ORIGINAL INVESTIGATIONS

Results of a 24-week open-label, non-interventional study on the efficacy and safety of olokizumab therapy in patients with rheumatoid arthritis after switching from anti-B-cell therapy during the SARS-CoV-2 pandemic

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In the context of the new coronavirus infection (NCI) COVID-19 pandemic, the rheumatological community is facing new challenges in the treatment of immune-inflammatory rheumatic diseases (IIRDs). It has been shown that rheumatological patients have an increased risk of infections and a severe course of NCI and that IIRD therapy also influences the disease outcomes. In particular, the use of the anti-B-cell medication rituximab (RTM) is associated with a higher risk of severe NCI and increased mortality. The COVID-19 pandemic has highlighted the need to find alternative and safe treatment options for these patients. This work is the continuation of a 12-week study on the efficacy and safety of olokizumab (OKZ) therapy in patients with rheumatoid arthritis (RA) after switching from anti-B-cell therapy during the SARS-CoV-2 pandemic.

Objective: *to evaluate the efficacy and safety of OKZ (Artlegia®; solution for subcutaneous administration, 160 mg/ml – 0.4 ml) for the treatment of patients with RA in real-life clinical practice after switching from RTM during the COVID-19 pandemic.*

Material and methods. *The study included 19 patients with a confirmed diagnosis of RA who had received RTM at a dose of 500–1000 mg twice every 14 days at least 6 months ago. As disease activity increased, RTM was replaced with OKZ while therapy with synthetic disease-modifying anti-rheumatic drugs (DMARDs) was continued. At weeks 0, 4, 8, 12 and 24 after switching the biologic DMARD, the number of tender (TJN) and swollen (SJN) joints out of 28, pain intensity on a visual analogue scale, ESR, CRP level, disease activity indices CDAI, DAS28-ESR, DAS28-CRP, HAQ index and the safety profile of the therapy were assessed at each visit.*

Results and discussion. *After 4, 8, 12 and 24 weeks of OKZ administration, there was a statistically significant decrease in mean TJN (from 10 to 6.0, 3.0, 5.0 and 4.0, respectively; $p<0.05$) and SJN (from 7.0 to 3.0 by week 4 and to 2.0 by weeks 8, 12 and 24; $p<0.05$). At the same time, a decrease in CRP and ESR values was also observed: median CRP decreased from 18 to 0.6 mg/l by week 4 and to 0.5 mg/l by weeks 8, 12 and 24 ($p<0.05$), ESR from 30 to 5 mm/h in each study period ($p<0.05$). CRP levels normalized by week 4, regardless of baseline values.*

All RA activity indices showed a positive dynamic compared to baseline values from week 4 onwards in each assessment period. After weeks 4, 8, 12 and 24, the median DAS28-ESR decreased from 5.50 to 3.57; 3.30; 3.08 and 3.01 ($p<0.05$); DAS28-CRP – from 5.30 to 3.46; 3.23; 3.26 and 3.12 ($p<0.05$); CDAI – from 27.0 to 17.0; 12.0; 15.0 and 12.0 ($p<0.05$), respectively. All patients showed a decrease in pain by the 4th week of observation. A statistically significant improvement in functional status was observed after the 4th week of therapy and was maintained until week 24. The median HAQ index decreased from 1.62 to 1.50 at weeks 4, 8 and 12 and to 1.12 at week 24 ($p<0.05$).

Conclusion. *The study showed that the non-medical switch from RTM to OKZ during the COVID-19 pandemic was effective and safe.*

Keywords: *rheumatoid arthritis; COVID-19; olokizumab; rituximab.*

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In a setting of the new coronavirus infection (COVID-19) pandemic, the rheumatological community has faced new challenges related to the management of autoimmune inflammatory rheumatic disease (AIIRDs). Rheumatological patients have shown to have an increased risk of developing COVID-19 and subsequent hospitalization, compared to the overall population, and are at higher risk of adverse outcomes, associated with high disease activity, comorbidities and specific treatments, e.g. steroids and rituximab (RIX) [1-3]. Analysis of COVID-19 clinical outcomes in a cohort of patients treated with biologic DMARDs in Novosibirsk region demonstrated that 47.5% of them received RIX and the risk of severe to very severe COVID-19 course, with pneumonia, was statistically significantly higher; all deaths occurred only in patients exposed to RIX [4]. In most rheumatological patients treated with immunosuppressive agents vaccination against SARS-CoV-2, i.e. the pathogen causing COVID-19, provides benefits, but B-cell-depleting therapies reduce efficacy of immune response, therefore, limiting the use of RIX in a COVID-19 pandemic setting [5].

