ORIGINAL INVESTIGATIONS

Association between interleukin-6 gene polymorphism and age at onset of rheumatoid arthritis

Aboleshina A.V., Guseva I.A., Zotkin E.G., Samarkina E.Yu., Demidova N.V., Movsesyan A.A., Molova K.M., Makoeva M.A.

V.A. Nasonova Research Institute of Rheumatology, Moscow
34A, Kashirskoe Shosse, Moscow 115522, Russia

Genetic polymorphism of the IL-6 gene (-174 G/C, rs1800795) may affect interleukin-6 expression and contribute to the development of age-associated phenotypes of rheumatoid arthritis (RA).

Objective: *to study the distribution of IL-6 gene alleles and genotypes in RA patients depending on age at onset (AAO).*

Material and methods. *The study included 167 patients with RA. Group 1 included patients with RA AAO ≤45 years (median AAO 36 [29; 42] years; n=95); Group 2 included patients with RA AAO ≥60 years (median AAO 66.5 [62; 70] years; n=72). DNA from 301 healthy donors served as controls. All patients underwent genotyping of IL-6 gene polymorphisms using polymerase chain reaction.*

Results and discussion. *In patients with AAO ≥60 years, the CC genotype was detected more often than in patients with AAO ≤45 years (31.9% vs 12.6%, respectively; p=0.01). In RA patients with the CC genotype, the risk of developing the disease at the age of ≥60 years was almost three times higher compared with carriers of other genotypes (odds ratio 3.25; 95% confidence interval 1.39–7.65; p=0.004).*

Conclusion. *The established association of the CC genotype of the -174 G/C polymorphism of the IL-6 gene with the development of RA after 60 years allows this genetic variant to be considered a predictor of RA onset in older age, which supports the rationale for stratifying RA by age-related phenotypes and opens prospects for the development of diagnostic and preventive approaches.*

Keywords: *rheumatoid arthritis; older age; interleukin-6; gene polymorphism.*

Contact: *Aleksandra Vadimovna Aboleshina;* ***abolyoshina@yandex.ru***

For citation: *Aboleshina AV, Guseva IA, Zotkin EG, Samarkina EYu, Demidova NV, Movsesyan AA, Molova KM, Makoeva MA. Association between interleukin-6 gene polymorphism and age at onset of rheumatoid arthritis. Sovremennaya Revmatologiya=Modern Rheumatology Journal. 2026;20(2):29–34 (In Russ.). https://doi.org/10.14412/1996-7012-2026-2-29-34*

Introduction

Rheumatoid arthritis (RA) is an immune-mediated inflammatory (autoimmune) rheumatic disease of unknown etiology, characterized by chronic erosive arthritis and systemic involvement of internal organs [1]. An important clinical feature of RA is its significant heterogeneity, which manifests, among other aspects, as variability in the age at onset (AAO) of the disease. Epidemiological studies indicate that the peak incidence of RA occurs in at the age of 30–50 years, with an additional increase in new cases at older age (>60 years) termed late-onset RA [2].

Although the exact cause of RA remains unknown, numerous studies point to a combination of environmental and genetic factors [3]. According to current data, an imbalance in the production of pro-inflammatory and anti-inflammatory cytokines, chemokines, growth factors, and other active molecules plays an important role in the pathogenesis of RA; therefore, the study of genes encoding cytokines is of particular interest [4].

One of the key cytokines involved in sustaining inflammation in RA is interleukin-6 (IL-6) [5]. IL-6 is a pleiotropic cytokine synthesized by cells of the immune system (neutrophils, T- and B-lymphocytes, monocytes, and NK-cells), as well as by fibroblasts, osteoblasts, and endothelial cells [6]. The following main effects lead to progressive bone destruction in RA: leukocyte activation, stimulation of synoviocytes and osteoclast maturation [7], induction of cytotoxic T-lymphocyte and B-lymphocyte differentiation with subsequent production of autoantibodies, and stimulation of hepatocytes to produce acute-phase proteins such as C-reactive protein (CRP), fibrinogen, serum amyloid A, etc. These changes account for increased RA activity and the development of systemic manifestations [8].

