ORIGINAL INVESTIGATIONS

Use of olokizumab, a direct interleukin 6 inhibitor, in the treatment of rheumatoid arthritis: real-world evidence

Shesternya P.A.[1], Zagrebneva A.I.[2], Antipova O.V.[3], Arbuzova Yu.V.[4], Bannikova I.G.[5], Belozertseva L.V.[6], Bogdanova E.A.[7], Bykova S.A.[1,8], Vasilenko E.A.[9], Vinogradova I.B.[10], Davidyan S.Yu.[11], Epifanova O.E.[12], Zemerova E.V.[13], Zlobin M.V.[14], Ivanova L.V.[15], Ilyina N.A.[16], Ilyushina L.V.[17], Klyuchnikova E.P.[1,8], Makevnina A.V.[18], Myasoutova E.R.[19], Nakonechnaya E.E.[20], Pavlova A.B.[21], Plaksina T.V.[14], Rybin A.V.[22], Salnikova T.S.[23], Solodovnikova L.V.[24], Fedorova A.V.[25], Cherencova I.A.[26], Jakovleva E.V.[27], Yakupova S.P.[28], Alekseev E.N.[29], Lila A.M.[30,31]

[1]Prof. V.F. Voino-Yasenetsky Krasnoyarsk State Medical University, Ministry of Health of Russia, Krasnoyarsk; [2]City Clinical Hospital No.52 of Healthcare Department of Moscow, Moscow; [3]Irkutsk City Clinical Hospital №1, Irkutsk; [4]Regional Clinical Hospital, Omsk; [5]Surgut District Clinical Hospital, Surgut; [6]Zabaykalsky Regional Clinical Hospital, Chita; [7]Chelyabinsk Regional Clinical Hospital, Chelyabinsk; [8]Regional Clinical Hospital, Krasnoyarsk; [9]Gatchina Interregional Clinical Hospital, Gatchina; [10]Ulyanovsk Regional Clinical Hospital, Ulyanovsk; [11]National Medical Surgical Center named after N.I. Pirogov, Ministry of Health of Russia, Moscow; [12]Medical Center "RevmaMed", Syktyvkar; [13]Budget institution of the Khanty-Mansiysk Autonomous Okrug Ugra "District Clinical Hospital", Khanty-Mansiysk; [14]N.A. Semashko Nizhny Novgorod Regional Clinical Hospital, Nizhniy Novgorod; [15]Republican Clinical Diagnostic Center of Ministry of Health of the Republic of Udmurtia, Izhevsk; [16]Research Institute of Fundamental and Clinical Immunology, Novosibirsk; [17]Clinical Cardiological Dispensary, Syktyvkar; [18]Moscow Regional Research and Clinical Institute named after M.F. Vladimirsky, Moscow; [19]Republican Clinical Hospital, Ministry of Health of Republic of Tatarstan, Kazan; [20]Clinical Cardiological Dispensary, Omsk; [21]"RZhD-Medicine", Ulan-Ude; [22]Ivanovo Regional Clinical Hospital, Ivanovo; [23]Tula Regional Clinical Hospital, Tula; [24]Mordovian Republican Central Clinical Hospital, Saransk; [25]Research Institute of Clinical and Experimental Lymphology – Branch of the Institute of Cytology and Genetics, Siberian Branch of Russian Academy of Sciences, Novosibirsk; [26]Regional Clinical Hospital named after S.I. Sergeev, Khabarovsk; [27]Research Institute – Regional Clinical Hospital №1 named after Prof. S.V. Ochapovsky, Ministry of Health of Krasnodar Region, Krasnodar; [28]Kazan State Medical University, Ministry of Health of Russia, Kazan; [29]R-Pharm, Moscow; [30]V.A. Nasonova Research Institute of Rheumatology, Moscow; [31]Russian Medical Academy of Continuing Professional Education, Ministry of Health of Russia, Moscow

[1]1, Partizan Zheleznyak Street, Krasnoyarsk 660022, Russia; [2]3, Pehotnaya Street, Moscow 123182, Russia; [3]118, Baikalskaya Street, Irkutsk 664046, Russia; [4]3, Berezovaya Street, Omsk 644012, Russia; [5]24, Energetikov Street, Build. 3, Surgut 628408, Russia; [6]7, Kokhansky Street, Chita 672038, Russia; [7]70, Vorovsky Street, Chelyabinsk 454048, Russia; [8]3A, Partizan Zheleznyak Street, Krasnoyarsk 660022, Russia; [9]15A, Roshinskaya Street, Build. 1, Gatchina 188300, Russia; [10]7, III Internatzionala Street, Ulyanovsk 432017, Russia; [11]70, Nizhnyaya Pervomaiskaya Street, Moscow 105203, Russia; [12]50, Klary Zetkin Street, Syktyvkar 167031, Russia; [13]40, Kalinin Street, Khanty-Mansiysk 628012, Russia; [14]190, Rodionova Street, Nizhniy Novgorod 603093, Russia; [15]87Б, Lenina Street, Izhevsk 426009, Russia; [16]6, Zalesskogo Street, Build. 9, Novosibirsk 630047, Russia; [17]1, Markova Street, Syktyvkar 167981, Russia; [18]61/2, Shepkina Street, Moscow 129110, Russia; [19]138, Orenburgskiy Trakt, Kazan 420064, Russia; [20]41, Lermontov Street, Omsk 644044, Russia; [21]1Б, Komsomolskaya Street, Ulan-Ude 670002, Russia; [22]1, Lyubimova Street, Ivanovo 153000, Russia; [23]1A, Yablochkova Street, Tula 300053, Russia; [24]14/5, Pobedy Street, Build. 1, Saransk 430013, Russia; [25]2, Timakov Street, Novosibirsk 630060, Russia; [26]9Б, Krasnodarskaya Street, Khabarovsk 680009, Russia; [27]167, 1st May Street, Krasnodar 350086, Russia; [28]49, Butlerov Street, Kazan 420012, Russia; [29]111, Leninsky Prospect, Build. 2, Moscow 119421, Russia; [30]34A, Kashirskoe Shosse, Moscow 115522, Russia; [31]2/1, Barrikadnaya Street, Build. 1, Moscow 125993, Russia

ORIGINAL INVESTIGATIONS

Objective: *To study the efficacy and safety of olokizumab (OKZ) in patients with rheumatoid arthritis (RA) in real-life clinical practice.*
Material and methods. *The observational program was conducted in 73 centers across Russia from Dec 1, 2022 to Jan 31, 2025. It was based on a retrospective analysis of real clinical practice data. Information on patients was collected and analyzed at baseline and after 1, 6, and 12 months of treatment.*
Results and discussion. *A total of 1,576 patients (81.7% women) with RA, aged 55.0 [44.0; 63.0] years and with RA duration of 100.0 [50.0; 156.0] months, were included in the program. After 6 and 12 months of OKZ therapy, the treatment target (remission/low activity) was achieved in 63.3% and 79.8% of patients by DAS28-CRP, and in 55.4% and 75.5% by CDAI respectively. Gender, age, seropositivity, and use of biologic disease-modifying antirheumatic drugs did not significantly affect the achievement of the treatment goal. During the observation period, a significant proportion of patients were able to discontinue glucocorticoids (GCs): 51.1% of patients received GCs initially, after 6 months, 27.6% of patients still received GCs, and after 12 months, 17.0%. During the observation, OKZ treatment was discontinued in 148 (9.5%) patients: in 50 (3.2%) patients due to insufficient efficacy, in 63 (4.0%) patients due to adverse events, and in 35 (2.2%) patients due to other reasons.*
Conclusion. *IL-6 inhibition with OKZ is both effective and safe for achieving RA therapy goals in real-world clinical settings.*