One of the manifestations of immune response to COVID-19 is the elevation of tumor necrosis factor alpha (TNFα), interleukin (IL) 1β (for 1-2 days) and IL-6 (for longer periods) [6, 7]. Some biologic DMARDS (bDMARDs) and targeted synthetic DMARDS (tsDMARDS) used in AIIRDs do not increase the risk of adverse outcomes in COVID-19, but furthermore, are even specifically administered in a severe course of such infection, complicated by cytokine storm [8]. In such cases bDMARDs belonging to the fol-

lowing classes are recommended: IL-6 receptor inhibitors (IL6Ri), IL-6 inhibitors (IL6i), IL-1α/IL-1β receptor inhibitors; additionally, Janus kinase inhibitors (JAKi) are recommended [7-9].

Agents belonging to the IL6i class are of particular interest within such context. Some studies have demonstrated significant elevation of IL-6 levels in patients with severe COVID-19, which, in association with CRP hyperproduction, provides relatively high specificity and sensitivity in predicting respiratory failure, including cases requiring respiratory support [10]. Furthermore, IL-6 may stimulate secretion of various acute phase proteins, contributing to the activation of immune cells and damaging target organs during cytokine storm [10]. Therefore, patients treated with IL6i for AIIRDs were advised to chemotherapy such therapy during the COVID-19 pandemic.

Currently in the Russian Federation olokizumab (OKZ, Artlegia®, R-Pharm, Russia) is used as an IL-6 inhibitor in clinical practice; it is a humanized (containing a hypervariable fragment attached) monoclonal antibody of IgG4κ isotype, selectively binding to human IL-6 and effectively neutralizing its activity both in vivo and in vitro. OKZ efficacy and safety were established within the international clinical development program CREDO that consisted of three 24-week clinical trials and one follow-up extension of up to 126 weeks, enrolling 2444 patients from 19 countries, with moderate to severe rheumatoid arthritis (RA) and lack of efficacy or intolerance to DMARDs (including biologic). Patients previously exposed to RIX could enroll, provided it had been discontinued no less than 24 weeks before baseline.

Taking into account the high risk of severe course and adverse outcomes of COVID-19 in patients with AIIRDs, particularly treated with RIX, a B-cell-depleting bDMARD, alternative treatment options had to be considered in a setting of the COVID-19 pandemic.

Previously results of a 12-week study investigating the safety of 12-week OKZ treatment in RA patients were published, demonstrating that switching from RIX to OKZ was a safe and effective strategy in a setting of the COVID-19 pandemic [11]. Extended follow-up for such patients is important to assess response maintenance, record delayed-onset adverse events (AEs) and taking into account new emerging SARS-CoV-2 variants characterized by modified COVID-19 clinical course [7, 11].

The objective of the study was to evaluate OKZ efficacy and safety in the treatment of RA patients in real-world clinical practice, after switching from RIX for non-medical reasons in a setting of the COVID-19 pandemic.

Materials and methods. The study was conducted at rheumatology departments of the following clinics: Institute of Clinical and Experimental Lymphology – branch of the Institute of Cytology and Genetics of the Siberian Branch of the Russian Academy of Sciences, Novosibirsk; and Research Institute of Fundamental and Clinical Immunology, Novosibirsk. The study protocol was approved by the local Ethics Committee of the Institute of Clinical and Experimental Lymphology – branch of the Institute of Cytology and Genetics of the Siberian Branch of the Russian Academy of Sciences, as of 22.11.2021.

The study enrolled male and female patients aged 18 years or above diagnosed with RA, meeting ACR/EULAR American College of Rheumatology / European Alliance of Associations for Rheumatology) criteria 2010 and previously exposed to at least 1 treatment cycle of RIX, discontinued for administrative reasons. OKZ (Artlegia®) for solution for subcutaneous administration 160 mg/mL – 0.4 mL – was prescribed according to the national clinical recommendations on RA treatment and the manufacturer's label. No less than 6 months had elapsed between the last RIX infusion before the initiation of OKZ treatment. Switching from RIX to OKZ did not affect the nature or scope of background antirheumatic treatment. Patients continued treatment with previously prescribed DMARDs, steroids in stable doses of <15 mg/day and non-steroidal anti-inflammatory drugs (NSAIDs) pro re nata. The total duration of the study was 24 weeks, including visits for OKZ administration and follow-up visits. Prior to eligibility assessment for tissues trial all patients had undergone screening for latent tuberculosis, viral hepatitis infections and HIV.

The study included 19 patients with RA aged 26 to 74 years; median age was 60 years, median disease duration was 15 years.

