Медицинская иммунология
2023, Т. 25, № 5,
стр. 1079-1084

Краткие сообщения
Short communications

Medical Immunology (Russia)/
Meditsinskaya Immunologiya
2023, Vol. 25, №5, pp. 1079-1084

МИЕЛОИДНЫЕ СУПРЕССОРНЫЕ КЛЕТКИ В КАЧЕСТВЕ БИОМАРКЕРОВ ЭФФЕКТИВНОСТИ ТЕРАПИИ НОВЫМИ БИОЛОГИЧЕСКИМИ ПРЕПАРАТАМИ У БОЛЬНЫХ АКСИАЛЬНЫМ СПОНДИЛОАРТРИТОМ

Тыринова Т.В.[1], Моренкова А.Ю.[1], Федорова А.В.[2], Тихонова М.А.[1], Ильина Н.А.[1], Чумасова О.А.[1], Сизиков А.Э.[1]

[1] ФГБНУ «Научно-исследовательский институт фундаментальной и клинической иммунологии», г. Новосибирск, Россия

[2] Научно-исследовательский институт клинической и экспериментальной лимфологии – филиал ФГБНУ «Федеральный исследовательский центр Институт цитологии и генетики Сибирского отделения Российской академии наук», г. Новосибирск, Россия

Резюме. Большое значение в патогенезе аксиального спондилоартрита (АксСп) отводится клеткам врожденного иммунитета, в том числе клеткам миелоидного ряда – супрессорным клеткам миелоидного происхождения (МС). МС представляют гетерогенную популяцию незрелых клеток, способных подавлять реакции врожденного и приобретенного иммунитета с наиболее выраженной супрессорной активностью в отношении Т-клеток. Терапия генно-инженерными биологическими препаратами позволяет снизить клинико-лабораторную активность заболевания у больных АксСп, однако их эффективность широко варьирует у разных пациентов. Настоящее исследование направлено на изучение различных субпопуляций МС и их супрессорного потенциала при АксСп, в зависимости от ответа на терапию генно-инженерными биологическими препаратами. В исследование были включены пациенты с АксСп с продолжительностью заболевания 16,5 лет (медиана); HLA-B27 (+) статус был выявлен в 79% случаев. Все пациенты в течение как минимум последних 12 недель получали биологическую терапию, в том числе ингибиторы TNF (этанерцепт, цертолизумаб пэгол, адалимумаб или голимумаб) или ингибиторы IL-17 (секукинумаб, иксекизумаб или нетакимаб). Относительное содержание гранулоцитарных МС (Г-МС, $Lin^-HLA\text{-}DR^-CD33^+CD66b^+$), моноцитарных МС (М-МС, $HLA\text{-}DR^{low/-}CD14^+$), МС ранних стадий дифференцировки (П-МС, $Lin^-HLA\text{-}DR^-CD33^+CD66b^-$), а также внутриклеточную экспрессию аргиназы-1 оценивали методом проточной цитометрии. Пациенты со стабильным ответом на биологическую терапию значимо не отличались от здоровых доноров

Адрес для переписки:

Тыринова Тамара Викторовна
ФГБНУ «Научно-исследовательский институт фундаментальной и клинической иммунологии»
630099, Россия, г. Новосибирск, ул. Ядринцевская, 14.
Тел.: 8 (383) 228-21-01.
E-mail: tyrinova@bk.ru

Address for correspondence:

Tamara V. Tyrinova
Research Institute of Fundamental and Clinical Immunology
14 Yadrintsevskaya St
Novosibirsk
630099 Russian Federation
Phone: +7 (383) 228-21-01.
E-mail: tyrinova@bk.ru

Образец цитирования:

Т.В. Тыринова, А.Ю. Моренкова, А.В. Федорова, М.А. Тихонова, Н.А. Ильина, О.А. Чумасова, А.Э. Сизиков «Миелоидные супрессорные клетки в качестве биомаркеров эффективности терапии новыми биологическими препаратами у больных аксиальным спондилоартритом» // Медицинская иммунология, 2023. Т. 25, № 5. С. 1079-1084.
doi: 10.15789/1563-0625-MDS-2696

For citation:

T.V. Tyrinova, A.Yu. Morenkova, A.V. Fedorova, M.A. Tikhonova, N.A. Ilina, O.A. Chumasova, A.E. Sizikov "Myeloid-derived suppressor cells as biomarkers of the effectiveness of therapy with new biological agents in axial spondyloarthritis", Medical Immunology (Russia)/ Meditsinskaya Immunologiya, 2023, Vol. 25, no. 5, pp. 1079-1084.
doi: 10.15789/1563-0625-MDS-2696