Keywords: *rheumatoid arthritis; olokizumab; IL-6 inhibitor; real world evidence.*
Contact: *Pavel Anatolyevich Shesternya;* ***shesternya75@mail.ru***
For reference: *Shesternya PA, Zagrebneva AI, Antipova OV, Arbuzova YuV, Bannikova IG, Belozertseva LV, Bogdanova EA, Bykova SA, Vasilenko EA, Vinogradova IB, Davidyan SYu, Epifanova OE, Zemerova EV, Zlobin MV, Ivanova LV, Ilyina NA, Ilyushina LV, Klyuchnikova EP, Makevnina AV, Myasoutova ER, Nakonechnaya EE, Pavlova AB, Plaksina TV, Rybin AV, Salnikova TS, Solodovnikova LV, Fedorova AV, Cherencova IA, Jakovleva EV, Yakupova SP, Alekseev EN, Lila AM. Use of olokizumab, a direct interleukin 6 inhibitor, in the treatment of rheumatoid arthritis: real-world evidence. Sovremennaya Revmatologiya=Modern Rheumatology Journal. 2025;19(2):39–49.* ***DOI:*** *10.14412/1996-7012-2025-2-39-49*

Currently emerging evidence supports the recognition of the central role of interleukin (IL) 6 as the most important cytokine in the maintenance of autoimmune inflammation in rheumatoid arthritis (RA) [1, 2], therefore IL-6 is considered as one of the main targets of RA therapy [3].

Suppression of IL-6 effects can be achieved in two ways – by neutralizing cellular and soluble IL-6 receptors (IL-6R) and direct blockade of the cytokine itself [1, 3–5]. In 2020, the direct IL-6 inhibitor (IL-6i) olokizumab (OKZ) was approved in the Russian Federation for the first time in the world. It is a humanized monoclonal antibody that binds to site III of the IL-6 ligand, preventing formation of a signaling complex on the cell membrane. This, in turn, results in blockade of IL-6 effects during its hyperproduction and suppression of inflammation [5, 6]. In 2021, OKZ was included in the clinical guidelines for the treatment of RA [1] and the Vital and Essential Drugs List. During the COVID-19 pandemic, the second indication, cytokine release syndrome in the moderate-to-severe new coronavirus infection, was approved for the OKZ, and the drug was included in the clinical guidelines for the treatment of COVID-19 [6]. The drug is included in the standard of care for adults with RA [7].

Two mechanisms of IL-6 blockade have a number of differences. Thus, when using IL-6R inhibitors (IL-6Ri), there is an increase in the content of free active IL-6 in the blood. This is due to the disruption of IL-6 utilization, which under normal conditions goes through soluble IL-6R. The clinical significance of this effect is not yet clear and needs further evaluation [88]. Direct blockade leads to a decrease in free active IL-6, while total concentration of IL-6 increases due to an inactive cytokine associated with OKZ [9, 10]. The complex of OKZ+IL-6 is biologically inactive and is close to OKZ based on pharmacokinetics, with a half-life of about 31 days [9].

As new data on IL6 blockade have accumulated and new products in this group have emerged, clinical guidelines for the treatment of RA have undergone significant changes in the sections on biological DMARDs (bDMARDs) and, in particular, IL-6i. In clinical guidelines, the use of OKZ is considered even somewhat broader than in the drug label: the possibility of using monotherapy with OKZ in case of intolerance of conventional DMARDs, and intra-group switching in case of failure of bDMARDs are included [1].

What was already known about OKZ?

- OKZ is approved for the treatment of moderate to severe active RA in combination with methotrexate (MT) in patients who have not previously received bDMARDs and switched from inhibitors of tumor necrosis factor α (TNF α).
- OKZ is administered subcutaneously every 4 weeks (Q4W); in patients with DAS28 ≥6.9, it can be used every 2 weeks.
- Maintenance of efficacy and safety of OKZ treatment for at least 2 years was demonstrated

What is the added value of our observation?

- In real-world clinical settings, the efficacy of OKZ was independent of age, sex, seropositivity, concomitant DMARD treatment and prior bDMARD treatment.
- The use of OKZ reduced the proportion of patients taking steroids from 51.1% to 28% after 6 months and further to 17% after 12 months of treatment.
- No previously unknown adverse events were reported in 1,576 patients treated with OKZ for 12 months.

Direct IL-6 inhibitor OKZ is used for 5 years. Data on direct IL-6 inhibitors in real-world clinical practice can largely complement the results of randomized clinical trials (RCTs) [11–13].

A number of recent publications demonstrated the efficacy of switching from one IL-6R inhibitor to another, and provides new therapeutic opportunities [14–16]. In 2023, the results of the follow-up of 110 patients switched for non-medical reasons from treatment with IL6-R inhibitor to a direct IL-6 inhibitor OKZ were published, and the study showed the ability of OKZ to effectively maintain remission/low activity of RA achieved on IL6-Ri [17, 18]. Given the relatively short period of use of direct

IL-6i in the treatment of RA and the insufficient published data on the real-world use, such information is undoubtedly interesting.

The purpose of the study is to evaluate the efficacy and safety of OKZ[1] in a real-world setting.

Materials and methods. A multicenter, non-interventional, retrospective observational program designed to evaluate the outcomes of OKZ (Artlegia) use included data from 1,576 patients with RA who received this medication in real-world clinical practice across 73 sites in the Russian Federation between December 1, 2022 and November 30, 2023.

Patients over 18 years old with a diagnosis of RA and with failure/intolerance of previous treatment with DMARDs, bDMARDs, or targeted synthetic DMARDs (tsDMARDs) were included. The program also included patients switched to OKZ for non-medical reasons (usually related to the availability of bDMARDs/tsDMARDs).

All analyzed results were obtained in the routine clinical practice, no additional diagnostic and therapeutic procedures were performed. Data were recorded at the time of switching to OKZ (baseline visit), after 1, 6, and 12 months of treatment with this drug.

We recorded sex, age, history of the underlying disease: duration, previous treatment and reasons for prescribing a new drug; data on concomitant diseases with the assessment of the Rheumatic Disease Comorbidity Index (RDCI) [19]; duration of use and dosage regimen of the OKZ; changes of the RA activity indices (Disease Activity Score 28 using CRP [DAS28-CRP] and Clinical Disease Activity Index [CDAI]). All adverse events (AEs) were recorded according to the standard procedure, the relationship of the AE with OKZ treatment was determined by the Naranjo scale.

