ORIGINAL INVESTIGATIONS

Safety of COVID-19 vaccines in patients with immunoinflammatory rheumatic diseases (preliminary data)

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Objective: *to assess the safety of COVID-19 vaccines in patients with immunoinflammatory rheumatic diseases (IRD) in real clinical practice.*

Patients and methods*. A cross-sectional study of patients with IRD, who were admitted to V.A. Nasonova Research Institute of Rheumatology for inpatient or outpatient treatment. All patients received at least 1 dose of vaccine against COVID-19 (main group). The control group consisted of vaccinated persons without IRD. All participants were interviewed by the researcher by filling out a unified questionnaire, additional information was obtained from medical records.*

Results and discussion. *The study included 204 patients with IRD (151 of them were vaccinated with Sputnik V, 31 with Sputnik Light, 19 with CoviVac, 3 with EpiVacCorona; 173 patients received the second component of vaccine) and 131 subjects without IRD (101 of them were vaccinated with Sputnik V, 17 – CoviVak, 5 – Sputnik Light, 2 – EpiVacCorona, 6 – Pfizer/BioNTech; 124 patients received the second component of the vaccine). The number of patients with IRD who had both local and systemic reactions after administration of the first component of the vaccine was significantly less than in the control group (19.6 and 38.9%, respectively; p<0.001). Similar differences were noted after the administration of the second component (15.6 and 27.4%, respectively; p=0.013). Adverse events (AEs) such as pain at the injection site without restriction of movement, weakness, fever, arthralgia/myalgia and chills were significantly more common in the control group after the administration of the first component of the vaccine. After complete immunization, AEs were absent in 35.8% of patients with IRD and in 21% of controls (p=0.006). Exacerbations of IRD and new autoimmune phenomena were not registered in any case.*

Conclusion. *According to preliminary data, vaccination against COVID-19 in patients with IRD appears to be quite safe. Further studies are needed to investigate the safety, immunogenicity, and clinical efficacy of COVID-19 immunization in rheumatic patients.*

Key words: *immunoinflammatory rheumatic diseases; COVID-19; vaccination; safety; adverse events.*

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In December 2019, the first case of pneumonia caused by a novel coronavirus infection was reported in Wuhan, China. In February 2020, the World Health Organization (WHO) introduced the official term for all cases of this disease – "Coronavirus disease" (COVID-19), and the causative agent of infection, in agreement with the International Committee on the Taxonomy of Viruses, was named SARS-CoV-2 (Severe acute respiratory syndrome Coronavirus-2). The WHO declared the novel coronavirus outbreak a global pandemic because of the rapid spread of SARS-CoV-2 around the world [1]. So far, new cases of the disease have been registered in the world. As of early January 2022, there were more than 290 million confirmed cases worldwide with more than 5.4 million deaths [2].

The disease in most patients with COVID-19 is characterized by a mild or moderately severe course with subsequent recovery. However, in some cases (5–15%) pneumonia can occur, which requires hospitalization and ventilation support; and sometimes acute respiratory distress syndrome, coagulopathy with multiple organ failure may develop. The severe course of this disease, especially in patients requiring mechanical ventilation, results in death in 20–90% of cases [3].

The main risk factors for severe COVID-19 are older age and co-morbidities. Since in patients with immuno-inflammatory rheumatic diseases (IIRD) the incidence of any infections is increased due to the negative impact on the immune system of both the disease itself and immunosuppressive antirheumatic drugs, COVID-19 may be of particular danger to this population [4]. According to two meta-analyses, patients with IIRD have a higher incidence of COVID-19, as well as an increasing risk of hospitalization and death [5, 6].

Vaccination remains one of the most effective methods of preventing infectious diseases, including in patients with IIRD. It is known that vaccination against influenza and pneumococcal infection is safe and effective and indicated for the vast majority of patients with IIRD [7]. It is believed that in the case of COVID-19, immunization should also reduce the risk of infection and severe disease. The evidence to date on the efficacy and safety of COVID-19 vaccines in individuals without IIRD supports this notion. However, it seems incorrect to extrapolate the obtained results of studies to patients with IIRD. At the same time, data on the safety of vaccines against COVID-19 in patients with IIRD are limited, and (with the exception of one study) related to foreign vaccines that are not licensed in Russia. Therefore, we carried out our own study to evaluate the safety of COVID-19 vaccines in patients with IIRD.