Characteristics of patients (n=19), Me [25th; 75th percentile]

Parameter	Value
Age, years	60,0 [53,0; 67,0]
Age at disease onset, years	42,0 [32,0; 59,0]
Disease duration, years	15,0 [7,5; 20,5]
TJC (of 28)	10,0 [7,0; 16,0]
SJC (of 28)	8,0 [4,0; 10,0]
Pain assessed by the patient, VAS mm	50,0 [45,0; 60,0]
Disease activity assessed by the patient, VAS mm	50,0 [50,0; 60,0]
Disease activity assessed by the doctor, VAS mm	50 [45,0; 50,0]
CDAI	27 [20,0; 35,5]
DAS28-СОЭ	5,5 [5,05; 6,34]
DAS28-СРБ	5,32 [4,575; 5,975]
ESR, Westergren method, mm/h	30 [17,0; 54,5]
CRP, mg/L	18 [10,0; 38,89]
HAQ	1,625 [1,375; 1,94]
RF, U/mL	139,0 [29,0; 342,5]
ACCP, U/mL	98,0 [23,9; 300,0]
Number of RIX cycles before OKZ initiation	5,0 [2,5; 6,0]
Time between the last RIX administration and switching to OKZ, months	15,0 [14,0; 24,0]

Note. RF – rheumatoid factor; ACCP – antibody to cyclic citrullinated peptide.

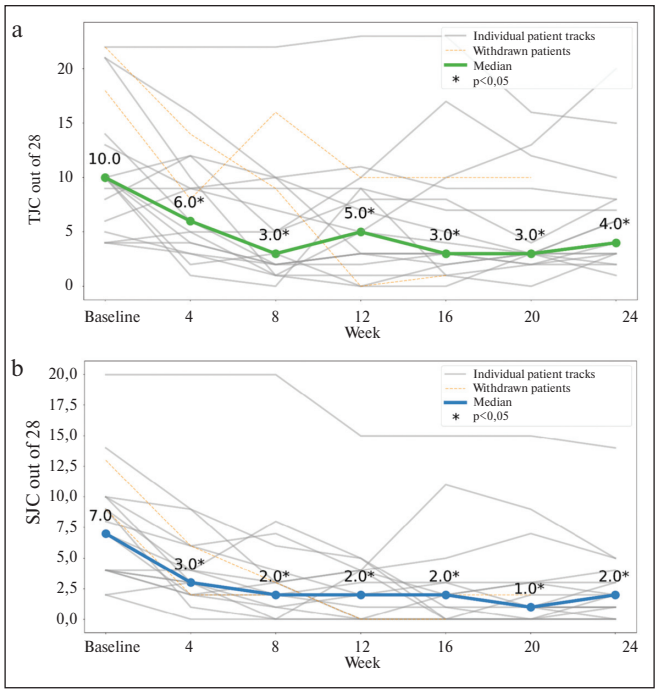

Fig. 1. *Dynamics of joint ccount test: a – TJN out of 28; b – SJN out of 28*

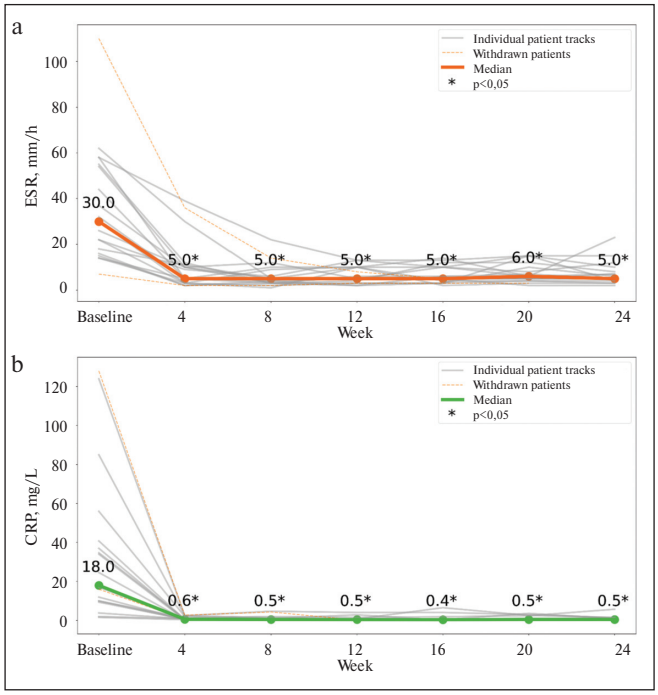

Fig. 2. *Dynamics of laboratory markers of inflammation: a – ESR according to Westergren; b – CRP*

Baseline median of DAS28-ESR was 5.5, DAS28-CRP was 5.32. Median number of RIX cycles before OKZ administration was 5, median time between the last RIX administration and switching to OKZ – 15 months (see Table).