Statistical processing of results was performed using standard methods of parametric and non-parametric analysis. Results are presented as median (Me) with interquartile range [25th; 75th percentiles]), mean (M) and standard deviation, binary variables are presented as absolute and relative frequencies. A t-test was used to determine the statistical significance of the differences between the variables. The χ^2 test was used to compare the proportions of patients with different RA activity in different subgroups. The relationship between the variables was determined using the Pearson correlation coefficient. Differences considered statistically significant at $p<0.05$.

Results

Baseline characteristics. Females predominated in the studied population (n=1287, 81.7%). The median age of patients was 55.0 [44.0; 63.0] years, and the median duration of the disease was 100.0 [50.0, 156.0] months. The vast majority of patients were positive for rheumatoid factor (RF; n=1351, 85.7%) and antibodies to cyclic citrullinated peptide (anti-CCP; n=1305, 82.8%).

In 1154 (73.2%) patients, comorbidities were reported. At least 1 concomitant disease was reported in 675 (42.8%) patients,

Table 1. Characteristics of patients

Parameter	Total	bDMARDs/ tsDMARDs-naive	Switched from bDMARDs/ tsDMARDs	P
Number of patients, n	**1576**	**1076**	**500**	–
Female, n (%)	1287 (81,7)	868 (80,7)	419 (83,8)	0,135
Age, yr, Me [25th; 75th percentiles]	55,0 [44,0; 63,0]	54,0 [44,0; 63,0]	56,0 [44,0; 64,0]	0,587
Длительность заболевания, мес, Me [25-й; 75-й перцентили]	100,0 [50,0; 156,0]	96,0 [48,0; 144,0]	120,0 [72,0; 180,0]	**<0,001**
RF+, n (%)	1351 (85,7)	928 (86,2)	423 (84,6)	0,385
Anti-CCP+, n (%)	1305 (82,8)	894 (83,1)	411 (82,2)	0,665
RA activity according to DAS28-CRP, n (%)				
Low or remission	52 (3,3)	11 (1,0)	41 (8,2)	
Moderate	590 (37,4)	361 (33,6)	229 (45,8)	**<0,001**
High	934 (59,3)	704 (65,4)	230 (46,0)	
RDCI, n (%)				
0	685 (43,5)	484 (45,0)	201 (40,2)	
1	568 (36,0)	402 (37,4)	166 (33,2)	**<0,001**
≥2	323 (20,5)	190 (17,6)	133 (26,6)	
DMARD treatment, n (%)				
MTX	959 (60,8)	682 (63,4)	277 (55,4)	
LEF	336 (21,3)	230 (21,4)	106 (21,2)	
SSZ	90 (5,7)	67 (6,2)	23 (4,6)	
HCQ	38 (2,4)	23 (2,1)	15 (3,0)	**<0,001**
AZA	1 (0,06)	1 (0,09)	0 (0,0)	
Second DMARD was administered	14 (0,9)	14 (1,3)	0 (0,0)	
DMARDs were not administered	152 (9,6)	73 (6,8)	79 (15,8)	
Steroids, n (%)	806 (51,1)	583 (54,2)	223 (44,6)	**<0,001**

Note. LEF – leflunomide; SSZ – sulfasalazine; HCQ – hydroxychloroquine; AZA – azathioprine.

[1]Artlegia (R-Pharm).

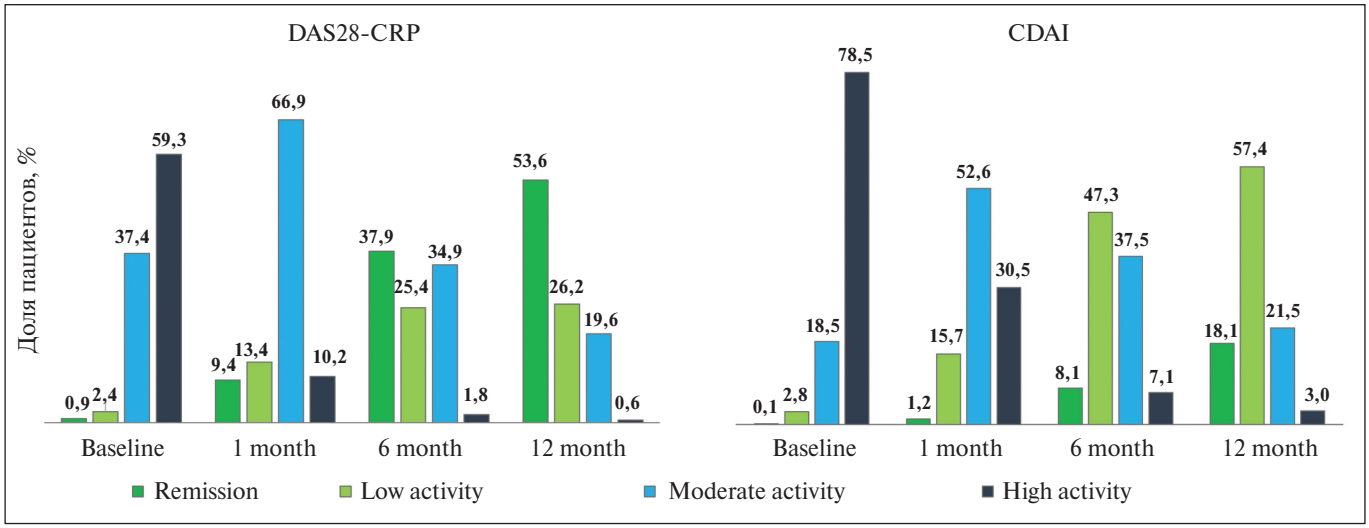

Fig. 1. *Changers of rheumatoid arthritis activity during OKZ treatment*

2 or more concomitant diseases were observed in 479 (30.4%) patients. 593 (37.6%) patients were diagnosed with cardiovascular diseases, 22 (1.4%) with cerebrovascular diseases, 71 (4.5%) with lung pathology, including interstitial lung disease, 105 (6.7%) with diabetes mellitus (both types), 237 (15.0%) with gastrointestinal (GI) and liver diseases, 270 (17.1%) had osteoarthritis, 239 (15.2%) had osteoporosis, 46 (2.9%) had thyroid disease, 62 (4.0%) had kidney disease, 57 (3.6%) had anemia, 17 (1.1%) had depression, 22 (1.4%) had a history of cancer, and 10 (0.6%) had other concomitant autoimmune diseases. RDCI=0 was reported in 685 (43.5%) patients, RDCI=1 in 568 (36.0%) patients and RDCI ≥2 in 323 (20.5%) patients.

959 (60.8%) patients received MTX, 152 (9.6%) patients did not receive bDMARDs, and 806 (51.1%) patients received steroids. 1076 (68.3%) patients were bDMARD/tsDMARD-naive and 500 (31.7%) were previously treated with bDMARDs/tsDMARDs. Detailed characteristics of the patients are presented in Table 1.

The frequency of administration of subcutaneous injections of OKZ solution (160 mg/mL) was determined by a rheumatologist: 1319 (83.7%) patients received the drug at a dose of 64 mg every 4 weeks, 257 (16.3%) every 2 weeks.