Objective. To study the safety of vaccines against COVID-19 in patients with IIRD in real clinical practice.

Patients and methods. The study was conducted from October 12, 2021 to December 20, 2021. The sample was formed by consecutive inclusion of patients who were admitted for inpatient treatment (n=181; 88.7%) or applied to the diagnostic center (n=23; 11.3%) of V.A. Nasonova Research Institute of Rheuma-

tology. After signing the informed consent, all participants were interviewed by a research doctor with the completion of a unified questionnaire; additional information was obtained from medical documentation. The control group consisted of 131 subjects without a history of any rheumatic disease.

Statistical processing of the results was performed using the Statistica 7.0 software package (StatSoft, USA). Differences were considered significant at $p<0.05$.

Results. The study included 204 patients with IIRD: 161 women, 43 men, mean age 50.7±14.6 years, duration of the disease 10.9±9.0 years. In the study sample, 119 patients had rheumatoid arthritis (RA), 25 – ankylosing spondylitis, 15 – Sjugren's syndrome, 13 – psoriatic arthritis, 9 – undifferentiated spondyloarthritis, 8 – systemic lupus erythematosus, 5 – systemic sclerosis, 4 – systemic vasculitis, 3 – metabolic arthropathies, 2 – adult Still's disease, 1 – polymyalgia rheumatica; 137 patients received disease-modifying antirheumatic drugs (DMARD): methotrexate – 64, leflunomide – 29, hydroxychloroquine – 20, sulfasalazine – 17, mofetil mycophenolate – 7. Eighty-six patients were treated with glucocorticoids; 88 patients received biologics or target DMARDs: rituximab – 65, tumor necrosis factor-α inhibitors – 13, abatacept – 4, tocilizumab – 2, interleukin-17A inhibitors – 2, belimumab and tofacitinib – 1. Monotherapy with nonsteroidal anti-inflammatory drugs was given to 17 patients. Eight patients did not receive therapy. The control group included 131 people without any rheumatic diseases (97 women, 34 men, mean age 36.9±14.5 years).

Arterial hypertension and obesity took the lead in the structure of co-morbidity, both in patients with IIRD and in persons without these conditions (Table 1). Nevertheless, both diseases occurred significantly more often in patients with IIRD, which, obviously, can be explained by the younger age of the control group. Persons from the control group were immunized against influenza significantly more often than patients with IIRD, while the frequency of vaccination against pneumococcal infection in both groups was comparable (see Table 1). In general, the coverage of patients with IIRD with vaccination against major vaccine-preventable infections is unsatisfactory, which requires active work with patients in this direction. It is also interesting that adverse events (AEs) after vaccination in the past were significantly more common in the control group.

One hundred fifty-one patients with IIRD were immunized with combined vector vaccine Gam-COVID-Vac (Sputnik V), 31 – single-dose vector-based vaccine Sputnik Light, 19 – inactivated whole virion vaccine CoviVac, 3 – antigen-based vaccine EpiVacCorona; 173 patients received the second dose of the vaccine (except those who were vaccinated with Sputnik Light). One hundred and one subjects from the control group were immunized with Gam-COVID-Vac, 17 – CoviVac, 5 – Sputnik Light, 2 – EpiVacCorona, 6 – mRNA vaccine BNT162b2 (Pfizer BioNTech); 124 of them received the second dose of the vaccine.

In general, local and systemic post-vaccination AEs were diagnosed both in patients with IIRD and in the control group (Table 2).

After the administration of the first component of the vaccine, only local AEs were observed in 22 (10.8%) patients with IIRD and in 11 (8.4%) patients in the control group, while systemic AEs were observed in 48 (23.5%) and 29 (22.1%), respectively. These differences were not statistically significant. However, the number of patients with IIRD who had both local and systemic reactions after the administration of the first component of the vaccine was significantly lower than in the control group (19.6% and 38.9%, respectively; $p<0.001$). In the control group, pain at the injection site without restriction of movements, weakness, fever, chills, myalgia/arthralgia were significantly more common. Any AEs after the introduction of the first component of the vaccines in patients with IIRD were absent significantly more often than in the control group (46.1% and 30.5%, respectively; $p=0.005$). In a 44-year-old patient with RA, after the introduction of Sputnik Light, a serious adverse reaction was documented – Quincke's edema, which later

Table 1. Co-morbidity and history of previous vaccinations in patients with IIRD and control group.