DOI: 10.15789/1563-0625-MDS-2696

по содержанию всех трех популяций МС в периферической крови. Пациенты с АксСп, не отвечающие на терапию, демонстрировали повышенное относительное и абсолютное количество Р-МС по сравнению со здоровыми донорами ($p_U = 0,01$ и $p_U = 0,02$ соответственно) и пациентами со стабильным ответом ($p_U = 0,03$ и $p_U = 0,07$ соответственно). При этом повышенное содержание Р-МС в случае отсутствия ответа на терапию ассоциировалось с показателями активности – СОЭ ($R_s = 0,821$; $p = 0,023$), СРБ ($R_s = 0,714$ $p = 0,07$) и $ASDAS_{СРБ}$ ($R_s = 0,829$; $p = 0,042$). В группе пациентов со стабильным ответом корреляционной зависимости между активностью заболевания и содержанием МС не обнаружено. Для оценки супрессорного потенциала МС была проанализирована экспрессия внутриклеточной молекулы аргиназа-1, которая участвует в ингибировании Т-клеточного ответа. Пациенты со стабильным ответом характеризовались повышенной экспрессией аргиназы-1 в Р-МС ($p_U = 0,02$). При отсутствии ответа на терапию значимых изменений в экспрессии Arg-1 не выявлено, однако доля Arg-1-экспрессирующих Г-МС находилась в прямой сопряженности с индексами воспаления $ASDAS_{СОЭ}$ ($R_s = 0,857$; $p = 0,014$) и BASDAI ($R_s = 0,785$; $p = 0,036$). Таким образом, Р-МС, а также экспрессия супрессорной молекулы Arg-1 в МС могут служить биомаркерами эффективности ответа на проводимую терапию генно-инженерными биологическими препаратами, а также выступать в роли потенциальных маркеров-кандидатов с точки зрения раннего предиктора ответа на проводимую терапию.

Ключевые слова: миелоидные супрессоры, аксиальный спондилоартрит, биологическая терапия, аргиназа-1, ингибитор TNF, ингибитор IL-17

MYELOID-DERIVED SUPPRESSOR CELLS AS BIOMARKERS OF THE EFFECTIVENESS OF THERAPY WITH NEW BIOLOGICAL AGENTS IN AXIAL SPONDYLOARTHRITIS

Tyrinova T.V.[a], Morenkova A.Yu.[a], Fedorova A.V.[b], Tikhonova M.A.[a], Ilina N.A.[a], Chumasova O.A.[a], Sizikov A.E.[a]

[a] *Research Institute of Fundamental and Clinical Immunology, Novosibirsk, Russian Federation*
[b] *Institute of Clinical and Experimental Lymphology, Branch of Institute of Cytology and Genetics, Siberian Branch, Russian Academy of Sciences, Novosibirsk, Russian Federation*

Abstract. Innate immune cells, including myeloid cells – myeloid derived suppressor cells (MDSCs) – are supposed to play an important role in the pathogenesis of axial spondyloarthritis (AxSp). Myeloid derived suppressor cells represent a heterogeneous population of immature cells capable of suppressing innate and adaptive immune responses with the most pronounced suppressor activity against T cells. Biological disease-modifying antirheumatic drugs (bDMARDs) can reduce the clinical and laboratory disease activity, but their effectiveness varies widely in different patients with AxSp. The present study is aimed at studying MDSCs subpopulations and their suppressive function depending on the response to bDMARD therapy in AxSp. The study included AxSp patients with a disease duration of 16.5 years (median); HLA-B27 (+) status was detected in 79% of cases. All patients received bDMARDs at least the past 12 weeks, including TNF inhibitors (etanercept, certolizumab pegol, adalimumab, or golimumab) or IL-17 inhibitors (secukinumab, ixekizumab, or netakimab). Percentage of granulocytic MDSCs (G-MDSCs, $Lin^-HLA\text{-}DR^-CD33^+CD66b^+$), monocytic MDSCs (M-MDSCs, $HLA\text{-}DR^{low/-}CD14^+$), MDSCs of early stage differentiation (E-MDSCs, $Lin^-HLA\text{-}DR^-CD33^+CD66b^-$), as well as intracellular expression of arginase-1 was assessed by flow cytometry. Frequency of circulating MDSC subpopulations of patients with a stable response to bDMARDs (responders) did not differ significantly compared to healthy donors. Patients not responding to bDMARDs therapy showed increased relative and absolute number of E-MDSCs compared to healthy donors ($p_U = 0.01$ and $p_U = 0.02$, respectively) and the responders ($p_U = 0.03$ and $p_U = 0.07$, respectively). Increased percentage of E-MDSCs was positively correlated to disease activity – ESR ($R_s = 0.821$; $p = 0.023$), CRP ($R_s = 0.714$; $p = 0.07$) and $ASDAS_{CRP}$ ($R_s = 0.829$; $p = 0.042$) in the non-responder group. Responder patients exhibited no correlation between disease activity and circulating MDSCs. The suppressor potential of MDSCs was analyzed by the