IL-6 levels are elevated in the serum and synovial fluid of RA patients [9], and several studies report that blood IL-6 levels correlate with RA activity [10] and radiographic progression [11].

Polymorphisms in the promoter region of the IL-6 gene, located on the short arm of chromosome 7 (7p21), may lead to interindividual variations in transcription and protein expression. The most studied polymorphism of the IL-6 gene is the single-nucleotide polymorphism rs1800795, which represents a substitution of guanine (G) for cytosine (C) at position -174 [12]. A Russian study conducted on a cohort of patients with RA duration of up to 2 years established an association of the IL-6 -174G/C (rs1800795) polymorphism with markers of RA activity and progression: CRP, swollen joint count (SJC), DAS28-CRP (Disease Activity Score 28 using CRP), total Sharp score, as well as with RA AAO. Specifically, RA AAO was statistically significantly higher in C/C genotype carriers (n=20, 57.9±11.1 years) compared with C/G (47.9± 11.8 years) and G/G (47.4±12.34 years) carriers, p=0.005 [13].

Results from international studies have shown that the presence of the G allele at position -174 of the IL-6 promoter region increases transcriptional activity and, consequently, levels of this cytokine in serum and synovial fluid of RA patients [14]. In a study by Ceccarelli et al. [15], patients carrying the -174G allele exhibited higher disease activity according to the DAS28 index and faster radiographic progression.

Currently, substantial evidence has accumulated indicating an association of IL-6 gene polymorphisms with the risk of devel-

Table 1. General characteristics of RA patients (n=167)

Parameter	Value
Female/male, n(%)	127(76.1)/40(23.9)
AAO, years, Me [25th; 75th]	44 [33; 65]
RA duration, years, Me [25th; 75th]	12 [5.5; 22.5]
RF+, n(%)	113(67.6)
ACPA+, n(%)	99(59.3)
RF+, ACPA+, n(%)	87(52)
Erosive arthritis, n(%)	64(38.3)
Morning stiffness, min, Me [25th; 75th]	60 [20; 120]
SJC, Me [25th; 75th]	5 [3; 9]
TJC, Me [25th; 75th]	10 [6; 15]
CRP, g/L, Me [25th; 75th]	8.05 [1.9; 23.17]
DAS28-CRP, Me [25th; 75th]	3 [2.2; 4.6]
RF, IU/mL, Me [25th; 75th]	48.7 [9.5; 177]
ACPA, U/mL, Me [25th; 75th]	29.75 [1.9; 100]
HAQ, M±SD	1.075 ± 0.716

Note: SJC – swollen joint count; TJC – tender joint count; HAQ – Health Assessment Questionnaire.

oping RA in general, but the results of many studies are often contradictory and depend on the ethnicity of the population studied [16–19]. The influence of IL-6 gene polymorphisms on phenotypic features of RA, particularly on AAO, remains largely unexplored. It can be hypothesized that certain allelic variants associated with increased production of this cytokine may contribute to earlier disease onset, whereas other genetic variants may be associated with later onset.

Current data suggest the existence of age-associated RA phenotypes that differ in immunological profile, clinical presentation, and prognosis [20, 21]. Identifying genetic markers associated with RA AAO may have important practical implications for earlier identification of at-risk patients with potentially more severe disease, thereby enabling personalized therapeutic approaches.

Objective – to study the distribution of IL-6 gene alleles and genotypes in RA patients depending on AAO, and to assess their significance as molecular genetic markers of predisposition to developing RA at an older age.

Material and Methods

The study included 108 patients receiving outpatient and inpatient care at V.A. Nasonova Research Institute of Rheumatology in 2022–2023, who were enrolled in the fundamental research project FURS-2022-008 (state assignment №1021051503137-7). All patients provided informed consent to participate in the study. The study was approved by the local ethics committee of V.A. Nasonova Research Institute of Rheumatology (Protocol №24 dated 01.12.2022).

To increase the sample size, an additional 59 patients from the program "Early Arthritis: Diagnosis, Outcome, Criteria, Active Treatment (RADIKAL)," with disease duration not exceeding 2 years, were included in the analysis.

