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POSSIBILITIES OF JANUS KINASE INHIBITORS APPLICATION IN COMPLEX TREATMENT OF PATIENTS WITH COVID-19

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◆ ***Introduction.*** More than 30 million cases and more than 970 thousand fatalities from COVID-19 have been registered. The effectiveness of interleukin-6 and interleukin-1 antagonists and janus kinase inhibitors in the treatment of new coronavirus infection is still being analyzed. At present, the emphasis is placed on the introduction into a wide practice of a Russian vaccine named Sputnik V.

Purpose. To compare the effect of complex therapy with baricitinib and dexamethasone on the course of COVID-19 interstitial pneumonia.

Materials and methods. A retrospective analysis of the medical records of 122 people hospitalized at the North-Western State Medical University named after I.I. Mechnikov was carried out. All the patients were divided into three groups: the first one — 64 patients who received therapy including baricitinib; the second one — 33 patients whose therapy included dexamethasone; the third one — 25 patients in the comparison group.

Results. In the first group of patients the lung damage was 25-75% (2-3 degree CT) in 78.1% of the patients, more than 75% in 14.1% of the patients, which was accompanied by severe clinical symptomatology and high laboratory activity. Against the background of the tharapy, positive dynamics of CT was observed in 48.4% of the cases. In the second group of patients the volume of pulmonary tissue damage by CT of 2-3 degrees was observed in 84.9% of the examined patients, clinical and laboratory activity corresponded to the moderate course of the disease. Against the background of the complex therapy, positive dynamics according to CT examination was observed in 18.2% of the cases. In the comparison group, positive dynamics according to CT was observed in 56% of the patients against the background of the therapy. Normalization of clinical and laboratory parameters was observed in all the patients from three study groups on the background of treatment.

Conclusions. In the first group the majority of the patients had he highest number of comorbid pathologies and severe course of COVID-19. Normalization of clinical and laboratory parameters was observed in all the groups of patients. As a result of standard comprehensive therapy, as well as therapy involving baricitinib or dexamethasone, positive dynamics according to CT data was observed in 48.4%, 18.2% and 56% of the patients, respectively.

◆ **Keywords:** new coronavirus infection; baricitinib; dexamethasone; complex therapy; comorbidity; interstitial pneumonia.

ВОЗМОЖНОСТИ ПРИМЕНЕНИЯ ИНГИБИТОРОВ ЯНУС-КИНАЗ В КОМПЛЕКСНОМ ЛЕЧЕНИИ ПАЦИЕНТОВ С COVID-19

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◆ ***Введение.*** На сентябрь 2020 г. зарегистрировано более 30 млн случаев заболевания и более 970 тыс. летальных исходов от COVID-19. Продолжается анализ эффективности антагонистов интерлейкина-6, интерлейкина-1, ингибиторов янус-киназ в терапии новой коронавирусной инфекции. В настоящее время акцент сделан на внедрение в широкую практику российской вакцины от SARS-COV-2, которая получила название Спутник V.

Цель исследования — сравнить влияние комплексной терапии с применением барицитиниба и дексаметазона на течение интерстициальной пневмонии, вызванной COVID-19.

Материалы и методы. Проведен ретроспективный анализ историй болезни 122 человек, госпитализированных в центр по лечению больных COVID-19 клиники СЗГМУ им. И.И. Мечникова. Все пациенты были разделены на три группы: первая группа — 64 пациента, получавших комплексную терапию, включавшую барицитиниб; вторая группа — 33 пациента, в комплексную терапию которых входил дексаметазон; третья группа — 25 пациентов группы сравнения (стандартная комплексная терапия).

Результаты. В первой группе объем поражения легких у пациентов составлял 25–75 % (КТ II–III степеней) у 78,1 % больных, более 75 % — у 14,1 % больных, что сопровождалось тяжелыми клиническими проявлениями, высокими показателями лабораторных исследований. На фоне терапии положительная динамика по КТ наблюдалась в 48,4 % случаев. Во второй группе пациентов объем поражения легочной ткани по КТ II–III степеней наблюдался у 84,9 % обследуемых, клинико-лабораторные показатели соответствовали среднетяжелому течению. На фоне комплексной терапии положительная динамика по КТ отмечена в 18,2 % случаев. В группе сравнения на фоне терапии положительная динамика по КТ зарегистрирована у 56 % пациентов. У пациентов из трех групп на фоне лечения клинико-лабораторные показатели нормализовались.