intracellular expression of arginase-1 molecule which is involved in the inhibition of T cell response. Patients with the stable response were characterized by increased expression of arginase-1 in E-MDSCs compared to donors ($p_U = 0.02$). Non-responders did not demonstrate significant changes in Arg-1 expression, however, the percentage of arginase-1-expressing G-MDSCs was positively correlated to indexes $ASDAS_{ESR}$ ($R_s = 0.857$; $p = 0.014$) and BASDAI ($R_s = 0.785$; $p = 0.036$). Thus, E-MDSCs as well as arginase-1 expression in MDSCs may serve as biomarkers of effectiveness bDMARD therapy, and act as potential candidate predictors of response to therapy in AxSp.

Keywords: myeloid-derived suppressor cells, axial spondyloarthritis, biological therapy, arginase-1, TNF inhibitor, IL-17 inhibitor

The study was funded by budget of Research Institute of Fundamental and Clinical Immunology (theme No. 122011800108-0).

Introduction

Axial spondyloarthritis (AxSp) is a chronic inflammatory disease of the axial skeleton with frequent involvement of entheses and peripheral joints, as well as other organs and systems, in the pathological process. The leading role in the development and progression of AxSp is assigned to pro-inflammatory cytokines – IFNγ, TNFα, IL-1 and IL-6 [12]. Advances in understanding the immunopathogenesis of AxSp have served as the basis for the development of new therapies aimed at neutralizing the activity of these pro-inflammatory cytokines [2, 12]. The appointment of biological disease-modifying antirheumatic drugs (bDMARDs) allows to quickly reduce the clinical and laboratory disease activity, improve quality of life and slow radiographic AxSp progression [2, 7]. Despite the high efficiency, it has been reported failure of TNFα or IL-17 inhibitors in a significant percentage of AxSp patients [1, 4, 10]. The use of new biomarkers that could be considered predictors of good response/non-response to bDMARD therapy would effectively control the disease and reduce the economic burden of biological therapy.

As AxSp is believed to be more of an autoinflammatory than an autoimmune disease, innate immunity cells, in particular myeloid cells – myeloid derived suppressor cells (MDSCs) – play an important role in its pathogenesis. MDSCs represent a heterogeneous immature cell population of myeloid origin, capable of suppressing the innate and adoptive response with the most pronounced suppressor activity against T cells [3]. In humans, MDSCs includes granulocytic (polymorphonuclear), monocytic MDSCs, and MDSCs of early stage of differentiation (G-MDSCs, M-MDSCs, and E-MDSCs, respectively), which differ in morphological features, expression of membrane markers, and mechanisms of their suppressor activity. However, data on the functional activity of MDSCs in autoimmune and autoinflammatory diseases are controversial, including reports of intact suppressive activity of MDSCs, diminished or its complete absence [5, 6, 8, 11, 13].

The present study was aimed to analyzed circulating MDSC subpopulations and their suppressor function depending on response to bDMARDs in AxSp patients.

Materials and methods

The study included 28 patients with AxSp (19 men and 9 women aged 19 to 56 years) and 36 age-matched healthy donors. Informed consent was obtained from all patients and donors according to the Declaration of Helsinki. All patients met the modified New York criteria for diagnosis of AxSp and/or Assessment of Spondyloarthritis International Society criteria for AxSp. The disease duration was 16.5 years (median). Twenty-two patients (79%) were HLA-B27-positive. All patients received bDMARDs at least for the past 12 weeks. Nineteen out of 28 patients received TNF inhibitors (etanercept, certolizumab pegol, adalimumab, or golimumab); nine out of 28 patients received IL-17 inhibitors (secukinumab, ixekizumab, or netakimab).