At weeks 0, 4, 8, 12 and 24 after OKZ treatment initiation 28-joint tender (TJC) and swollen (SJC) joint counts, pain intensity using visual analogue scale (VAS), ESR using Westergren method, CRP, and HAQ (Health Assessment Questionnaire) were assessed. DAS28-ESR, DAS28-CRP and CDAI (Clinical Disease Activity Index) were used to measure treatment efficacy. Treatment safety was assessed based on AE frequency and severity.

Statistical analysis of data was performed on a personal computer using NumPy, Pandas, SciPy, Matplotlib and Seaborn libraries for Python. Data are presented as medians with interquartile ranges (medians [25th; 75th percentiles]. Pairwise measurements were compared using Wilcoxon non-parametric rank test.

Results. All patients after 4, 8, 12 and 24 x of OKZ administration demonstrated statistically significant reduction in median TJC (from 10.0 to 6.0, 3.0, 5.0 and 4.0 respectively; $p<0.05$; see Figure 1, a). Statistically significant improvement of SJC was also observed as early as after 4 weeks of treatment and maintained in 8, 12 and 24 weeks ($p<0.05$; see Figure 1, б).

Changes in laboratory inflammatory markers over time demonstrated a statistically significant reduction of CRP and ESR as early as at treatment Week 4. Improvement maintained at Weeks 8, 12 and 24. Median CRP concentration decreased from 18 to 0,6 mg/L by Week 4 and to 0.5 mg/L by Weeks 8, 12 and 24 ($p<0.05$), median ESR – from 30 to 5 mm/h (in all cases $p<0,05$; see Figures 2, a, b). Regardless of baseline values, CRP levels became normal.

Disease activity indices demonstrated improvements from baseline at weeks 4, 8, 12 and 24. Median DAS28-ESR reduced from 5.50 до 3.57; 3.30; 3.08 and 3.01 ($p<0,05$); DAS28-CRP – from 5.30 to 3.46; 3.23; 3.26 and 3.12 ($p<0,05$); CDAI – from 27.0 to 17.0; 12.0; 15.0 and 12.0 respectively ($p<0.05$; see Figure 3, a–b).

Clinically significant improvement of patients' performance status was observed as early as at treatment Week 4 and maintained at Weeks 8, 12 and 24 (see Figure 4). Median HAQ reduced from 1.62 to 1.50 at Weeks 4, 8 and 12, and to 1.12 by Week 24 ($p<0,05$).

In 4 weeks after treatment initiation all patients reported improvement in pain, maintained at Week 24 (see Figure 5). Median pain intensity as measured by VAS reduced from 50 to 40 mm at Week 4 and to 20 mm at Week 24 ($p<0,05$).

Safety: no AEs were reported during 6-month treatment with OKZ according to the approved label. No COVID-19 cases were reported during observation. Therefore, OKZ treatment was found to be safe and effective in a setting of the COVID-19 pandemic.

Discussion. The COVID-19 pandemic has demonstrated the need to adjust AIIRD management, taking into account the contribution of certain DMARDs, including biologic agents, to the adverse clinical course and outcomes of COVID-19 in rheumatological patients. According to the recommendations issued by the Russian Rheumatology Association on management of AIIRD patient during the COVID-19 pandemic, as well as EULAR guidelines, treatment with NSAIDs, DMARDs, immunosuppressive and biologic agents must be continued, except RIX [12, 13]. Advanced age, comorbidities, steroid use, mycophenolate mofetil and RIX administration are risk factors associated with severe COVID-19 course [14]. B-cell depletion on RIX treatment is associated with increased susceptibility to COVID-19, its severe course and higher mortality [15]. Unless there are vital indications to continue RIX, the need to use this agent must be reconsidered, choosing an alternative option [12, 13]. Therefore, during the COVID-19 pandemic it is important to switch patients on RIX according to their previous treatment plan to other bDMARDs with more robust safety profile.