Выводы. В первой группе преобладали пациенты с наибольшим количеством коморбидной патологии и тяжелым течением COVID-19. Во всех группах происходила нормализация клинико-лабораторных показателей. В результате стандартной комплексной терапии, а также терапии, включавшей барицитиниб или дексаметазон, положительная динамика по данным КТ наблюдалась у 48,4; 18,2 и 56 % пациентов соответственно.

◆ **Ключевые слова:** новая коронавирусная инфекция; барицитиниб; дексаметазон; комплексная терапия; коморбидность; интерстициальная пневмония.

Introduction

The COVID-19 pandemic represents one of the most challenging global healthcare problems. As of September 2020, more than 30 million cases of the disease and more than 900 thousand lethal outcomes from COVID-19 were registered. The virus initially emerged in China in December 2019 and spread worldwide, and on March 11, 2020, the World Health Organization announced that the situation had become a pandemic.

It is known that COVID-19 can be asymptomatic or cause mild clinical symptoms. However, disease progression to interstitial pneumonia and acute respiratory distress syndrome is registered in almost 10%–20% of cases, especially in older people with concomitant diseases. These patients have high levels of serum ferritin, C-reactive protein (CRP), and D-dimer, hepatic dysfunction, and a tendency to thrombogenesis and disseminated intravascular coagulation, suggesting the occurrence of macrophage activation syndrome, also known as secondary hemophagocytic lymphohistiocytosis [1, 2].

Some authors distinguish four disease stages. Stage 1 (early infection) starts during infection with the virus, can manifest with nonspecific symptoms (ailment, fever, sore throat, dry cough), and is often symptomatic. Stage 2 is characterized by increased reactivity of the immune system. Patients develop viral pneumonia with possible hypoxia and increased levels of systemic inflammation markers. Stage 3, along with the manifestations noted in the previous stages, a state of hypercoagulation occurs. In stage 4, multiple organ failure develops [3].

Currently, work is underway to find effective treatment regimens to treat the new coronavirus infection. Many drugs (antiviral, antibacterial drugs, glucocorticoids, interleukin-1 inhibitors, Janus kinase inhibitors, low molecular weight heparins) are used based on their pharmacological properties that affect the course of pneumonia. Inhibitors of interleukin-6, namely sarilumab, tocilizumab, can be used to block the cytokine storm [4–7]. The current emphasis is currently on introducing the Russian vaccine into widespread practice. It is based on an adenovirus vector registered by the Ministry of Health of Russia on August 11. It became the

first SARS-COV-2 vaccine on the market and was named Sputnik V [8].

This study aims to compare the effect of the complex therapy with baricitinib and dexamethasone on the course of interstitial pneumonia caused by COVID-19.

Materials and methods

A retrospective analysis of the case histories of 122 patients hospitalized in the center for the treatment of patients with the new coronavirus infection caused by SARS-COV-2, the clinic of the Mechnikov North Western State Medical University. All patients received treatment according to clinical recommendations of versions 6 (from 04/28/2020) and 7 (from 06/03/2020), which included the use of antibacterial drugs (azithromycin 500 mg per day, amoxiclav 1,000 mg twice a day, levofloxacin 500 mg twice a day), anticoagulant therapy (low molecular weight heparins, non-fractionated heparin at prophylactic and therapeutic doses), hydroxychloroquine 400 mg/day, and glucocorticoids in the form of dexamethasone. All patients with diabetes mellitus were switched to insulin therapy during hospitalization. For other concomitant conditions, therapy was conducted in full (infusion, antihypertensive, antiemetic, antidiarrheal, mucolytic, and antipyretic). Swabs from all patients' oropharynx and nasopharynx were tested by the polymerase chain reaction method for SARS-CoV-2. The changes in body temperature, the presence of cough, general asthenia, nausea, vomiting, diarrhea, and anosmia/ageusia were assessed as clinical manifestations in all hospitalized patients. In all patients, the degree of respiratory failure (RF) was assessed, and the oxygen saturation level and the amount of oxygen therapy during the hospital stay before and after therapy. The severity of pneumonia was determined at admission and before patient discharge and analyzed by computed tomography (CT), which was performed. Laboratory parameters (the levels of CRP, ferritin, fibrinogen, D-dimer, transaminase activity, and changes in the clinical blood test) were assessed over time, namely on the day of admission and 14 after the start of therapy.