General patient characteristics at enrollment are presented in Table 1. At the time of inclusion, the median RA duration was 12 [5.5; 22.5] years, with a predominance of females (76.1%). Most patients were seropositive for rheumatoid factor (RF, 67.6%) and anti-cyclic citrullinated peptide antibodies (ACPA, 59.3%), with more than a half (52%) being positive for both types of autoantibodies.

Patients were divided into two groups based on AAO: Group 1 included patients with RA AAO from 18 to 45 years (n=95); Group 2 included patients with RA AAO ≥60 years (n=76). DNA from 301 healthy blood donors served as controls. Donors had no autoimmune pathology and were comparable in sex and age to the patient groups.

Venous blood samples were collected from all patients upon admission, put into K2EDTA tubes and stored frozen at -70°C until DNA extraction and genotyping. Genotyping of the IL-6 gene polymorphism (-174G/C, rs1800795) was performed using real-time polymerase chain reaction with original sequence-specific primers and probes labeled with different fluorescent dyes (Syntol, Russia). Genotyping was conducted according to the manufacturer's instructions. Automatic registration and interpretation of results were performed using the domestic innovative detecting amplifier "DTprime" (DNA-Technology, Russia).

Statistical analysis. Quantitative variables are presented as mean and standard deviation (M±SD), and where normal distribution was absent, as median with interquartile range (Me [25th; 75th percentiles]). Normality of distribution was tested using the Shapiro–Wilk test. Qualitative variables are presented as absolute values and relative frequencies (%). Differences in allele and genotype distribution between groups were assessed using the chi-square (χ^2) independence test. To estimate the risk of disease development, the odds ratio (OR) and 95% confidence interval (CI) were calculated using logistic regression analysis. Differences were considered statistically significant at $p<0.05$.

Results

Comparative analysis of 167 RA patients revealed significant differences between groups with early (≤45 years) and late (≥60 years) AAO. Despite comparability in sex and disease duration ($p>0.05$), the serological profile differed: patients with AAO ≤45 years were significantly more often ACPA-positive than those with late AAO (66.3% vs. 50.0%, respectively; p=0.034). Meanwhile, the late-onset RA group showed significantly higher CRP levels (p=0.023) and more pronounced functional impairment according to HAQ (p=0.015). SJC, tender joint count (TJC), and DAS28-CRP did not differ significantly between the groups (Table 2).

The distribution of IL-6 (rs1800795) CC, CG, and GG genotypes differed statistically significantly between the two patient groups (p=0.01; Table 3). The minor CC genotype was more

Table 2. Comparative clinical and laboratory characteristics of patients with early- and late-onset RA

Parameter	Group 1 (n=95), AAO RA ≤45 years	Group 2 (n=72), AAO RA ≥60 years	p
Female/male, n(%)	75(78.9) / 20(21.1)	52(72.2)/20(27.8)	0.314
AAO, years, Me [25th; 75th]	36 [29; 42]	66.5 [62; 70]	**0.000**
RA duration, years, Me [25th; 75th]	12 [7; 22]	8 [5; 24]	0.167
RF+, n(%)	66(69.5)	47(65.3)	0.566
ACPA+, n(%)	63(66.3)	36(50)	**0.034**
RF+, ACPA+, n(%)	55(57.9)	32(44.4)	0.085
Erosive arthritis, n(%)	33(34.7)	31(43.06)	0.274
Morning stiffness, min, Me [25th; 75th]	60 [30; 120]	52.5 [16.25; 120]	0.662
SJC, Me [25th; 75th]	5 [3; 9]	6 [3; 10]	0.441
TJC, Me [25th; 75th]	9 [5; 15]	10 [7; 15]	0.488
CRP, g/L, Me [25th; 75th]	6.6 [1.1; 19]	10.6 [3; 24]	**0.023**
DAS28-CRP, Me [25th; 75th]	2.98 [2.08; 4.28]	3.06 [2.4; 5.3]	0.239
RF, IU/mL, Me [25th; 75th]	44.9 [9.5; 167]	49 [9.5; 180]	0.920
ACPA, U/mL, Me [25th; 75th]	48.8 [3.25; 100]	11.4 [0.7; 100]	0.117
HAQ, M±SD	0.95 ± 0.68	1.23 ± 0.73	**0.015**

frequent in the AAO ≥60 years group than in the AAO≤45 years group (31.9% vs. 12.6%; p=0.002) and in the control group (31.9% vs. 17.9%, respectively; p=0.01; see Figure).