OKZ was prescribed as part of combination treatment to 1390 (88.92%) patients, as the monotherapy to 186 (11.48%) patients. After 6 months, the monotherapy regimen was maintained in 112 (59.7%) patients (in 11 – discontinuation due to AE, in 8 – due to lack of efficacy, in 55 - bDMARD was added), and after 12 months – in 97 (52.1%) patients (in 9 – bDMARDs were added, in 5 – discontinuation due to AEs, 1 patient was lost to follow-up). The likelihood of maintaining OKZ monotherapy during the first 6 months of treatment had a statistically significant weak negative correlation with the baseline tender joints count (TJC, R=-0.13; p<0.05) and the baseline frequency of OKZ administration – once every 4 weeks was associated with continuation of monotherapy (R=0.16; p<0.05). Quite noteworthy, monotherapy success in the first 6 months of treatment is the basis for its further continuation – retention of monotherapy after 6 months was the strongest predictor of its retention after 12 months (R=0.86, p<0.05).

Table 2. Safety of OKZ therapy, n (%)*

Parameter	Months of treatment			Total
	0–1	2–6	7–12	
	AEs			
Total, AEs, leading to treatment discontinuation	**23 (1,5)** 14 (0,9)	**42 (2,7)** 32 (2,0)	**26 (1,6)** 17 (1,1)	**91 (5,8)** 63 (4,0)
Infections	4 (0,3)	13 (0,8)	5 (0,3)	22 (1,4)
Laboratory abnormalities**	11 (0,7)	12 (0,8)	8 (0,5)	31 (2,0)
Skin allergic reactions	5 (0,3)	5 (0,3)	4 (0,3)	14 (0,9)
Local injection site reactions	–	–	2 (0,1)	2 (0,1)
Malignancies	–	2 (0,1)	3 (0,2)	5 (0,3)
Gastrointestinal and hepatic disorders	–	4 (0,3)	1 (0,1)	5 (0,3)
Other	2 (0,1)	2 (0,1)	3 (0,2)	7 (0,4)
	Serious AEs			
Total	**1 (0,1)**	**4 (0,3)**	**–**	**5 (0.3)**
Death (myocardial infarction)	–	1 (0,1)	–	1 (0,1)
Death (GI bleeding)	–	1 (0,1)	–	1 (0,1)
Myocardial infarction	–	1 (0,1)	–	1 (0,1)
Hemorrhagic stroke	1 (0,1)	–	–	1 (0,1)
Perforated diverticulitis	–	1 (0,1)	–	1 (0,1)

Note: *n – number of patients with AE; % – percentage of patients with AE out of all patients who received at least one injection of the drug; ** – most often an increase in the level of AST, ALT (≤3 ULN), leukopenia (≥1,5·10⁹).

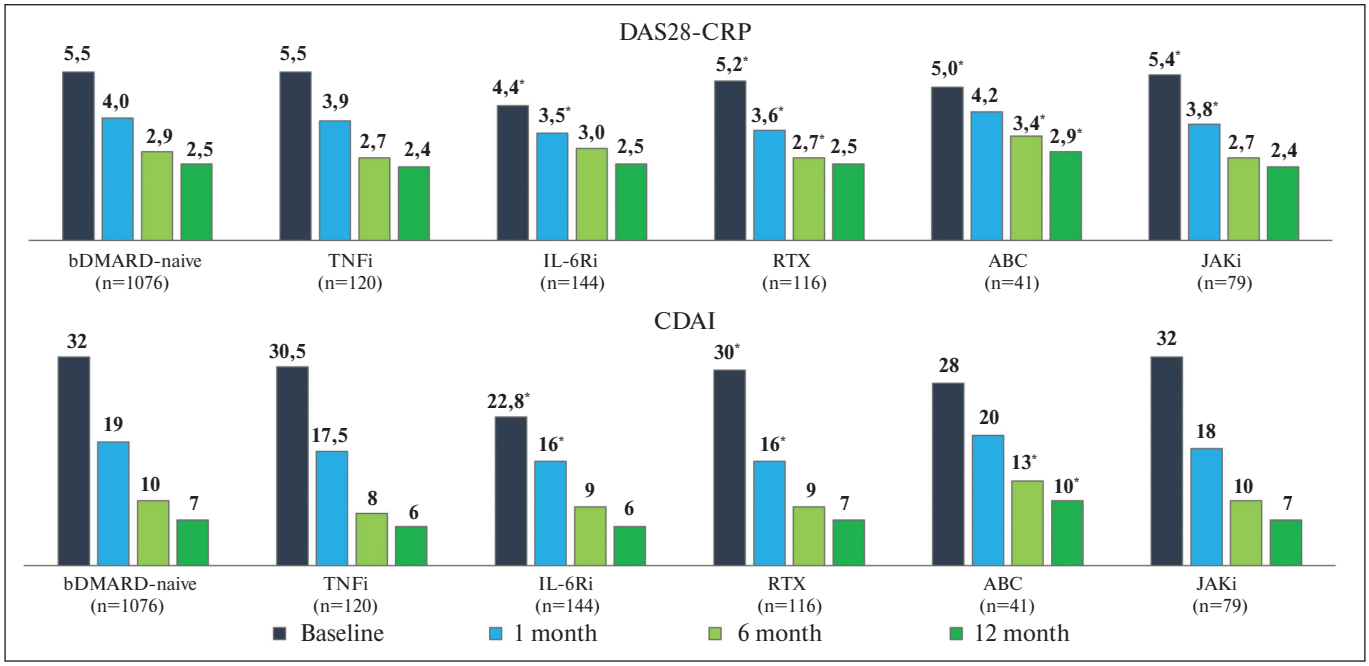

Fig. 2. *Changes of rheumatoid arthritis activity during OKZ treatment depending on previous treatment (median). RTX – rituximab; ABC – abatacept; and JAKi – Janus kinase inhibitors. * – p<0.05 vs b/tsDMARDs-naive patients*

Overall efficacy. At baseline, at the time of treatment initiation, 59.3%, 37.4% and 3.3% of patients had high, moderate, low activity/remission assessed by DAS28-CRP, and 78.5%, 18.5% and 2.9% patients, respectively, had high, moderate, low activity/remission assessed by CDAI. After 6 and 12 months of OKZ treatment, the proportion of patients who achieved remission/low activity according to DAS28-CRP was 63.3 and 79.8%, according to CDAI – 55.4 and 75.5%, respectively. Moderate and high activity according to DAS28-CRP at 6 and 12 months was observed in 36.7 and 20.2% patients, according to CDAI – in 44.6 and 24.5% (Fig. 1).

Baseline medians of DAS28-CRP and CDAI were 5.4 [4.7; 6.1] and 31.0 [24.0; 39.0], after 6 and 12 months of OKZ treatment – 2.9 [2.3; 3.5] and 2.5 [1.9; 3.1]; 10.0 [6.0; 14.0] and 7.0 [3.3; 10.0], respectively.