All patients were distributed into three groups. Group 1 included 64 patients examined, whose average age was 57.3 ± 13.6 years, 43 (67.2%) were men. Lung lesions characteristic of grade I by CT were noted in five (7.8%) patients, grade II was detected in 24 (37.5%) cases, grade III was revealed in 26 (40.6%) patients, and grade IV was noted in nine (14.1%) cases. High values of clinical and laboratory parameters were registered. Namely, the CRP levels were 120.96 ± 51.47 mg/l, and ferritin was 1609.48 ± 816.29 μg/l. RF events were recorded in all patients of this group, including stage III RF in 48.4% of cases. The severity of the disease course was moderate or severe. Complex therapy with baricitinib at a dosage of 4 mg for seven days was prescribed to the patients examined in group 1. Group 2 consisted of 33 patients whose average age was 55.1 ± 8.6 years, and there were 22 (64.7%) men. Lung lesions corresponding to grade III were noted in four (12.1%) patients, grade II was registered in 15 (45.5%) cases, grade III was detected in 13 (39.4%) cases, and grade IV was revealed in one (3.03%) patient. Clinical and laboratory parameters indicated a moderate disease course (CRP 72.95 ± 53.52 mg/l, ferritin 786.02 ± 364.86 μg/l). RF corresponded to a degree I in 22 (66.7%) patients, and degree II was noted in 12 (36.4%) cases. Group 2 patients received complex therapy with dexamethasone at 10.48 ± 2.87 mg per day. Group 3, the control group, consisted of 25 patients whose average age was 52 ± 8.3 years, and 15 (60%) were men. Lung lesions by CT corresponding to grade III were found in two (8%) patients, grade II in 18 (72%) cases, and grade III in five (20%) patients. The level of inflammation markers indicated 49.372 ± 37.9 mg/l of CRP and 560.09 ± 356.82 μg/l of ferritin. Also, I degree RF was noted in 23 (92%) patients, and II degree RF was registered in two (8%) cases. Group 3 patients received treatment with antibacterial drugs, low molecular weight heparins, and therapy for concomitant conditions (antihypertensive drugs, insulin therapy, mucolytic and antipyretic drugs) in full.

The most frequent pathologies in patients examined with COVID-19 were obesity, type 2 diabetes mellitus (T2DM), coronary heart disease, bronchial asthma/chronic obstructive pulmonary disease, hypertensive disease (HD), cardiac arrhythmias, a history of cardiovascular disasters, and chronic heart failure.

All patients were discharged from the hospital after complete resolution of RF, normalization of body temperature without requiring oxygen

therapy, and after normalization of laboratory parameters (CRP, ferritin, fibrinogen, D-dimer). However, not all patients resolved general asthenia symptoms.

Results

Table 1 presents the distribution of patients by gender, age, hospitalization period, and complex therapy with baricitinib and dexamethasone.

Table 1 shows that the patients who received complex therapy with baricitinib, dexamethasone and the comparison group patients were comparable by gender and age. The hospitalization period was 22.9 ± 7.5 days in the patient group receiving baricitinib in complex therapy, 18.3 ± 7.4 days in the complex therapy group with dexamethasone, and 15.4 ± 2.5 days in the comparison group. The difference in the duration of hospitalization was associated with the severity

Table 1 / Таблица 1

Distribution of patients by sex, age, duration of hospitalization, and therapy
Распределение пациентов по полу, возрасту, продолжительности госпитализации и терапии

Indicators	Group 1, baricitinib	Group 2, dexamethasone	Comparison group
Number of patients	64	33	25
Gender	Men — 43 (67.2%)	Men — 22 (64.7%)	Men — 15 (60%)
Age, years	57.3 ± 13.6	55.1 ± 8.6	52 ± 8.3
Period of hospitalization, days	22.9 ± 7.5	18.3 ± 7.4	15.4 ± 2.5