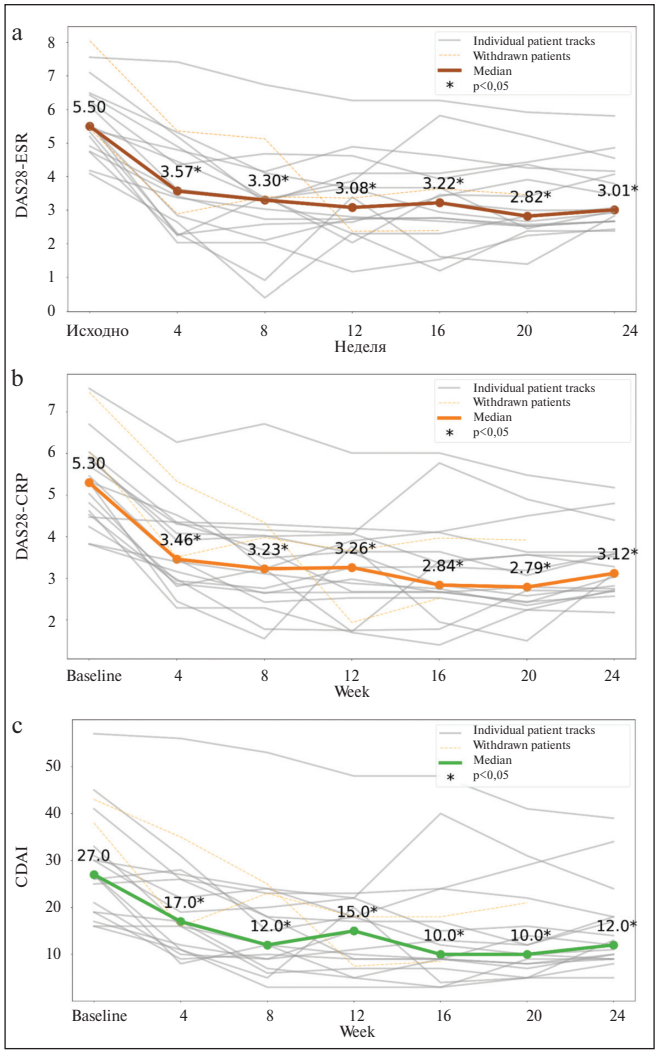

Fig. 3. *Dynamics of activity indices: a – DAS28-ESR; b – DAS28-CRP; c – CDAI*

Currently there is lack of literature evidence about switching RA patients from RIX to OKZ. The study closes in its design to ours was done by A.A. Baranov et al. [6], analyzing safety and efficacy of switching from RIX to tocilizumab (an IL6Ri) in patients with juvenile idiopathic arthritis. Results of that study demonstrated arthritis remission achieved in 64% cases after 6 months of treatment, remission of systemic manifestations in 80% after 12 months of treatment, with compatible rate of infectious AEs. Therefore, studies of similar design demonstrate efficacy of anti-IL6R monoclonal antibodies when switching from RIX, not increasing the risk of infectious AEs.

When selecting a bDMARD to switch to from RIX in a setting of the COVID-19 pandemic one should consider potential treatment efficacy, as well as safety profile, particularly focusing on viral and bacterial infections. According to J.A. Sparks et al. [17], during the COVID-19 pandemic treatment with RIX or JAKi was associated with a more severe course of COVID-19, whereas no such relationship was described for IL6Ri agents. According to the analysis done by B. MacKenna et al. [18], RIX treatment was also found to be associated with a higher risk of COVID-19 mortality, whereas bDMARD belonging to other classes, including IL6Ri demonstrated favorable safety profile and

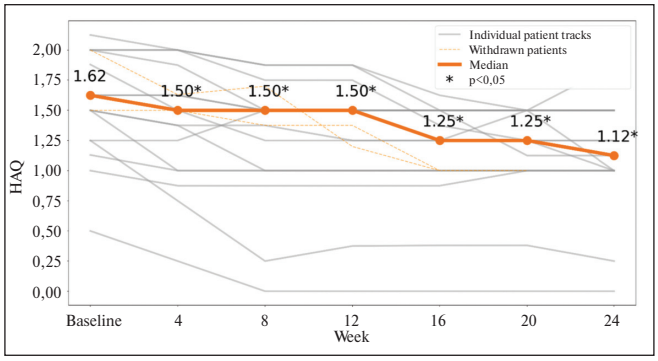

Fig. 4. *Dynamics of the HAQ index*

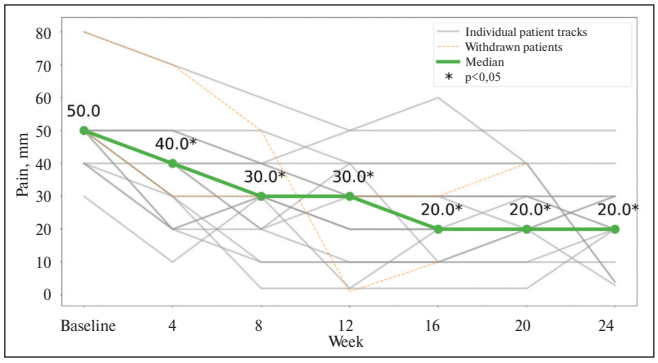

Fig. 5. *Dynamics of pain intensity according to VAS*

could be used to treat COVID-19 complications. The WHO report based on pharmacovigilance data established an inverse relationship between IL6Ri treatment and COVID-19 severity, confirming robust safety of such agents in AIIRD [19].

