детей. *Медицинская иммунология* 2023; 25 (5): 1071–1078. <https://doi.org/10.15789/1563-0625-COC-2704>.
9. Куклина Е.М., Глебездина Н.С. Идентификация Th1-поляризованных клеток Th17: решение проблемы. *Медицинская иммунология*. 2023; 25 (4): 731–734. <https://doi.org/10.15789/1563-0625-IOT-2770>.