Disease activity was determined according to $ASDAS_{ESR}$ and/or $ASDAS_{CRP}$ indexes. Most patients (20/28, 71%) demonstrated low/moderate AxSp activity (ASDAS index < 2.1). In 29% of cases (8/28) high/very high AxSp activity was determined (ASDAS index ≥ 2.1). Additionally, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) were used to evaluate the activity and severity of functional limitations, respectively.

The frequencies of G-MDSCs ($Lin^-HLA\text{-}DR^-CD33^+CD66b^+$), M-MDSCs ($CD14^+HLA\text{-}DR^{low/-}$), and E-MDSCs ($Lin^-HLA\text{-}DR^-CD33^+CD66b^-$) was assessed by flow cytometry using anti-Lineage Cocktail 1 (CD3, CD14, CD16, CD19, CD20, CD56; FITC, BD Biosciences, USA), anti-CD14 (FITC, BD Biosciences), anti-CD33 (PerCP-Cy5.5, BD Biosciences), anti-CD66b (APC, BioLegend, USA), anti-HLA-DR (FITC, APC-Cy7, PerCP, BD Biosciences) monoclonal antibodies. The number of MDSC subpopulations are presented as a percentage of mononuclear cells (MNCs). The absolute number of MDSCs was calculated using data on the percentage

TABLE 1. MYELOID-DERIVED SUPPRESSOR CELL SUBPOPULATIONS DEPENDING ON THE PATIENT RESPONSE TO bDMARD THERAPY IN AxSp

MDSCs	Donors (n = 21-36)	AxSp patients	
		Responders (n = 17-18)	Non-responders (n = 7-10)
G-MDSCs (%)	0.05 (0.04-0.07)	0.08 (0.02-0.16)	0.13 (0.04-0.24)
E-MDSCs (%)	0.82 (0.662-1.340)	1.1 (0.62-1.58)	1.9* # (1.0-2.6)
M-MDSCs (%)	1.7 (1.2-2.4)	2.1 (1.57-3.00)	1.6 (1.2-2.7)
MNCs (× 10^9/L)	2.5 (2.1-2.7)	2.9* (2.6-3.4)	2.8* (2.5-3.2)
G-MDSCs (× 10^6 cells/mL)	1.4 (1.1-2.0)	2.8 (0.7-5.2)	2.6 (0.9-5.1)
E-MDSCs (× 10^6 cells/mL)	25.4 (13.0-31.4)	32.2 (17.3-44.8)	47.9* (29.3-58.0)
M-MDSCs (× 10^6 cells/mL)	46.3 (28.2-71.6)	56.6 (42.4-95.5)	50.6 (24.7-86.8)

Note. Relative (%) and absolute (× 10^6 cells/ml) numbers of granulocytic (G-MDSCs), early-stage MDSCs (E-MDSCs) and monocytic (M-MDSCs) MDSCs in peripheral blood samples are shown as median and interquartile range (IQR) in the donor group and the responders and non-responders to biological disease-modifying antirheumatic drugs; *, p_U value < 0.05 compared to donors; #, p_U value < 0.05 compared to responders.

TABLE 2. ARGINASE-1 EXPRESSION IN MYELOID-DERIVED SUPPRESSOR CELL SUBPOPULATIONS DEPENDING ON THE PATIENT RESPONSE TO bDMARD THERAPY IN AxSp

Arg-1$^+$ cells (%)	Donors (n = 16-32)	AxSp patients	
		Responders (n = 8-13)	Non-responders (n = 7)
Arg-1$^+$G-MDSCs	70.0 (43.0-89.4)	86.3 (71.3-96.6)	75.0 (29.0-87.2)
Arg-1$^+$E-MDSCs	16 (5.8-31.0)	44.3* (33.9-50.7)	19.0 (16.0-36.0)
Arg-1$^+$M-MDSCs	19.8 (11.4-38.8)	14.2 (6.5-26.7)	7.0 (4.5-21.3)

Note. Data are presented as median and interquartile range (Me ($Q_{0.25}$-$Q_{0.75}$) of the percentage of arginase-1-positive cells among granulocytic (G-MDSCs), monocytic (M-MDSCs) and early-stage MDSCs (E-MDSCs) in peripheral blood of donors and AxSp patients with different response to biological disease-modifying antirheumatic drugs; *, p_U value < 0.05 compared to donors.

of MDSC subpopulations and the absolute number of MNCs (lymphocytes + monocytes; blood test).