Table 2 / Таблица 2

Clinical characteristics of patients with COVID-19 who received baricitinib complex therapy
Клиническая характеристика пациентов с COVID-19, получавших комплексную терапию с применением барицитиниба

Indicator	During therapy	After complex therapy
CT degree	Grade I — 5 (7.8%); Grade II — 24 (37.5%); Grade III — 26 (40.6%); Grade IV — 9 (14.1%)	Improvement — 31 (48.4%): Grade I — 3 (4.7%); Grade II — 9 (14.1%); Grade III — 14 (21.9%); Grade IV — 5 (7.8%). Deterioration — 3 (4.7%): Grade III — 1 (1.6%); Grade IV — 2 (3.1%). Control was not performed — 30 (46.9%)
Respiratory failure	Degree I — 6 (9.4%); Degree II — 27 (42.2%); Degree III — 31 (48.4%)	Resolution of respiratory failure — 52 (81.25%)
Saturation, %	85 ± 11.9	97.6 ± 1.24
Oxygen therapy, L	6.2 ± 4.65	–
Temperature	Subfebrile — 26 (40.6%), febrile — 38 (59.4%)	Normalization — 59 (92.2%)
Cough, patients	60 (93.75%)	8 (12.5%)
Asthenia, patients	64 (100%)	23 (36%)
Diarrhea/vomiting/nausea, patients	22 (34.4%)	0
Anosmia/ageusia, patients	41 (64.1%)	17 (26.6%)

N o t e. CT degree — the degree of lung tissue changes according to a particular computed tomography of the chest organs.

of the disease course in group 1 patients, which required a longer therapy using Janus kinase inhibitors.

The clinical characteristics of the examined patients who received baricitinib during complex therapy are presented in Table 2.

Lung lesions by CT, characteristic of grade I was noted in five (7.8%) patients, grade II in 24 (37.5%) cases, grade III in 26 (40.6%) patients, and grade IV in nine (14.1%) cases. RF events were registered in all patients of this group, including degree I RF in six (9.4%) cases, degree II RF in 27 (42.2%) cases, and degree III RF in 31 (48.4%) patients, which corresponded to moderate and severe disease courses. This group's saturation level was 85% ± 11.9%, which required an oxygen therapy volume of 6.2 ± 4.65 liters. Febrile fever was noted in 38 patients (59.4%), and subfebrile fever was registered in 26 (40.6%) cases.

During the complex therapy with baricitinib, an improvement on CT was detected in 31 (48.4%) patients, and deterioration was noted in three (4.7%) cases. RF was resolved in 52 (81.25%) patients, body temperature returned to normal in 59 (92.2%) patients, and saturation recovered to 97.6% ± 1.24%.

Table 3 presents the clinical characteristics of the examined patients who received dexamethasone during complex therapy.

Lung lesions corresponding to grade I CT was registered in four (12.1%) patients, that of grade II by CT was noted in 15 (45.5%), that of grade III by CT was detected in 13 (39.4%) of cases, and that of grade IV by CT was registered in one (3.03%) case. Clinical manifestations indicated a moderate course of the disease when RF corresponded to the degree I in 22 (66.7%) patients, and that of grade II was in 12 (36.4%) patients. Saturation was 92.24 ± 4.24%, the volume of oxygen therapy was 3.67 ± 1.68 L. Subfebrile temperature was noted in 22 (66.7%) patients, and the febrile temperature was registered in 11 (33.3%) patients.

During therapy, positive changes on CT were revealed in six (18.2%) patients, and deterioration was found in five (15.2%) cases. RF was resolved in 30 (90.9%) patients, body temperature returned to normal in 30 (90.9%) patients, and saturation recovered to 98.21 ± 0.73%.