A detailed analysis of OKZ efficacy did not reveal any significant differences depending on the gender and age of patients. To analyze the effect of immunological changes on the treatment efficacy, four subgroups of patients were identified: RF+/ACCP+ (n=1225, 77.8%), RF+/ACCP- (n=126, 8.0%), RF-/ACCP+ (n=80, 5.1%) and RF-/ACCP- (n=145, 9.2%). There were no differences between the subgroups after 6 and 12 months of treatment. The exception was the subgroup RF-/ACCP+ after 12 months, in which the proportion of patients who achieved remission/low activity was statistically significantly higher than in the RF+ subgroups of patients.

bDMARDs/tsBDMARDs-nanve vs bDMARDs/tsBDMARDs-experienced patients. High activity of RA at baseline in the bDMARDs/tsBDMARDs-naive group of patients occurred somewhat more often than in patients switched from other bDMARDs/tsBDMARDs: according to DAS28-CRP in 65.4 and 46.0%, according to CDAI – in 83.4 and 68.5% patients, respectively (p<0.05). Differences persisted after 1 month of OKZ treatment and up to 6 months – according to DAS28-CRP. After 12 months of treatment, any significant differences between these groups had dissipated. In the bDMARD/tsBDMARD-naive group of patients, the frequency of remission/low activity according to DAS28-CRP at 6 and 12 months was 63.3 and 80.1%, according to CDAI – 55.1 and 75.9%, and in the group of switched patients – 62.9 and 78.4%; 56.0 and 74.2%, respectively.

Analysis of changes in RA activity in patients when switching from different classes of biologics compared to bDMARD-naive patients revealed similar changes in all subgroups. The changes of RA activity depending on previous treatment with bDMARDs/tsBDMARDs is presented in Fig. 2.

Combination treatment with OKZ and DMARDs and monotherapy with OKZ. There were no significant differences in the RA activity changes between the groups of combination treatment of OKZ and MTX, OKZ and LEF, OKZ and SSZ, OKZ and HCQ at 6 and 12 months.

Two groups were identified for the analysis of OKZ efficacy in combination with DMARD and as monotherapy. The first group (n=802) was treated with OKZ in combination with other DMARD, while the second group (n=97) was treated with OKZ monotherapy for 12 months. At baseline, the proportion of patients with high RA activity was lower in the monotherapy group than in the combination treatment group (44.0 and 60.4% according to DAS28-CRP, 62.5 and 80.4% according to CDAI), and the proportion of patients with moderate activity was higher (45.0 and 36.3%; 33.7 and 15.9%, respectively). After 6 months of treatment, the proportion of patients who achieved remission/low activity in the combination treatment group was 65.9%, in the monotherapy group – 58.7% according to DAS28-CRP, 55.8 and 47.1% according to CDAI, respectively, and after 12 months of treatment – 80.8 and 79.8%; 76.1 and 74.0%, respectively.

Use of steroids. At baseline, 806 (51.1%) patients received steroids. After 6 months of OKZ treatment, data on the use of steroids were available in 1284 patients, after 12 months – in 1061 (148 patients discontinued OKZ treatment, and steroid intake data were not available retrospectively for the remainder part).

During the follow-up period, a significant proportion of patients were able to discontinue steroids. After 6 months, steroid treatment continued in 27.6% of patients, and after 12 months – in 17.0%.

In addition, a decrease in the daily dose of steroids after 6 months of OKZ treatment was reported in 213 patients, and after 12 months – in 48 patients more. The steroid dose within the first 6 months of OKZ treatment decreased on average from 7.0±3.9 to 4.6±2.3 mg/day ($p<0.05$), and after 12 months – to 4.3±2.5 mg/day ($p<0.05$ compared with the baseline value and data after 6 months).

The most significant predictors of the continuation of steroid treatment were age above 60 years (relative risk, HR 1.24; 95% confidence interval, CI 1.04-1.48), duration of RA more than 5 years (HR 1.41; 95% CI 1.15–1.72), RDCI ≥2 (HR 1.25; 95% CI 1.04–1.50).

Safety assessments. During the entire follow-up period, OKZ was discontinued in 148 patients (9.5%), including in 50 patients (3.2%) due to lack of efficacy, in 63 patients (4.0%) due to AEs, and in 35 patients (2.2%) due to other reasons, including pregnancy (n=3), patient decision (n=14), preparation for surgery (n=3), and doctor's decision (n=15). AEs were recorded in 91 (5.8%) patients. In 28 (1.8%) patients, despite the development of an AE, treatment with OKZ was continued, and in 63 (4.0%) patients, treatment with OKZ was interrupted (Table 2).

Among the AEs not resulting in withdrawal of the OKZ, the most common were transaminase elevation <3 ULN (n=10, 0,63%), minor leukopenia (n=7, 0,44%), respiratory and skin infections (n=6, 0,38%). Among the AEs leading to OKZ withdrawal, the most common were infections (n=16, 1.0%), skin allergic reactions, including rash and dermatitis (n=12, 0.76%), clinically significant leukopenia (n=7, 0.44%) and transaminases elevation (n=6, 0.38%).

During the follow-up period, 2 deaths were recorded. In one case, death was due to acute myocardial infarction in a 66-year-old man with a prior cardiac history, and in the second case, death was due to GI bleeding in a 48-year-old woman with a prior peptic ulcer disease. In both cases, there was no clear association with the use of OKZ (Naranjo score 2).

Infections of various locations were reported in 22 (1.4%) patients, including 5 (0,3%) cases of herpes infection, 4 (0.25%) cases of tuberculosis. No severe infectious complications were recorded.

Discussion. This cohort of patients is typical of the all-Russian population of patients with RA in terms of sex and age, immunologic status, treatment and comorbidities [20]. According to the Russian Register of RA Patients, the frequency of prescribing biologics is 28.6%, and 49.4% of patients receive steroids [20]. In this study, respective parameters were comparable – 31.7 and 51.1%, respectively.

At the same time, the studied cohort of patients has a number of differences from patients included in the RCTs. Efficacy and safety of OKZ have been investigated in the global international CREDO program. This program continued from 2016 to 2022, and included 3 Phase III RCTs and 1 long-term open-label study. CREDO enrolled 2,444 patients in 19 countries worldwide [21–25]. CREDO 1–2 included bDMARD/ts-DMARD-naive patients, CREDO 3 included patients with failure of TNFi. In addition, as part of these RCTs, the treatment of OKZ was carried out exclusively in combination with MTX [21–25]. In the presented work, the range of drugs used in combination with OKZ was much wider, and doctors were allowed to change their doses. In real-world practice, there are cases when specific DMARDs cannot be administered for various reasons, and one has to proceed with bDMARD monotherapy instead.