To assess the intracellular expression of arginase-1 (Arg-1), MNCs were stained with fluorochrome-conjugated monoclonal antibodies to G-MDSCs, M-MDSCs, E-MDSCs according to the standard method for determining surface antigens. Then, cells were permeabilized using Fixation/permeabilization solution kit (BD Cytofix/Cytoperm™, USA) according to the manufacturer s instructions and incubated with PE- or APC-conjugated anti-Arg-1 (BD PharMingen, USA) monoclonal antibodies. The relative amount of MDSCs expressing Arg-1 was assessed among Lin$^-$HLA-DR$^-$CD33$^+$CD66b$^+$, Lin$^-$HLA-DR$^-$CD33$^+$CD66b$^-$ and CD14$^+$HLA-DR$^{low/-}$ cells. In each experiment, isotype-matched control monoclonal antibodies were used to determine non-specific background staining.

Statistical data processing was performed using the Statistica 6.0 (StatSoft) and GraphPad Prism 8 software package. Data are presented as median (Me) and interquartile range ($Q_{0.25}$-$Q_{0.75}$). To identify significant differences, the nonparametric Mann–Whitney U-test was used for independent samples. Correlation analysis was performed using Spearman's rank correlation (R_s). Differences were considered statistically significant at p value < 0.05.

Results and discussion

In patients with a stable response to bDMARDs (during the last 12 weeks of therapy; responders), including 13 patients receiving TNF inhibitors and 5 patients receiving IL-17 inhibitors, the frequency of circulating G-MDSCs, M-MDSCs and E-MDSCs was not significantly different from healthy donors (Table 1). Patients who did not respond to bDMARDs (according to the criteria for the absence of effectiveness; non-responders), including 6 patients receiving TNF inhibitors and 4 patients with IL-17 inhibitors, showed an almost two-fold increase in the relative and absolute number of E-MDSCs compa-

red with healthy donors (p_U = 0.01 and p_U = 0.02, respectively). Besides, non-responders were characterized by a significantly increased percentage (p_U = 0.03) and tendency to higher absolute number of E-MDSCs (p_U = 0.07) compared with the responder group.

In the non-responder group, the increased frequency of E-MDSCs was associated with inflammation activity. The frequency of E-MDSCs was revealed to have a high correlation with ESR (R_s = 0.821; p = 0.023), CRP (R_s = 0.714; p = 0.07) and $ASDAS_{CRP}$ (R_s = 0.829; p = 0.042). Absolute E-MDSC count was correlated as a trend with ESR (R_s = 0.607; p = 0.15) and CRP (R_s = 0.607; p = 0.15). In the group of patients with the stable response to bDMARDs, no correlation between AxSp activity and MDSCs was found.

To assess the suppressor potential of MDSCs in AxSp, intracellular expression of Arg-1 molecule (Table 2) involved in the arginine depletion in the extracellular space and inhibiting the T cell activation was analyzed. Non-responders demonstrated a tendency to reduced expression of Arg-1 in M-MDSCs (p_U = 0.12), whereas the responder group had no difference with the donor group. Responders to bDMARDs were characterized by more than 2.5-fold increased expression of Arg-1 in E-MDSCs (p_U = 0.02). Non-responders did not demonstrate significant changes in Arg-1-expressing E-MDSCs.

In the responder group, Arg-1 expression in G-MDSCs directly correlated with the BASDAI index (R_s = 0.667; p = 0.07), and in E-MDSCs it inversely associated with the BASDAI index (R_s = -0.691; p = 0.057). In the non-responder group, the percentage of Arg-1-expressing G-MDSCs was positively correlated to indexes $ASDAS_{ESR}$ (R_s = 0.857; p = 0.014) and BASDAI (R_s = 0.785; p = 0.036).

Thus, the present study has shown that the ineffectiveness of bDMARD therapy in AxSp patients was associated with the increased number of E-MDSCs, as well as the trend towards the decrease in the Arg-1-expressing M-MDSCs. The achievement of stable response to therapy with bDMARDs was associated with the similar Arg-1 expression in M-MDSCs and significantly increased expression of Arg-1 in E-MDSCs comparable with the donors.