Safety and efficacy of IL6i agents in a setting of the COVID-19 pandemic have also been demonstrated. T.V. Goma et al. [20], analyzing experience with OKZ in patients with COVID-19, noted its favorable influence on clinical and laboratory parameters of inflammation in severe patients with strong inflammatory response and impaired respiratory function. According to V.N. Antonov et al, [21], in 600 patients with COVID-19 OKZ treatment was associated with improvement of clinical and laboratory parameters. As reflected in the provisional guidelines on preventing, diagnosing and treating COVID-19 issued by the Ministry of Health of the Russian Federation, OKZ was approved to treat patients with moderate, severe and critical course of COVID-19, which was considered a decisive benefit delivered by this bDMARD in a pandemic setting, particularly in patients at high risk of infectious complications [22]. The choice of a direct IL6i to be switched to was significantly influenced by reports suggesting that IL6R blockade may be associated with elevation of plasma levels of the free cytokine. Such effect reduced the remission rate in patients with RA [23], was associated with a risk of subclinical inflammation and early exacerbations in giant-cell arteritis [24] and caused worse outcomes of COVID-19 [25]. Therefore, both literature evidence and results obtained in this study suggest that OKZ, a direct IL6i, is the preferred agent of choice for RA patients switched from RIX.

Another important observation made in our study is rapid normalization of CRP level, regardless of baseline values. E.g. as early as by Week 4 OKZ treatment median CRP concentrations decreased from 18.0 to 0.6 mg/L. High CRP in RA is a marker of

systemic inflammation and radiological progression, associated with high cardiovascular risk, certainly contributing to higher mortality risk [26, 27]. This suggests that assessment of CRP changes over time in RA is important to prevent devastating cardiovascular outcomes, among other considerations.

Results of this study are consistent with other publications, both Russian and international: OKZ, an anti-IL-6 monoclonal antibody, has demonstrated its safety and efficacy in patients switched from RIX in a setting of the COVID-19 pandemic. No increase in the risk of COVID-19 development, serious infectious AEs or deaths was observed in this study. All study subjects demonstrated rapid improvement in laboratory markers of inflammation and disease activity indices.

Conclusion. This study has demonstrated efficacy and safety of switching from RIX to OKZ in a setting of the COVID-19 pandemic.