Table 3 / Таблица 3

Clinical characteristics of patients with COVID-19 receiving dexamethasone complex therapy
Клиническая характеристика пациентов с COVID-19, получавших комплексную терапию с применением дексаметазона

Indicators	During therapy	After complex therapy
CT degree	Grade I — 4 (12.1%); Grade II — 15 (45.5%); Grade III — 13 (39.4%); Grade IV — 1 (3.03%)	Improvement — 6 (18.2%): Grade II — 5 (15.2%); Grade III — 1 (3.03%). Deterioration — 5 (15.2%): Grade II — 1 (3.03%); Grade III — 4 (12.1%). Control was not performed — 22 (66.7%)
Respiratory failure	Degree I — 22 (66.7%); Degree II — 12 (36.4%)	Resolution of respiratory failure — 30 (90.9%)
Saturation, %	92.24 ± 4.24	98.21 ± 0.73
Oxygen therapy, L	3.67 ± 1.68	No oxygen therapy was performed
Temperature	Subfebrile — 22 (66.7%), febrile — 11 (33.3%)	Normalization — 30 (90.9%)
Cough, patients	23 (69.7%)	0
Asthenia, patients	33 (100%)	14 (42.4%)
Diarrhea/vomiting/nausea, patients	2 (6.1%)	0
Anosmia/ageusia, patients	19 (57.6%)	9 (27.3%)

N o t e. CT degree — the degree of changes in the lung tissue according to a particular computed tomography of the chest organs.

Table 4 / Таблица 4

Clinical characteristics of patients with COVID-19 from the comparison group
Клиническая характеристика пациентов с COVID-19 из группы сравнения

Indicators	During therapy	After complex therapy
CT degree	Grade I — 2 (8%); Grade II — 18 (72%); Grade III — 5 (20%)	Improvement — 14 (56%): Grade II — 11 (44%); Grade III — 3 (12%). Deterioration — 2 (8%): Grade II — 1 (4%); Grade III — 1 (4%). Control was not performed — 9 (36 %)
Respiratory failure	Degree I — 23 (92%); Degree II — 2 (8%)	Resolution of respiratory failure — 25 (100%)
Saturation, %	94.8 ± 4.64	98.24 ± 0.77
Oxygen therapy, L	3.25 ± 1.4	No oxygen therapy was performed
Temperature	Subfebrile — 18 (72%), febrile — 7 (28%)	Normalization — 25 (100%)
Cough, patients	20 (80%)	0
Asthenia, patients	25 (100%)	9 (36%)
Diarrhea/vomiting, patients	0	0
Anosmia/ageusia, patients	16 (64%)	0

N o t e. CT degree — the degree of changes in the lung tissue according to a particular computed tomography of the chest organs.

Table 5 / Таблица 5

Dynamics of laboratory indices in the examined groups before and after the therapy
Динамика лабораторных показателей в обследованных группах до и после терапии

Indicators	Group 1, baricitinib		Group 2, dexamethasone		Comparison group	
	before	after	before	after	before	after
C-reactive protein, mg/l	120.96 ± 51.47	10.63 ± 4.84	72.95 ± 53.52	12.51 ± 6.22	49.372 ± 37.9	3.7 ± 2.59
Ferritin, μg/l	1609.48 ± 816.29	791.23 ± 342.75	786.02 ± 364.86	180.8 ± 72.55	560.09 ± 356.82	496.47 ± 271.23
AST, U/l	73.53 ± 36.73	53.08 ± 24.4	66.94 ± 22.59	35.79 ± 14.85	40.16 ± 22.56	40.2 ± 26.33
ALT, U/l	69.55 ± 26.75	98.27 ± 41.40	56.67 ± 17.21	67.18 ± 38.27	38.12 ± 24.28	66.48 ± 55.93
CPK, U/l	550.66 ± 192.91	103.28 ± 38.69	–	–	76.5 ± 34.29	55.13 ± 19.12
LDH, U/l	405.94 ± 188.54	238.14 ± 100.06	–	–	219.64 ± 56.57	176.43 ± 48.79
Creatinine, μmol/l	104.22 ± 53.22	90.52 ± 28.88	88.11 ± 16.89	90.52 ± 28.88	80.36 ± 23.05	81.16 ± 17.92
Glucose, mmol/l	6.91 ± 3.23	6.35 ±3.28	5.51 ± 0.72	5.73 ± 1.45	6.32 ± 1.98	6.03 ± 2.31
Hematocrit, %	0.41 ± 0.048	0.39 ± 0.05	0.43 ± 0.044	0.41 ± 0.03	0.41 ± 0.041	0.39 ± 0.04
Leukocytes, 10^9 cells/l	7.03 ± 2.63	7.09 ± 2.76	6.22 ± 2.03	9.43 ± 3.46	6.42 ± 2.40	5.6 ± 1.33
Neutrophils, 10^3 cells/μl	5.21 ± 2.39	4.14 ± 1.75	4.36 ± 1.96	1.85 ± 1.04	4.42 ± 2.34	2.8 ± 0.79