Previously, we have shown that patients with AxSp were characterized by an increased number of G-MDSCs and M-MDSCs both in the first line of therapy and in bDMARD therapy [9]. However, we did not take into account the responsiveness of patients to bDMARDs. The data obtained in the present study have demonstrated no differences in the number of MDSC subpopulations between the donors and patients with the stable response to bDMARDs. The inhibition of TNF or IL-17, as the key cytokines in maintaining chronic inflammation, may be also accompanied by blocking the differentiation of myeloid progenitors into immature myeloid cells. Accumulation of E-MDSCs in the non-responders to TNF or IL-17 inhibitors seems to be due to the involvement of other factors in AxSp pathogenesis, which determine resistance to bDMARDs.

Therapy with bDMARDs may lead to changes in Arg-1 expression in MDSCs. The responder group have demonstrated significantly increased expression of Arg-1 in E-MDSCs, which may be important in terms of the regulation of inflammation. The decrease in expression of Arg-1 in M-MDSCs detected at high / very high AxSp activity in non-responders can be one of the pathogenetic mechanisms of development and maintenance of the inflammatory process in AxSp.

Conclusion

Taken together, we conclude that E-MDSCs, as well as the Arg-1 expression in MDSCs can serve as biomarkers of the effectiveness of the response to bDMARD therapy, and also act as potential candidate markers in terms of an early predictor of response to bDMARD therapy.

References

1. Biggioggero M., Favalli E.G. Ten-year drug survival of anti-TNF agents in the treatment of inflammatory arthritides: anti-TNF in inflammatory arthritides. *Drug Dev. Res., 2014, Vol. 75, Suppl. 1, pp. S38-S41.*

2. Expósito-Molinero R., García-Portales R., Lamua-Riazuelo L., Urruticoechea-Arana A., Navarro-Alonso P., Rey-Rey J., Fernandez-Prada M., Gonzalez Fernandez C.M. Effectiveness and retention rate of certolizumab pegol in spondyloarthritis. Real life data. *Ann. Rheum. Dis., 2017, Vol. 69, Suppl. 10, 1550.* doi: 10.1136/annrheumdis-2018-eular.5552.

3. Gabrilovich D.I. Myeloid-derived suppressor cells. *Cancer Immunol. Res., 2017, Vol. 5, no. 1, pp. 3-8.*

4. Gaydukova I.Z., Rebrov A.P., Aparkina A.V., Khondkaryan E.V. Stable high interleukin-17A concentration in patients with ankylosing spondylitis treated with tumor necrosis factor-α inhibitors during a year. *Ter. Arch., 2017, Vol. 89, no. 4, pp. 80-85.* (In Russ.)

5. Guo C., Hu F., Feng Zh., Li Ch., Shi L., Li Y., Liu H., Yu X., Wang H., Li J., Li Z., Wang X.-Y. Myeloid-derived suppressor cells have a proinflammatory role in the pathogenesis of autoimmune arthritis. *Ann. Rheum. Dis., 2016, Vol. 75, no. 1, pp. 278-285.*

6. Jiao Z., Hua S., Wang W., Wang H., Gao J., Wang X. Increased circulating myeloid-derived suppressor cells correlated negatively with Th17 cells in patients with rheumatoid arthritis. *Scand. J. Rheumatol., 2013, Vol. 42, no. 2, pp. 85-90.*

7. Lapshina S.A., Dubinina T.V., Badokin V.V., Bochkova A.G., Bugrova O.V., Gaidukova I.Z., Godzenko A.A., Dubikov A.A., Ivanova O.N., Korotaeva T.V., Nesmeyanova O.B., Nikishina I.P., Otteva E.N., Raskina T.A., Rebrov A.P., Rumyantseva O.A., Sitalo A.V., Smirnov A.V., Erdes S.F. Tumor necrosis factor-α inhibitors in the treatment of axial spondyloarthritis, including ankylosing spondylitis. *Rheumatology Science and Practice, 2016, Vol. 54, Suppl. 1, pp. 75-79.* (In Russ.)

8. Liu Y.F., Zhuang K.H., Chen B., Li P.W., Zhou X., Jiang H., Zhong L.M., Liu F.B. Expansion and activation of monocytic-myeloid-derived suppressor cell via STAT3/arginase-I signaling in patients with ankylosing spondylitis. *Arthritis Res. Ther., 2018, Vol. 20, no. 1, 168.* doi: 10.1186/s13075-018-1654-4

9. Morenkova A.Yu., Tikhonova M.A., Tyrinova T.V., Batorov E.V., Sizikov A.E., Chumasova O.A., Sulutian A.E., Ostanin A.A., Chernykh E.R. Expansion of myeloid-derived suppressor cells in the peripheral blood of patients with ankylosing spondylitis. *Medical Immunology (Russia), 2021, Vol. 23, no. 2, pp. 327-338.* (In Russ.) doi: 10.15789/1563-0625-EOM-2143.