REFERENCES

1. Ahmed S, Gasparyan AY, Zimba O. Comorbidities in rheumatic diseases need special consideration during the COVID-19 pandemic. *Rheumatol Int*. 2021 Feb;41(2):243-256. doi: 10.1007/s00296-020-04764-5.
2. Bournia VK, Fragoulis GE, Mitrou P, et al. Different COVID-19 outcomes among systemic rheumatic diseases: a nation-wide cohort study. *Rheumatology (Oxford)*. 2023 Mar 1;62(3): 1047-1056. doi: 10.1093/rheumatology/keac422
3. Conway R, Grimshaw AA, Konig MF, et al. COVID-19 Global Rheumatology Alliance. SARS-CoV-2 Infection and COVID-19 Outcomes in Rheumatic Diseases: A Systematic Literature Review and Meta-Analysis. *Arthritis Rheum*. 2022 May;74(5):766-775. doi: 10.1002/art.42030.
4. Королев МА, Летягина ЕА, Сизиков АЭ и др. Иммуновоспалительные ревматические заболевания и COVID-19: анализ клинических исходов по данным регистра пациентов Новосибирской области, получающих терапию генно-инженерными биологическими препаратами. Терапевтический архив. 2022;94(5):636-641.
[Korolev MA, Letyagina EA, Sizikov AE, et al. Immuno-inflammatory rheumatic diseases and COVID-19: Analysis of clinical outcomes according to the data of the register of patients of the Novosibirsk region receiving therapy with genetically engineered biological drugs. *Terapevticheskii arkhiv*. 2022;94(5):636-641 (In Russ.)].
5. Grainger R, Kim AHJ, Conway R, et al. COVID-19 in people with rheumatic diseases: risks, outcomes, treatment considerations. *Nat Rev Rheumatol*. 2022 Apr;18(4):191-204. doi: 10.1038/s41584-022-00755-x
6. Ladani AP, Loganathan M, Danve A. Managing rheumatic diseases during COVID-19. *Clin Rheumatol*. 2020 Nov;39(11):3245-3254. doi: 10.1007/s10067-020-05387-8.
7. Авдеев СН, Адамян ЛВ, Алексеева УИ и др. Временные методические рекомендации. Профилактика, диагностика и лечение новой коронавирусной инфекции (COVID-19). 2023.
[Avdeev SN, Adamyan LV, Alekseeva EI, Bagnenko SF, Baranov AA, et al. Interim Guidelines: Prevention, diagnosis and treatment of novel coronavirus infection (COVID-19). 2023]. https://normativ.kontur.ru/document?moduleId=1&documentId=458540
8. Gianfrancesco MA, Hyrich KL, Gossec L, et al. COVID-19 Global Rheumatology Alliance Steering Committee. Rheumatic disease and COVID-19: initial data from the COVID-19 Global Rheumatology Alliance provider registries. *Lancet Rheumatol*. 2020 May;2(5): e250-e253. doi: 10.1016/S2665-9913(20)30095-3
9. Mikuls TR, Johnson SR, Fraenkel L, et al. American College of Rheumatology Guidance for the Management of Rheumatic Disease in Adult Patients During the COVID-19 Pandemic: Version 2. *Arthritis Rheum*. 2020 Sep;72(9):e1-e12. doi: 10.1002/art.41437.
10. Yang L, Xie X, Tu Z, et al. Correction: The signal pathways and treatment of cytokine storm in COVID-19. *Signal Transduct Target Ther*. 2021 Aug 31;6(1):326. doi: 10.1038/s41392-021-00744-8.
11. Акимова АА, Банщикова НЕ, Сизиков АЭ и др. Результаты 12-недельного открытого неинтервенционного исследования эффективности и безопасности терапии препаратом олокизумаб у пациентов с ревматоидным артритом после переключения с анти-В-клеточной терапии в условиях пандемии SARS-CoV-2. Научно-практическая ревматология. 2023;61(1):25-33.
[Akimova AA, Banshchikova NE, Sizikov AE, et al. Results of a 12-week open-label, noninterventional study of the efficacy and safety of olokizumab therapy in patients with rheumatoid arthritis after switching from anti-B-cell therapy during the SARS-CoV-2 pandemic (review). *Nauchno-Prakticheskaya Revmatologia*. 2023;61(1):25-33. (In Russ.)].
12. Куликов АН, Муравьева НВ, Белов БС. Факторы риска тяжелого течения COVID-19 у больных ревматическими заболеваниями. Научно-практическая ревматология. 2024;62(1):24-31.
[Kulikov AN, Muravyeva NV, Belov BS. Risk factors for severe COVID-19 in patients with rheumatic diseases. *Nauchno-Prakticheskaya Revmatologia*. 2024;62(1):24-31. (In Russ.)].
13. Насонов ЕЛ. Пандемия коронавирусной болезни 2019 (COVID-19) и аутоиммунные ревматические заболевания: итоги и перспективы. Научно-практическая ревматология. 2024;62(1):32-54.
[Nasonov EL. Coronavirus disease 2019 (COVID-19) pandemic and autoimmune rheumatic diseases: Outcomes and prospects. *Nauchno-Prakticheskaya Revmatologia*. 2024; 62(1):32-54. (In Russ.)].
14. Landewe RBM, Kroon FPB, Alunno A, et al. EULAR recommendations for the management and vaccination of people with rheumatic and musculoskeletal diseases in the context of SARS-CoV-2: the November 2021 update. *Ann Rheum Dis*. 2022 Dec;81(12): 1628-1639. doi: 10.1136/annrheumdis-2021-222006. Epub 2022 Feb 23.
15. Насонов ЕЛ, Лила АМ, Мазуров ВИ и др. Коронавирусная болезнь 2019 (COVID-19) и иммуновоспалительные ревматические заболевания. Рекомендации Общероссийской общественной организации «Ассоциация ревматологов России». Научно-практическая ревматология, 2021;59(3):239-254.
[Nasonov EL, Lila AM, Mazurov VI, et al. Coronavirus Disease 2019 (COVID-19) and Immune-mediated Rheumatic Diseases. Recommendations of the Association of Rheumatologists of Russia. *Nauchno-prakticheskaya revmatologiya*. 2021;59(3):239–254. (In Russ.)].
16. Баранов АА, Алексеева ЕИ, Бзарова ТМ, и др. Протокол ведения пациентов с ювенильным артритом. Вопросы современной педиатрии. 2013;12(1):37-56.
[Baranov AA, Alexeeva EI, Bzarova TM, et al. Management protocol for patients with juvenile arthritis. *Voprosy sovremennoi pediatrii*. 2013;12(1):37-56. (In Russ.)].
17. Sparks JA, Wallace ZS, Seet AM, et al. Associations of baseline use of biologic or targeted synthetic DMARDs with COVID-19 severity in rheumatoid arthritis: Results from the COVID-19 Global Rheumatology Alliance physician registry. *Ann Rheum Dis*. 2021 Sep; 80(9):1137-1146. doi: 10.1136/annrheumdis-2021-220418.
18. MacKenna B, Kennedy NA, Mehrkar A, et al. Risk of severe COVID-19 outcomes associated with immune-mediated inflammatory diseases and immune-modifying therapies: a nationwide cohort study in the OpenSAFELY platform. *Lancet Rheumatol*. 2022 Jul;4(7): e490-e506. doi: 10.1016/S2665-9913(22) 00098-4.
19. Dernoncourt A, Schmidt J, Duhaut P, et al. COVID-19 in DMARD-treated patients with inflammatory rheumatic diseases: Insights from an analysis of the World Health Organization pharmacovigilance database. *Fundam Clin Pharmacol*. 2022 Feb;36(1):199-209. doi: 10.1111/fcp.12695.
20. Гома ТВ, Калягин АН, Рыжкова ОВ, Соловьева НС. Эффективность применения препарата олокизумаб у пациентов с COVID-19. Acta biomedica scientifica. 2022; 7(5-2):86-95.
[Goma TV, Kalyagin AN, Ryzhkova OV, Soloveva NS. Efficacy of olocizumab in treatment of COVID-19 patients. *Acta biomedica scientifica*. 2022;7(5-2):86-95. (In Russ.)].
21. Антонов ВН, Игнатова ГЛ, Прибыткова ОВ и др. Опыт применения олокизума-