When compared with the control group, RA patients carrying the CC genotype had nearly three times higher risk of developing the disease at an age ≥60 years compared with carriers of GG+GC genotypes (OR 3.25 [1.39–7.65]; p=0.004).

Correlation analysis to identify associations of IL-6 genotypes and alleles with clinical and laboratory parameters revealed no statistically significant differences.

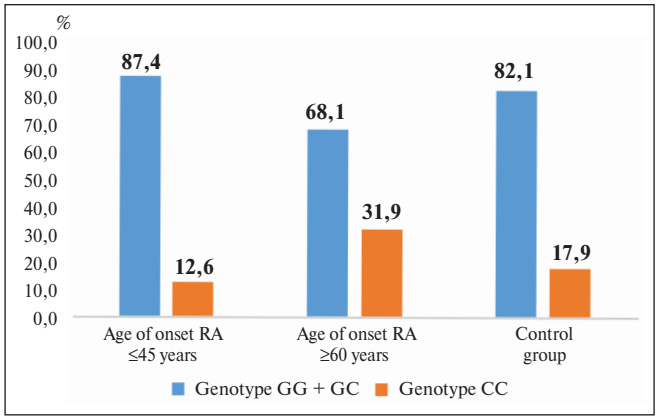
Discussion

The association of IL-6 -174G/C (rs1800795) polymorphism with susceptibility to RA has been repeatedly confirmed in genetic studies; however, these data are contradictory, as the distribution of polymorphic variants differs depending on the population studied. For example, a case-control study conducted in Delhi (India) found that the C allele was more frequent in RA patients than in controls (OR 0.1928; 95% CI 0.0926–0.3928; p=0.00001), and the CC genotype was associated with increased RA risk in North Indians (OR 40.902; 95% CI 2.208–757.6; p=0.013). A meta-analysis by the same authors, including 12 studies in Asian, Caucasian, and mixed populations, showed that the CC genotype was associated with RA risk in Asian populations (OR 4.886; 95% CI 1.830–13.043; p=0.002), but this was not confirmed in the Caucasian population (OR 1.138; 95% CI 0.809–1.600; p=0.458) [16]. In contrast, studies in Turkish and Mexican populations demonstrated that the IL-6 -174G/C (rs1800795) polymorphism was not associated with RA risk [17, 18]. A study by Russian authors also found no statistically significant differences in genotype and allele frequencies between RA patients and healthy donors, but stratification by age revealed an association of the above polymorphism with RA AAO [19].

Existing data on the association of the IL-6 -174G/C polymorphism with RA AAO are scarce. It is hypothesized that the same genetic variants may play a protective role or contribute to disease development at different ages. For instance, a case-control study in the United Kingdom found that the IL-6 -174G/C polymorphism was significantly associated with susceptibility to systemic juvenile rheumatoid arthritis, with the strongest association in children with disease onset <5 years. In this patient group, genotype distribution differed significantly from controls, with a significant

Table 3. Frequency of genotypes and alleles of the *-174 G/C (rs1800795)* polymorphism of the *IL-6* gene in RA patients depending on AAO, n (%)

Genotypes/alleles -174 G/C	Group 1 (n=95), AAO RA ≤45 years	Group 2 (n=72), AAO RA ≥60 years	Control group (n=301)	p (AAO RA ≤45 vs. ≥60)
GG	36 (37,9)	25 (34,7)	85 (28,3)	
GC	47 (49,5)	24 (33,4)	162 (53,8)	$\chi^2 = 9.91$
CC	12 (12,6)	23 (31,9)	54 (17,9)	0,01
G	119 (62,6)	74 (51,4)	332 (55,1)	
C	71 (37,4)	70 (48,6)	270 (44,9)	0,04



Comparison of the frequency of CC and GG + GC genotypes in the study groups

predominance of the heterozygous GC genotype (64% vs. 44%) and a statistically significant reduction in the homozygous CC genotype (7% vs. 18%; overall genotype distribution p=0.01). The homozygous CC genotype was significantly associated with lower RA risk (OR 0.34; 95% CI 0.12–0.98; p=0.04) [22].