10. Nuriakhmetova T.Yu., Abdulganieva D.I. Inefficacy of tumor necrosis factor α inhibitors and potential options for its overcoming. *Practical Medicine, 2018, Vol. 16, no. 7 (part 2), pp. 72-80.* (In Russ.)

11. Rajabinejad M., Salari F., Karaji A.G., Rezaiemanesh A. The role of myeloid-derived suppressor cells in the pathogenesis of rheumatoid arthritis; anti- or pro-inflammatory cells? *Artif.Cells Nanomed. Biotechnol., 2019, Vol. 47, no. 1, pp. 4149-4158.*

12. Tsukazaki H., Kaito T. The Role of the IL-23/IL-17 pathway in the pathogenesis of spondyloarthritis. *Int. J. Mol. Sci., 2020, Vol. 21, no. 17, 6401.* doi: 10.3390/ijms21176401.

13. Zhanga H., Wanga S., Huangb Y., Wanga H., Zhaoa J., Gaskinc F., Yanga N., Fud S.M. Myeloid-derived suppressor cells are proinflammatory and regulate collagen-induced arthritis through manipulating Th17 cell differentiation. *Clin. Immunol., 2015, Vol. 157, no. 2, pp. 175-186.*

Авторы:

Тыринова Т.В. *— д.б.н, ведущий научный сотрудник ФГБНУ «Научно-исследовательский институт фундаментальной и клинической иммунологии», г. Новосибирск, Россия*

Моренкова А.Ю. *— очный аспирант ФГБНУ «Научно-исследовательский институт фундаментальной и клинической иммунологии», г. Новосибирск, Россия*

Федорова А.В. *— младший научный сотрудник, Научно-исследовательский институт клинической и экспериментальной лимфологии — филиал ФГБНУ «Федеральный исследовательский центр Институт цитологии и генетики Сибирского отделения Российской академии наук», г. Новосибирск, Россия*

Тихонова М.А. *— к.б.н., старший научный сотрудник ФГБНУ «Научно-исследовательский институт фундаментальной и клинической иммунологии», г. Новосибирск, Россия*

Ильина Н.А. *— к.м.н., врач-ревматолог ФГБНУ «Научно-исследовательский институт фундаментальной и клинической иммунологии», г. Новосибирск, Россия*

Чумасова О.А. *— к.м.н., врач-ревматолог ФГБНУ «Научно-исследовательский институт фундаментальной и клинической иммунологии», г. Новосибирск, Россия*

Сизиков А.Э. *— к.м.н., заведующий отделением ФГБНУ «Научно-исследовательский институт фундаментальной и клинической иммунологии», г. Новосибирск, Россия*

Authors:

Tyrinova T.V., *PhD, MD (Biology), Leading Research Associate , Research Institute of Fundamental and Clinical Immunology, Novosibirsk, Russian Federation*

Morenkova A.Yu., *Postgraduate Student, Research Institute of Fundamental and Clinical Immunology, Novosibirsk, Russian Federation*

Fedorova A.V., *Junior Research Associate, Institute of Clinical and Experimental Lymphology, Branch of Institute of Cytology and Genetics, Siberian Branch, Russian Academy of Sciences, Novosibirsk, Russian Federation*

Tikhonova M.A., *PhD (Biology), Senior Research Associate, Research Institute of Fundamental and Clinical Immunology, Novosibirsk, Russian Federation*

Ilyina N.A., *PhD (Medicine), Rheumatologist, Research Institute of Fundamental and Clinical Immunology, Novosibirsk, Russian Federation*

Chumasova O.A., *PhD (Medicine), Rheumatologist, Research Institute of Fundamental and Clinical Immunology, Novosibirsk, Russian Federation*

Sizikov A.E., *PhD (Medicine), Head of Department, Research Institute of Fundamental and Clinical Immunology, Novosibirsk, Russian Federation*

Поступила 06.04.2023
Принята к печати 11.04.2023

Received 06.04.2023
Accepted 11.04.2023