ба у больных COVID-19. Терапевтический архив. 2020;92(12):148-154.
[Antonov VN, Ignatova GL, Pribytkova OV, et al. Experience of olokizumab use in COVID-19 patients. *Terapevticheskii arkhiv.* 2020;92(12): 148-154. (In Russ.)].
22. Насонов ЕЛ, Лила АМ, Мазуров ВИ и др. Коронавирусная болезнь 2019 (COVID-19) и иммуновоспалительные ревматические заболевания. Рекомендации Общероссийской общественной организации «Ассоциация ревматологов России». Научно-практическая ревматология. 2021;59(3):239-254.
[Nasonov EL, Lila AM, Mazurov VI, et al. Coronavirus disease 2019 (COVID-19) and immune-mediated rheumatic diseases. Recommendations of the Association of Rheumatologists of Russia. *Nauchno-Prakticheskaya Revmatologia*. 2021;59(3):239-254. (In Russ.)].
23. Shimamoto K, Ito T, Ozaki Y, et al. Serum interleukin 6 before and after therapy with tocilizumab is a principal biomarker in patients with rheumatoid arthritis. *J Rheumatol.* 2013 Jul;40(7):1074-81. doi: 10.3899/jrheum.121389.
24. Berger CT, Rebholz-Chaves B, Recher M, et al. Serial IL-6 measurements in patients with tocilizumab-treated large-vessel vasculitis detect infections and may predict early relapses. *Ann Rheum Dis.* 2019 Jul;78(7):1012-1014. doi: 10.1136/annrheumdis-2018-214704.
25. Luo P, Liu Y, Qiu L, et al. Tocilizumab treatment in COVID-19: A single center experience. *J Med Virol.* 2020 Jul;92(7):814-818. doi: 10.1002/jmv.25801. Epub 2020 Apr 15.
26. Pope JE, Choy EH. C-reactive protein and implications in rheumatoid arthritis and associated comorbidities. *Semin Arthritis Rheum*. 2021 Feb;51(1):219-229. doi: 10.1016/j.semarthrit.2020.11.005.
27. Омельченко ВО, Летягина ЕА, Королев МА, Поспелова ТИ. Атеросклеротическое поражение брахиоцефальных артерий при ревматоидном артрите и его ассоциация с факторами сердечно-сосудистого риска. Сибирский журнал клинической и экспериментальной медицины. 2019; 34(1):107-117.
[Omelchenko VO, Letyagina EA, Korolev MA, Pospelova TI. Atherosclerotic lesion of carotid arteries in rheumatoid arthritis and its association with cardiovascular risk factors. *Sibirskii zhurnal klinicheskoi i eksperimental'noi meditsiny.* 2019;34(1):107-117. (In Russ.)].

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