The broad spectrum of comorbidities in this observational study was comparable to that in the CREDO program, but lacked a number of limitations. RCTs did not include patients with concomitant serious and/or uncontrolled medical conditions that, according to the investigator,

Table 3. Comparison of main parameters of efficacy and safety of OKZ therapy in real clinical practice vs randomized clinical trials data, %

Parameter	24 weeks						52 weeks					
	Total		bDMARD-naive		Switched to OKZ from other bDMARDs		Total		bDMARD-naive		Switched to OKZ from other bDMARDs	
	OOS (n=1576)	RCT (n=1527)	OOS (n=1076)	RCT (n=1228)	OOS (n=500)	RCT (n=299)	OOS (n=1576)	RCT (n=1527)	OOS (n=1076)	RCT (n=1228)	OOS (n=500)	RCT (n=299)
Efficacy parameters												
DAS28-CRP <2,6	37,8	29,0	36,1	29,9	41,5	25,4	53,1	38,8	52,6	40,7	54,2	31,1
DAS28-CRP <3,2	63,3	49,1	63,5	50,4	62,9	43,8	79,5	56,1	80,0	58,0	78,4	48,8
CDAI <2,8	8,0	10,2	7,2	10,7	9,9	8,0	17,3	13,2	16,7	14,2	18,6	9,4
CDAI <10	55,3	43,0	55,1	44,4	56,0	37,5	75,2	49,8	75,2	51,2	75,3	43,8
SDAI <3,3	11,2	12,2	10,5	12,9	13,0	9,0	23,9	15,7	24,0	16,6	23,6	11,7
Treatment discontinuation due lack of efficacy	1,6	0,3	1,3	0,3	2,2	0,3	3,2	1,0	3,2	1,0	4,0	1,0
Safety parameters												
Treatment discontinuations due to AE	2,9	4,0	2,8	3,7	3,4	5,0	4,0	5,1	3,7	5,1	5,4	5,0

Note. OOS – ongoing observational study; RCTs (pooled Phase III RCTs and overall open-label follow-up in CREDO 4); SDAI – Simplified Disease Activity Index.

may have biased the results of the study [21]. In real-world clinical practice, the use of OKZ was limited only by the prescribing information and clinical guidelines for the treatment of RA [1].

The results of this study are comparable to CREDO 4 [24], which also included bDMARD/tsDMARD-naive patients and patients switched from TNFi (Table 3). The fact that the results obtained in real clinical practice were slightly better than in RCTs may be due to the baseline lower RA activity. In real-world clinical practice, switching to OKZ occurred not only due to the failure of previous treatment, but also for other reasons, including non-medical ones (about 14% of recorded cases). In this study, patients were switched from all groups of bDMARDs/tsDMARDs. In addition to the lower baseline activity, it is likely that treatment efficacy in real-world practice was influenced by the ability of the physician to modify the treatment – to replace the DMARD, to add steroids, and in some cases to increase the frequency of OKZ administrations.

In a previously published analysis of CREDO data, it was shown that the comorbidity index has no effect on OKZ efficacy [26]. The observational study showed no significant effect of sex, age, duration of disease, and DMARD used on the efficacy of OKZ. Despite the known positive correlation between the levels of IL-6 and RF [27, 28], in our study, the positivity or negativity for RF and anti-

CCP did not have a significant impact on OKZ efficacy.

In addition to the use of all available DMARDs, and not only MTX, as in the CREDO program, a significant part of our patients received OKZ as a single agent. At the same time, there were no statistically significant differences in the efficacy of OKZ administered in combination with DMARDs and as monotherapy. Similar data were obtained in a 12-month follow-up of 110 patients with RA switched from IL-6R inhibitor to OKZ for non-medical reasons [17, 18]. If it is necessary to switch to monotherapy, it is important to consider baseline clinical and laboratory markers of RA activity, especially the pain intensity. As shown in our observational study, a higher baseline TJC determined the need to add DMARDs.

The CREDO 3 program examined the use of OKZ in case of TNFα inhibitor failure [24]. In the present study, patients were switched to OKZ after treatment with any bDMARDs/tsDMARDs used in RA. bDMARD/tsDMARD-naive and treatment-experienced patients had significant differences at baseline in terms of the disease activity, DMARD treatment and comorbidity index (Table 1). However, there were no significant differences in OKZ efficacy after 6 and 12 months of treatment.

Efficacy of OKZ in the group of patients previously exposed to IL-6Ri is noteworthy. Most of them switched to OKZ for non-medical reasons (usually related to the availability of previously used medicine). Feasibility and efficacy of such a switch were previously demonstrated by Baranov A.A. et al. [17] and Shesternya P.A. et al. [18]. Patients who were switched to OKZ due to failure of other IL6-Ri (n=40) achieved remission/low activity according to DAS28-CRP and CDAI in 56.7 and 47.1% of cases by Month 6 of OKZ treatment, and in 64.0 and 60.0% of cases by Month 12 of treatment, respectively. In summary, switching within the class of IL-6i from IL-6Ri to direct IL-6i is a convenient and effective therapeutic option.

Published evidence regarding the steroid-sparing effect of bDMARDs is conflicting. In some research studies, it was possible to reduce the frequency of steroid use by 30% or more [29–32], while this finding was not reproduced in others publications [33]. Current guidelines emphasize the need to reduce the duration and dose of steroids [1, 34]. In our observational study, a decrease in daily doses and the number of patients taking steroids was noted. Adverse predictors that determined the need to continue steroid use were age over 60 years, disease duration for more than 5 years, high comorbidity index.

OKZ withdrawal rate due to lack of efficacy in this study was 3.2%. This rate was slightly higher than in the CREDO program, in which treatment discontinuation rate for this reason did not exceed 1% [21–24]. The safety analysis revealed no special patterns in the distribution or severity of AEs, although the incidence of AEs in real-world practice was slightly lower. This is likely due to the higher frequency of RCT visits (every 2 weeks) and the heterogeneity of the studied patient cohort.

Conclusion. The results of OKZ use in real-world clinical practice generally align with evidence collected in RCTs, supporting the role of OKZ as a versatile medication for effective and safe control of RA activity. Additional extended follow-up is necessary to determine the long-term OKZ treatment retention in real-world rheumatological practice.

REFERENCES

1. Клинические рекомендации "Ревматоидный артрит".
[Clinical guidelines for Rheumatoid Arthritis]. https://www.consultant.ru/document/cons_doc_LAW_495885/8efd5f17af55cb35a770f73937590c642437b7eb/
2. Hunter CA, Jones SA. IL-6 as a keystone cytokine in health and disease. *Nat Immunol.* 2015 May;16(5):448-57. doi: 10.1038/ni.3153.
3. Aletaha D, Kerschbaumer A, Kastrati K, et al. Consensus statement on blocking interleukin-6 receptor and interleukin-6 in inflammatory conditions: an update. *Ann Rheum Dis.* 2023 Jun;82(6):773-787. doi: 10.1136/ard-2022-222784. Epub 2022 Aug 11.
4. Avci AB, Feist E, Burmester GR. Targeting IL-6 or IL-6 Receptor in Rheumatoid Arthritis: What Have We Learned? *BioDrugs.* 2024 Jan;38(1):61-71. doi: 10.1007/s40259-023-00634-1. Epub 2023 Nov 21.
5. Насонов ЕЛ, Файст Е. Перспективы ингибиции интерлейкина-6 при ревматоидном артрите: олокизумаб (новые моноклональные антитела к ИЛ-6). Научно-практическая ревматология. 2022;60(5):505-518.
[Nasonov EL, Feist E. Prospects of interleukin-6 inhibition in rheumatoid arthritis: olokizumab (new monoclonal antibodies to IL-6). *Nauchno-prakticheskaya revmatologiya.* 2022;60(5):505-518. (In Russ.)].
6. https://grls.rosminzdrav.ru/Grls_View_v2.aspx?routingGuid=f2bc77b4-6298-4b2e-8f37-18e1baa0b63c
7. http://publication.pravo.gov.ru/document/0001202309010013
8. Nishimoto N, Terao K, Mima T, et al. Mechanisms and pathologic significances in increase in serum interleukin-6 (IL-6) and soluble IL-6 receptor after administration of an anti-IL-6 receptor antibody, tocilizumab, in patients with rheumatoid arthritis and Castleman disease. *Blood.* 2008 Nov 15;112(10):3959-64. doi: 10.1182/blood-2008-05-155846. Epub 2008 Sep 10.
9. Kretsos K, Golor G, Jullion A, et al. Safety and pharmacokinetics of olokizumab, an anti-IL-6 monoclonal antibody, administered to healthy male volunteers: A randomized phase I study. *Clin Pharmacol Drug Dev.* 2014 Sep;3(5):388-95. doi: 10.1002/cpdd.121.