Interestingly, a study conducted in the Republic of Belarus reported alternative findings on the association of the IL-6 -174G/C polymorphism with RA and juvenile idiopathic arthritis (JIA). In JIA patients, a significant association with disease risk was found: the homozygous CC genotype (OR 2.19; 95% CI 1.31–3.67; p=0.01) and the C allele (OR 1.44; 95% CI 1.04–2.00; p=0.03) were significantly more frequent than in controls. However, in adults with RA, this association did not reach statistical significance [23].

It should be noted that RA and JIA are distinct nosological forms that may differ in the inductive and effector phases of pathogenesis; therefore, the differential role of the IL-6 -174G/C (rs1800795) polymorphism in these diseases cannot be excluded. For example, Pascual et al. [24] found no significant differences in genotype distribution or allele frequencies of the IL-6 -174G/C (rs1800795) between RA patients and healthy donors. However, the authors concluded that IL-6 genotype may influence the AAO. Significant differences were found in the mean AAO between patients homozygous for the C allele (43.2±16 years) and those homozygous for the G allele (51.25±12 years), p=0.03, with CG heterozygotes having a mean AAO of 48.8±13 years.

Our study demonstrated statistically significant differences in genotype distribution between patients with early and late RA onset, confirming the genetic heterogeneity of the disease depending on AAO. The CC genotype of the -174 G/C polymorphism in the IL-6 gene was identified as a significant risk factor for RA developing at an age ≥60 years. This allows this genetic variant to be considered a predictor of RA onset at an older age, which may serve as a basis for distinguishing a separate RA phenotype with older age onset [25]. Additionally, we found that patients with AAO ≥60 years, unlike those with early onset, had higher CRP levels, while the frequency of ACPA positivity was significantly lower in this group. Despite comparable DAS28 scores in both groups, functional impairment according to HAQ was significantly more pronounced in late-onset patients. Thus, RA with onset in the older age group is associated with a higher acute-phase response and greater functional impairment, but a less pronounced autoimmune component. Our results are consistent with data reported by other authors [26, 27].

Another important aspect of our study was the examination of the association of the IL-6 -174G/C (rs1800795) polymorphism with phenotypic features such as RF, ACPA, and the presence of erosions. However, no statistically significant association was found between these parameters, which is consistent with data from national and international studies [17, 19].

Conclusion

The results of this study indicate that the examined polymorphism plays an important role as a genetic marker of predisposition to RA at an older age, emphasizing the validity of distinguishing RA phenotypes based on the AAO of the disease. In the future, studying genetic predisposition to RA may facilitate the development of more precise algorithms for individual risk assessment and preventive strategies in rheumatology depending on patient age.