	Patients with IIRD (n=204)		Control group (n=131)		
	n	%	n	%	p
Co-morbidity:					
Arterial hypertension	80	39.2	17	13.0	<0.001
Obesity	39	19.1	10	7.6	0.004
Ischemic heart disease	16	7.8	1	0.8	
Diabetes mellitus	13	6.4	4	3.1	
Chronic heart failure	5	2.5	1	0.8	
Pulmonary tuberculosis	4	2.0	0	0	
Cerebrovascular accident	4	2.0	0	0	
Atrial fibrillation	3	1.5	1	0.8	
Chronic kidney disease	3	1.5	1	0.8	
Bronchial asthma	3	1.5	0	0	
Myocardial infarction	2	1.0	0	0	
Primary biliary cholangitis	2	1.0	0	0	
Chronic hepatitis B	2	1.0	0	0	
Another disease	10	4.9	0	0	
Vaccination in previous 3 years:					
Influenza vaccines	41	20.1	69	52.7	<0.001
Pneumococcal vaccines	25	12.3	12	9.2	>0.05
AE after vaccination	10	4.9	23	17.6	<0.001

Table 2. Adverse events (AEs) after the administration of the first and second components of COVID-19 vaccines

AE	First component					Second component				
	Patients with IIRD (n=204)		Control group (n=131)			Patients with IIRD (n=173)		Control group (n=124)		
	n	%	n	%	p	n	%	n	%	p
Local AE										
Pain at the injection site: without restriction of limb movements	40	19.6	47	35.9	<0.001	26	15.0	34	27.4	0.009
with restriction of limb movements	19	9.3	11	8.4	>0.05	9	5.2	8	6.5	
Edema or hyperemia	17	8.3	14	10.7	>0.05	13	7.5	16	12.9	>0.05
Systemic AE										
Weakness	54	26.5	51	38.9	0.017	51	29.5	32	25.8	>0.05
Body temperature >37,0 ºC	45	22.1	54	41.2	<0.001	39	22.5	33	26.6	>0.05
Arthralgia/myalgia	26	12.7	35	26.7	0.002	23	13.3	22	17.7	>0.05
Headache	18	8.8	20	15.3	>0.05	15	8.7	10	8.1	>0.05
Chills	10	4.9	32	24.4	<0.001	9	5.2	12	9.7	
Nausea or vomiting	7	3.4	2	1.5		4	2.3	1	0.8	
Drowsiness	5	2.5	2	1.5		4	2.3	0	0	
Increase in blood pressure	3	1.5	2	1.5		3	1.7	2	1.6	
Dizziness	3	1.5	1	0.8		2	1.2	0	0	
Metallic taste in the mouth	2	1.0	0	0		0	0	0	0	
Sweating	1	0.5	1	0.8		3	1.7	0	0	
Diarrhea	0	0	1	0.8		3	1.7	0	0	
Rash	0	0	0	0		2	1.2	0	0	
Quincke's edema	1	0.5	0	0		0	0	0	0	
Other	6	2.9	4	3.1		4	2.3	3	2.4	

resolved without any consequences after prescribing 500 μg of epinephrine intramuscularly and a bolus dose of prednisolone (90 mg) intravenously.

After the administration of the second component of the vaccine, the proportion of patients with IIRD who had only systemic AEs was significantly higher than among the control group – 26.6% and 15.3%, respectively (p=0.021). Among the AEs after the second component of the vaccine, the most common were pain at the injection site without restriction of movement, weakness, fever, myalgia/arthralgia, and headache. The number of patients with IIRD who had a combination of local and systemic AEs after the administration of the second component of the vaccine was significantly lower than in the control group and amounted to 27 (15.6%) and 34 (27.4%), respectively, p=0.013. After the introduction of the second component of the vaccine, AEs in patients with IIRD were also absent more often than in controls (50.3% and 44.4% of cases, respectively; p>0.05), however, the differences were statistically insignificant. No serious AEs have been reported after the introduction of the second component of the vaccines.

After complete immunization in patients with IIRD, AEs were absent significantly more often than in controls – in 35.8% and 21% of cases, respectively (p=0.006). These data may support a better tolerability of COVID-19 vaccination in patients with IIRD.