Epub 2014 May 26.
10. Лапкина НА, Баранов АА, Левшин НЮ и др. Динамика клинических проявлений и концентрации цитокинов у больных ревматоидным артритом на фоне терапии олокизумабом. Научно-практическая ревматология. 2023;61(4):475-484.
[Lapkina NA, Baranov AA, Levshin NYu, et al. Dynamics of clinical manifestations and cytokine concentrations in patients with rheumatoid arthritis on the background of olokizumab therapy. *Nauchno-prakticheskaya revmatologiya*. 2023;61(4):475-484. (In Russ.)].
11. Garrison LP Jr, Neumann PJ, Erickson P, et al. Using real-world data for coverage and payment decisions: the ISPOR Real-World Data Task Force report. *Value Health*. 2007 Sep-Oct;10(5):326-35. doi: 10.1111/j.1524-4733.2007.00186.x.
12. Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices. Guidance for Industry and Food and Drug Administration Staff, issued 31 August 2017. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-real-world-evidence-support-regulatory-decision-making-medical-devices
13. Гольдина ТА, Суворов НИ. Исследования рутинной клинической практики: от получения данных к оценке медицинских технологий и принятию решений в здравоохранении. Медицинские технологии. Оценка и выбор. 2018;(1):21-29.
[Gol'dina TA, Suvorov NI. Routine clinical practice research: from data acquisition to evaluation of medical technologies and decision-making in healthcare. *Meditsinskie tekhnologii. Otsenka i vybor.* 2018;(1):21-29. (In Russ.)].
14. Tony HP, Feist E, Aries PM, et al. Sarilumab reduces disease activity in rheumatoid arthritis patients with inadequate response to janus kinase inhibitors or tocilizumab in regular care in Germany. *Rheumatol Adv Pract.* 2022 Feb 1;6(1):rkac002. doi: 10.1093/rap/rkac002. eCollection 2022.
15. Emery P, van Hoogstraten H, Thangavelu K, et al. Subcutaneous Sarilumab in Patients With Rheumatoid Arthritis who Previously Received Subcutaneous Sarilumab or Intravenous Tocilizumab: An Open-Label Extension of a Randomized Clinical Trial. *ACR Open Rheumatol.* 2020 Nov;2(11):672-680. doi: 10.1002/acr2.11188. Epub 2020 Nov 8.
16. Загребнева АИ, Симонова ЕН, Мезенова ТВ и др. Московский опыт применении ингибиторов рецептора интерлейкина 6 в терапии ревматоидного артрита в условиях пандемии COVID-19. Современная ревматология. 2022;16(6):73-79.
[Zagrebneva AI, Simonova EN, Mezenova TV, et al. Interleukin 6 receptor inhibitors in the treatment of rheumatoid arthritis during the COVID-19 pandemic, Moscow experience. *Sovremennaya revmatologiya = Modern Rheumatology Journal.* 2022;16(6):73-79. (In Russ.)]. doi: 10.14412/1996-7012-2022-6-73-79
17. Баранов АА, Виноградова ИБ, Аношенкова ОН и др. Ведение больных ревматоидным артритом в реальной клинической практике: опыт переключения с терапии ингибитором рецепторов интерлейкина 6 на прямой ингибитор интерлейкина 6 (олокизумаб). Научно-практическая ревматология. 2023;61(3):307-319.
[Baranov AA, Vinogradova IB, Anoshenkova ON, et al. Management of patients with rheumatoid arthritis in real clinical practice: experience of switching from therapy with an interleukin 6 receptor inhibitor to a direct interleukin 6 inhibitor (olokizumab). *Nauchno-prakticheskaya revmatologiya*. 2023;61(3):307-319. (In Russ.)].
18. Шестерня ПА, Баранов АА, Виноградова ИБ и др. Переключение с ингибиторов рецепторов интерлейкина 6 на прямой ингибитор интерлейкина 6 олокизумаб у пациентов с ревматоидным артритом: эффективность и безопасность в течение 1 года терапии. Современная ревматология. 2024;18(5):54-64.
[Shesternya PA, Baranov AA, Vinogradova IB, et al. Switching from interleukin-6 receptor inhibitors to the direct interleukin-6 inhibitor olokizumab in patients with rheumatoid arthritis: efficacy and safety during one year of therapy. *Sovremennaya revmatologiya = Modern Rheumatology Journal*. 2024;18(5):54-64. (In Russ.)]. doi: 10.14412/1996-7012-2024-5-54-64
19. England BR, Sayles H, Mikuls TR, et al. Validation of the rheumatic disease comorbidity index. *Arthritis Care Res (Hoboken)*. 2015 May;67(6):865-72. doi: 10.1002/acr.22456.
20. Насонов ЕЛ, Каратеев ДЕ, Сатыбалдыев АМ и др. Ревматоидный артрит в Российской Федерации по данным Российского регистра больных артритом (сообщение I). Научно-практическая ревматология. 2016;54:50-62.
[Nasonov EL, Karateev DE, Satybaldyev AM, et al. Rheumatoid arthritis in the Russian Federation according to the Russian Register of Patients with Arthritis (Message I). *Nauchno-prakticheskaya revmatologiya*. 2016;54:50-62. (In Russ.)].
21. Nasonov E, Fatenejad S, Feist E, et al. Olokizumab, a monoclonal antibody against interleukin 6, in combination with methotrexate in patients with rheumatoid arthritis inadequately controlled by methotrexate: efficacy and safety results of a randomised controlled phase III study. *Ann Rheum Dis.* 2022 Apr;81(4):469-479. doi: 10.1136/annrheumdis-2021-219876. Epub 2021 Aug 3.
22. Smolen JS, Feist E, Fatenejad S, et al. Olokizumab versus Placebo or Adalimumab in Rheumatoid Arthritis. *N Engl J Med.* 2022 Aug 25;387(8):715-726. doi: 10.1056/NEJMoa2201302.
23. Feist E, Fatenejad S, Grishin S, et al. Olokizumab, a monoclonal antibody against interleukin-6, in combination with methotrexate in patients with rheumatoid arthritis inadequately controlled by tumour necrosis factor inhibitor therapy: efficacy and safety results of a randomised controlled phase III study. *Ann Rheum Dis.* 2022 Dec;81(12):1661-1668. doi: 10.1136/ard-2022-222630. Epub 2022 Sep 15.
24. Feist E, Fleischmann RM, Fatenejad S, et al. Olokizumab plus methotrexate: safety and efficacy over 106 weeks of treatment. *Ann Rheum Dis.* 2024 Oct 21;83(11):1454-1464. doi: 10.1136/ard-2023-225473.
25. Ho Lee Y, Gyu Song G. Comparison of the efficacy and safety of tocilizumab, sarilumab, and olokizumab in patients with active rheumatoid arthritis: a network meta-analysis of randomized controlled trials. *Z Rheumatol.* 2024 Feb;83(Suppl 1):97-106. doi: 10.1007/s00393-022-01315-0. Epub 2023 Jan 6.
26. https://acrabstracts.org/abstract/the-impact-of-comorbidities-on-the-efficacy-of-il-6-inhibitor-olokizumab-compared-to-adalimumab/
27. Favalli EG. Understanding the Role of Interleukin-6 (IL-6) in the Joint and Beyond: A Comprehensive Review of IL-6 Inhibition for the Management of Rheumatoid Arthritis. *Rheumatol Ther.* 2020 Sep;7(3):473-516. doi: 10.1007/s40744-020-00219-2. Epub 2020 Jul 30.
28. Zeb S, Khan Z, Ashraf, et al. Relationship Between Serum Interleukin-6 Levels, Systemic Immune-Inflammation Index, and Other Biomarkers Across Different Rheumatoid Arthritis Severity Levels. *Cureus*. 2024 Oct 24;16(10):e72334. doi: 10.7759/cureus.72334. eCollection 2024 Oct.
29. Berardicurti O, Ruscitti P, Pavlych V, et al. Glucocorticoids in rheumatoid arthritis: the silent companion in the therapeutic strategy. *Expert Rev Clin Pharmacol*. 2020 Jun;13(6):593-604. doi: 10.1080/17512433.2020.1772055. Epub 2020 Jun 8.
30. Lauper K, Mongin D, Bergstra SA, et al. Oral glucocorticoid use in patients with rheumatoid arthritis initiating TNF-inhibitors, tocilizumab or abatacept: Results from the international TOCERRA and PANABA observational collaborative studies. *Joint Bone Spine*. 2024 Mar;91(2):105671. doi: 10.1016/j.jbspin.2023.105671. Epub 2023 Nov 30.
31. Wallace BI, England BR, Baker JF, et al. Lowering Expectations: Glucocorticoid Tapering Among Veterans With Rheumatoid Arthritis Achieving Low Disease Activity on Stable Biologic Therapy. *ACR Open Rheumatol.* 2023 Sep;5(9):437-442. doi: 10.1002/acr2.11584. Epub 2023 Jul 25.
32. Karateev AE, Polishchuk EY, Filatova ES, et al. Olokizumab effect on chronic pain in rheumatoid arthritis: Results of the PROLOGUE observational study. *Int J Rheum Dis.* 2024 Oct;27(10):e15320. doi: 10.1111/1756-185X.15320.
33. Потапова АС, Каратеев АЕ, Полищук ЕЮ и др. Снижение потребности в