REFERENCES

1. Насонов ЕЛ, редактор. Ревматология. Российские клинические рекомендации. Москва: ГЭОТАР-Медиа; 2020.
Nasonov EL, editor. Rheumatology. Russian clinical recommendations. Moscow: GEOTAR-Media; 2020.
2. Gabriel SE, Crowson CS, O'Fallon WM. The epidemiology of rheumatoid arthritis in Rochester, Minnesota, 1955-1985. *Arthritis Rheum.* 1999 Mar;42(3):415-20. doi: 10.1002/1529-0131(199904)42:3<415::AID-ANR4>3.0.CO;2-Z.
3. Kurky J, Besenyei T, Laki J, et al. Genetics of rheumatoid arthritis – a comprehensive review. *Clin Rev Allergy Immunol.* 2013 Oct; 45(2):170-9. doi: 10.1007/s12016-012-8346-7.
4. Okada Y, Wu D, Trynka G, et al. Genetics of rheumatoid arthritis contributes to biology and drug discovery. *Nature.* 2014 Feb 20; 506(7488):376-81. doi: 10.1038/nature12873.
5. Yoshida Y, Tanaka T. Interleukin 6 and rheumatoid arthritis. *Biomed Res Int.* 2014; 2014:698313. doi: 10.1155/2014/698313.
6. Nishimoto N, Kishimoto T. Interleukin 6: from bench to bedside. *Nat Clin Pract Rheumatol.* 2006 Nov;2(11):619-26. doi: 10.1038/ncprheum0338.
7. Malysheva K, de Rooij K, Lowik CW et al. Interleukin 6/Wnt interactions in rheumatoid arthritis: interleukin 6 inhibits Wnt signaling in synovial fibroblasts and osteoblasts. *Croat Med J.* 2016 Apr 23;57(2):89-98. doi: 10.3325/cmj.2016.57.89.
8. Kishimoto T. Interleukin-6: from basic science to medicine-40 years in immunology. *Annu Rev Immunol.* 2005;23:1-21. doi: 10.1146/annurev.immunol.23.021704.115806.
9. Magyari L, Varszegi D, Kovesdi E, et al. Interleukins and interleukin receptors in rheumatoid arthritis: Research, diagnostics and clinical implications. *World J Orthop.* 2014 Sep 18;5(4):516-36. doi: 10.5312/wjo.v5.i4.516.
10. Wang J, Platt A, Upmanyu R, et al. IL-6 pathway-driven investigation of response to IL-6 receptor inhibition in rheumatoid arthritis. *BMJ Open.* 2013 Aug 19;3(8):e003199. doi: 10.1136/bmjopen-2013-003199.
11. Kotake S, Sato K, Kim KJ, et al. Interleukin-6 and soluble interleukin-6 receptors in the synovial fluids from rheumatoid arthritis patients are responsible for osteoclast-like cell formation. *J Bone Miner Res.* 1996 Jan;11(1): 88-95. doi: 10.1002/jbmr.5650110113.
12. Terry CF, Loukaci V, Green FR. Cooperative influence of genetic polymorphisms on interleukin 6 transcriptional regulation. *J Biol Chem.* 2000 Jun 16;275(24):18138-44. doi: 10.1074/jbc.M000379200.
13. Guseva I, Demidova N, Soroka N, et al.