End of Table 5 / Окончание табл. 5

Indicators	Group 1, baricitinib		Group 2, dexamethasone		Comparison group	
	before	after	before	after	before	after
Lymphocytes, 10^3 cells/μl	1.19 ± 0.67	2.065 ± 1.7	1.20 ± 0.45	4.63 ± 0.44	1.416 ± 0.51	2.05 ± 0.72
Erythrocytes, 10^{12} cells/μl	4.58 ± 0.55	4.46 ± 0.59	4.87 ± 0.54	4.63 ± 0.45	4.73 ± 0.55	4.57 ± 0.55
Hemoglobin, g/l	137.4 ± 17.73	132.95 ± 18.16	154 ± 20.35	137.18 ± 10.91	145.92 ± 16.6	134.44 ± 13.77
Platelets, 10^3 cells/μl	240.02 ± 91.183	410.31 ± 131.93	205.42 ± 81.38	362.36 ± 143.94	245.92 ± 92.34	339.68 ± 120.29
ESR, mm/h	21.09 ± 14.11	21. 89 ± 13.15	25 ± 13.89	22. 38 ± 13.42	19.72 ± 5.61	25.82 ± 15.31
Fibrinogen, g/l	5.01 ± 1.84	4.98 ± 1.37	5.1 ± 1.24	3.57 ± 1.11	5.38 ± 1.47	4.26 ± 0.85
D-dimer, g/l	1.96 ± 0.58	0.72 ± 0.58	1.55 ± 0.69	0.41 ± 0.26	1.09 ± 0.67	0.55 ± 0.42

N o t e. ALT — alanine aminotransferase; AST — aspartate aminotransferase; CPK — creatine phosphokinase; LDH — lactate dehydrogenase; ESR — erythrocyte sedimentation rate.

Table 4 presents the clinical characteristics of the examined patients from the comparison group.

Lung lesions by CT corresponding to grade I were revealed in two (8%) patients, grade II in 18 (72%) cases, and grade III in five (20%) patients. Signs of the degree I RF were noted in 23 (92%) patients, and those of degree II RF were registered in two (8%) patients. Saturation was 94.8 ± 4.64% the volume of oxygen therapy was 3.25 ± 1.4 liters. Subfebrile fever was noted in 18 (72%) patients, and febrile fever was registered in seven (28%) cases.

During therapy, an improvement on CT was detected in 14 (56%) patients, whereas deterioration was noted in two (8%) cases. RF resolution and temperature normalization were recorded in 100% of patients.

Table 5 presents the changes in laboratory parameters in patients receiving complex therapy with baricitinib, dexamethasone, and patients of the comparison group before and after therapy.

In group 1 patients, high activity in laboratory parameters was noted. This elevated activity was confirmed by high levels of CRP (120.96 ± ± 51.47 mg/l), ferritin (1609.48 ± 816.29 μg/l), fibrinogen (5.01 ± 1.84 g/l), and D-dimer (1.96 ± 0.58 g/l). Also, there was the high activity of alanine aminotransferase (ALT, 69.55 ± ± 26.75 U/l) and aspartate aminotransferase (AST, 73.53 ± 36.73 U/l), and a decrease in the lymphocyte level to 1.19 ± 0.67 · 10^3 cells/μl.

In group 2 patients, the level of CRP was 72.95 ± 53.52 mg/l, ferritin was 786.02 ± ± 364.86 μg/l, fibrinogen was 5.1 ± 1.24 g/l, and D-dimer was 1.55 ± 0.69 g/l. Also, the activity of ALT was 56.67 ± 17.21 U/l and AST was 66.94 ± 22.59 U/l, and the lymphocyte level was 1.20 ± 0.45 · 10^3 cells/μl.