глюкокортикоидах на фоне терапии генно-инженерными биологическими препаратами и ингибиторами янус-киназ при ревматоидном артрите: данные реальной клинической практики. Терапевтический архив. 2024;96(5):465-470.
[Potapova AS, Karateev AE, Polishchuk EYu, et al. Reduction of the need for glucocorticoids against the background of therapy with genetically engineered biological drugs and janus kinase inhibitors in rheumatoid arthritis: evidence from real clinical practice. *Terapevticheskii arkhiv.* 2024;96(5):465-470. (In Russ.)].
34. Beuschlein F, Else T, Bancos I, et al. European Society of Endocrinology and Endocrine Society Joint Clinical Guideline: Diagnosis and Therapy of Glucocorticoid-induced Adrenal Insufficiency. *J Clin Endocrinol Metab*. 2024 Jun 17;109(7):1657-1683. doi: 10.1210/clinem/dgae250.

Received/Reviewed/Accepted
11.02.2025/23.03.2025/27.03.2025

Conflict of Interest Statement

Data collection and statistical processing were carried out with the sponsorship of R-Pharm, JSC. The conflict of interest has not affected the results of the investigation.

The authors are solely responsible for submitting the final version of the manuscript for publication. All the authors have participated in data collection, developing the concept of the article and in writing the manuscript. The final version of the manuscript has been approved by all the authors.

Shesternya P.A. https://orcid.org/0000-0001-8652-1410
Zagrebneva A.I. https://orcid.org/0000-0002-3235-1425
Antipova O.V. https://orcid.org/0000-0002-6133-4034
Arbuzova Yu.V. https://orcid.org/0000-0002-6952-9100
Bannikova I.G. https://orcid.org/0009-0002-3753-3460
Belozertseva L.V. https://orcid.org/0000-0002-0932-0284
Bogdanova E.A. https://orcid.org/0000-0003-3330-2761
Bykova S.A. https://orcid.org/0009-0008-8338-8202
Vasilenko E.A. https://orcid.org/0000-0003-2153-5429
Vinogradova I.B. https://orcid.org/0000-0001-5052-912X
Davidyan S.Yu. https://orcid.org/0000-0002-3403-8731
Epifanova O.E. https://orcid.org/0009-0009-3659-2646
Zemerova E.V. https://orcid.org/0009-0000-5076-8120
Zlobin M.V. https://orcid.org/0000-0002-8200-3293
Ivanova L.V. https://orcid.org/0000-0003-0411-6118
Ilyina N.A. https://orcid.org/0000-0002-8633-0662
Ilyushina L.V. https://orcid.org/0009-0000-4380-1834
Klyuchnikova E.P. https://orcid.org/0009-0009-0843-5520
Makevnina A.V. https://orcid.org/0009-0008-5383-2536
Myasoutova E.R. https://orcid.org/0000-0003-4654-4153
Nakonechnaya E.E. https://orcid.org/0009-0002-7822-1009
Pavlova A.B. https://orcid.org/0009-0009-7158-3796
Plaksina T.V. https://orcid.org/0000-0002-6927-1752
Rybin A.V. https://orcid.org/0009-0001-0968-2269
Salnikova T.S. https://orcid.org/0000-0001-5206-5357
Solodovnikova L.V. https://orcid.org/0009-0008-6808-9079
Fedorova A.V. https://orcid.org/0009-0004-3285-0568
Cherencova I.A. https://orcid.org/0007-0009-8936-6111
Jakovleva E.V. https://orcid.org/0000-0003-3428-6425
Yakupova S.P. https://orcid.org/0000-0002-8590-4839
Alekseev E.N. https://orcid.org/0009-0003-4252-5008
Lila A.M. https://orcid.org/0000-0002-6068-3080