IL-6(-174G/C) and MCP-1(-2581A/G) gene polymorphisms are associated with radiographic joint damage and disease activity in patients with early rheumatoid arthritis: a two-year prospective study. *Ann Rheum Dis.* 2010; 69(Suppl.3):661.
14. Wielinska J, Dratwa M, Swierkot J, et al. Interleukin 6 gene polymorphism is associated with protein serum level and disease activity in Polish patients with rheumatoid arthritis. *HLA*. 2018 Dec;92 Suppl 2:38-41. doi: 10.1111/tan.13355.
15. Ceccarelli F, Perricone C, Fabris M, et al. Transforming growth factor 869C/T and interleukin 6 -174G/C polymorphisms relate to the severity and progression of bone-erosive damage detected by ultrasound in rheumatoid arthritis. *Arthritis Res Ther.* 2011 Jul 8;13(4): R111. doi: 10.1186/ar3396.
16. Dar SA, Haque S, Mandal RK et al. Interleukin-6-174G > C (rs1800795) polymorphism distribution and its association with rheumatoid arthritis: A case-control study and meta-analysis. *Autoimmunity*. 2017 May;50(3): 158-169. doi: 10.1080/08916934.2016. 1261833.
17. Arman A, Coker A, Sarioz O, et al. Lack of association between IL-6 gene polymorphisms and rheumatoid arthritis in Turkish population. *Rheumatol Int.* 2012 Jul;32(7): 2199-201. doi: 10.1007/s00296-011-2057-x.
18. Zavaleta-Muniz SA, Martin-Marquez BT, Gonzalez-Lopez L, et al. The -174G/C and -572G/C interleukin 6 promoter gene polymorphisms in mexican patients with rheumatoid arthritis: a case-control study. *Clin Dev Immunol.* 2013;2013:959084. doi: 10.1155/2013/959084.
19. Гусева ИА, Демидова НВ, Сорока НЕ и др. Исследование полиморфизмов генов-кандидатов иммунного ответа как маркеров риска развития ревматоидного артрита и продукции аутоантител. Научно-практическая ревматология. 2016;54(1):21-30.
Guseva IA, Demidova NV, Soroka NE, et al. Investigation of candidate gene polymorphisms in an immune response as markers for the risk of developing rheumatoid arthritis and producing autoantibodies. *Nauchno-Prakticheskaya Revmatologia*. 2016;54(1):21-30 (In Russ.).
20. Сатыбалдыев АМ, Демидова НВ, Гриднева ГИ и др. Клиническая характеристика трех когорт раннего ревматоидного артрита с поздним началом (в возрасте 50 лет и старше). Обобщение 40-летнего опыта. Научно-практическая ревматология. 2020; 58(2):140-146.
Satybaldyev AM, Demidova NV, Gridneva GI et al. Clinical characteristics of three cohorts of patients with early- and late-onset rheumatoid arthritis (at 50 years or older). Generalization of 40 years' experience. *Nauchno-Prakticheskaya Revmatologia*. 2020;58(2):140-146. (In Russ.).
21. Innala L, Berglin E, Möller B, et al. Age at onset determines severity and choice of treatment in early rheumatoid arthritis: A prospective study. *Arthritis Res Ther.* 2014 Apr 14; 16(2):R94. doi: 10.1186/ar4540.
22. Fishman D, Faulds G, Jeffery R, et al. The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis. *J Clin Invest.* 1998 Oct 1;102(7):1369-76. doi: 10.1172/JCI2629.
23. Яцкив АА, Большакова ДВ, Чичко АМ и др. Влияние полиморфизма -174G/C гена IL-6 на вероятность развития ревматоидного артрита у детского и взрослого населения Республики Беларусь. Доклады национальной акададемии наук Беларуси. 2018;62(5):608-614.
Yatskiv AA, Bol'shakova DV, Chichko AM, et al. Goncharova R. I. Influence of -174G/C IL-6 gene polymorphism on the susceptibility to rheumatoid arthritis in children and adults in the Republic of Belarus. *Doklady natsional'noi akadademii nauk Belarusi*. 2018;62(5): 608-614.
24. Pascual M, Nieto A, Matarбn L, et al. IL-6 promoter polymorphisms in rheumatoid arthritis. *Genes Immun*. 2000 Jun;1(5):338-40. doi: 10.1038/sj.gene.6363677.
25. Kobak S, Bes C. An autumn tale: geriatric rheumatoid arthritis. *Ther Adv Musculoskelet Dis.* 2018 Jan;10(1):3-11. doi: 10.1177/ 1759720X17740075.
26. Zhang JF, Ye XL, Duan M, et al. Clinical characteristics of elderly and younger onset rheumatoid arthritis. *Zhonghua Yi Xue Za Zhi*. 2020 Dec 22;100(47):3788-3792. doi: 10.3760/ cma.j.cn112137-20200506-01439.
27. Lahaye C, Tatar Z, Dubost JJ, et al. Management of inflammatory rheumatic conditions in the elderly. *Rheumatology (Oxford)*. 2019 May 1;58(5):748-764. doi: 10.1093/ rheumatology/key165.

Received/Reviewed/Accepted
20.11.2025/18.01.2026/23.01.2026

Conflict of Interest Statement

The article was prepared within the framework of the fundamental research project FURS-2022-008 (state assignment №1021051503137-7). The study received no external funding. There are no conflicts of interest. The authors are solely responsible for submitting the final version of the manuscript for publication. All authors participated in developing the concept of the article and in writing the manuscript. The final version of the manuscript has been approved by all authors.

Aboleshina A.V. https://orcid.org/0000-0003-3431-5580
Guseva I.A. https://orcid.org/0000-0002-4906-7148
Zotkin E.G. https://orcid.org/0000-0002-4579-2836
Samarkina E.Yu. https://orcid.org/0000-0001-7501-9185
Demidova N.V. https://orcid.org/0000-0003-3065-4235
Movsesyan A.A. https://orcid.org/0009-0002-3473-2480
Molova K.M. https://orcid.org/0009-0005-9730-8224
Makoeva M.A. https://orcid.org/0000-0003-3468-8707