After full vaccination, exacerbation of IIRD in the form of arthralgia with short-term morning stiffness was initially assumed in 2 (1%) patients with RA. However, in the process of dynamic examination and monitoring of the patients, these symptoms regressed on their own without additional treatment, while acute-phase inflammatory markers (erythrocyte sedimentation rate, C-reactive protein) remained within the normal values. After a collegial discussion, the assumption of RA exacerbation was rejected in both cases, and these manifestations were regarded as a post-vaccination reaction. No new autoimmune phenomena were identified.

When comparing the safety of vaccines in patients with IIRD in two age groups (20–59 years and 60–83 years), the most common adverse reactions after the introduction of both the first and second components of the vaccine were pain at the injection site without restriction of movement, weakness, fever, myalgia/arthralgia and headache. However, despite the trend towards less frequent occurrence of these symptoms in the group of people over 60 years, a statistically significant difference was observed only in the frequency of development of weakness after the introduction of the first component (30.5% and 17.5%, respectively; p<0.001). In general, despite the small sample size, it can be assumed that the tolerability of COVID-19 vaccines does not differ significantly in the considered age groups.

The assessment of the clinical efficacy and immunogenicity of vaccination was not conducted in the present study. However, it should be noted that after full vaccination, 6.9% of patients with IIRD and 8.1% of those without these conditions reported developing COVID-19. The authors are planning to study the features of the course of COVID-19 in vaccinated individuals in the future.

Discussion. Our preliminary data indicate the safety of vaccines against COVID-19 registered in the Russian Federation for patients with IIRD, which is consistent with the only work of domestic researchers available to date, in which the tolerability of the Sputnik V vaccine was assessed [8]. The main group consisted of 157 patients with IIRD, the control group consisted of 168 subjects without IIRD. The authors showed that AEs were less common in the main group compared to the controls both after the full vaccination (78.3% and 89.3%, respectively; p=0.01) and after the administration of the first (but not the second) component (72% and 82.7% respectively, p=0.024). Similar data on the safety of vaccination in patients with IIRD were obtained by foreign researchers [9–12].

In our work, exacerbation of IIRD was initially assumed only in 1% of patients, however, during further observation, the clinical symptoms that occurred were regarded as a post-vaccination reaction. The low frequency of exacerbations of IIRD is also evidenced by the data of a number of foreign researchers [9, 12]. At

the same time, the above-mentioned work by Russian authors indicated that 16.5% of patients reported exacerbation of IIRD after vaccination [8]. However, these results should be interpreted carefully and with caution, since the data were obtained using an anonymous online questionnaire, which the participants in the study filled out on their own, which, together with the lack of contact between the patient and the doctor, as well as access to medical records, seems to be the "weak link" of this study. In The work of M. Barbhaiya et al. [13] indicated that exacerbation of IIRD after the introduction of the first component of the vaccine was registered in 23% of patients, after the second – in 42.5%, and after full vaccination – in 32.7%. However, it is not possible to establish the true frequency of exacerbations in this study since the data were also obtained through an online questionnaire.

In general, determining the association of exacerbations of IIRD with vaccination is not an easy task since the signs of disease activity are quite variable. In addition, the approaches to assessing exacerbations of IIRD differ in a doctor and a patient for obvious reasons. A true exacerbation of the disease after vaccination can be diagnosed with a greater probability only in the case of the appearance of clinical symptoms and relevant laboratory data against the background of a previously diagnosed clinical and laboratory remission of IIRD and with long-term follow-up. In addition, the similarity of the clinical picture (articular syndrome, fever, fatigue, myalgia), as well as a short time between vaccination and the onset of symptoms, can make it difficult to distinguish between the actual relapse of the disease and the expected post-vaccination AE.

Taking into account the minimal risk of exacerbation of the disease due to vaccination, the authors are absolutely convinced that this circumstance cannot be an obstacle to the use of vaccines against COVID-19 in patients with IIRD. Vaccination clearly reduces the risk of SARS-CoV-2 infection and a severe course of COVID-19. Currently, this point of view is approved and fully supported by experts from all international and national rheumatological scientific societies, including the Association of Rheumatologists of Russia [3].

Conclusion. According to the preliminary data of our study, immunization of patients with IIRD against COVID-19 using Russian-made vaccines seems to be quite safe. However, further studies are needed to evaluate the safety, immunogenicity, and clinical efficacy of COVID-19 immunization in patients with rheumatic diseases.

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Conflict of Interest Statement

The investigation has been conducted within scientific topic №1021051503137-7.

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