In the control group patients, the level of CRP was 49.372 ± 37.9 mg/l, ferritin was 560.09 ± ± 356.82 μg/l, fibrinogen was 5.38 ± 1.47 g/l, and D-dimer was 1.09 ± 0.67 g/l. Also, the activity of ALT was 38.12 ± 24.28 U/l and AST was 40.16 ± 22.56 U/l, and the lymphocyte level was 1.416 ± 0.51 · 10^3 cells/μl.

The incidence of comorbid conditions in the groups of patients with COVID-19 who received comprehensive therapy with baricitinib and dexamethasone is presented in Table 6.

The incidence of chronic diseases in patients who received complex therapy with baricitinib was higher than in group 2 and group 3 patients. So, obesity was detected in 54.7% of cases, T2DM was registered in 28.1% of the patients examined, and coronary heart disease was revealed in 26.6% of cases. Cardiac arrhythmias were recorded in 14.1% of cases, a history of cardiovascular accidents (generalized cerebrovascular accident, acute myocardial infarction) was noted in 15.6% of cases. Chronic heart failure was registered in 17.2% of patients, and chronic kidney disease was revealed in 25% of patients. The prevalence of HD was almost the same in the examined groups 1 and 2 and amounted to 76.5% and

Table 6 / Таблица 6

Frequency of comorbid conditions in patients with COVID-19 using baricitinib and dexamethasone
Частота коморбидных состояний у пациентов с COVID-19 с применением барицитиниба и дексаметазона

Indicators	Group 1, baricitinib	Group 2, dexamethasone	Control group
Obesity	Degree I — 16 (25%); Degree II — 14 (21.9%)**; Degree III — 5 (7.8%)	Degree I — 6 (18.2%); Degree II — 4 (12.1%); Degree III — 2 (9.1%)	Degree I — 5 (20%); Degree II — 2 (8%)
Type 2 diabetes mellitus	18 (28.1%)*	8 (24.4%)	3 (12%)
Ischemic heart disease	17 (26.6%)**	6 (18.2%)	3 (12%)
BA/COPD	2 (3.1%)*	1 (3.03%)	0
Hypertensive disease	Degree I — 5 (7.8%); Degree II — 34 (53.1%)**; Degree III — 10 (15.6%)**	Degree I — 9 (27.3%); Degree II — 13 (39.4%); Degree III — 2 (6.1%)	Degree I — 3 (12%) Degree II — 11 (44%); Degree III — 2 (8%)
Heart rhythm disorder	9 (14.1%)**	3 (9.1%)	1 (4%)
History of cardiovascular accidents	10 (15.6%)**	1 (3.03%)	2 (8%)
Chronic cardiac failure	Stage I — 5 (78 %); Stage IIA — 5 (7.8%); Stage IIB — 1 (1.6%)	Stage I — 3 (6.1%); Stage IIA — 2 (6.1%)	Stage I — 2 (8%)
Chronic renal disease	Stage I—2 (3.1%)**; Stage II—5 (7.8%)**; Stage IIIA—3 (4.7%); Stage IIIB—3 (4.7%)**; Stage IV—2 (3.1%)**; Stage V—1 (1.6%)**	Stage IIIA — 2 (6.1%)	Stage IIIA — 2 (8%)

N o t e. BA/COPD — bronchial asthma/chronic obstructive pulmonary disease. *Compared with the control group; **compared with the groups treated with dexamethasone and in the control group.

72.8% of cases, respectively. However, in the complex therapy group, in which patients received baricitinib, stage I HD was found in 7.8% of patients, stage II HD was revealed in 53.1%, and stage III HD was noted in 15.6% of cases. In the complex therapy group receiving dexamethasone, stage I HD was detected in 27.3%, stage II HD was revealed in 39.4%, and stage III HD was found in 6.1% of patients.

Discussion

In group 1 patients, the disease course was more severe than the patients in group 2 and group 3. Therefore, more prolonged therapy with the use of Janus kinase inhibitors was required. This was confirmed by clinical and laboratory parameters. The RF of degrees II–III was registered in 90.6% of cases. The saturation level was 85 ± 11.9%, which required oxygen therapy in a volume of 6.2 ± 4.65 liters. A cough was noted in 93.8% of the patients examined. Febrile fever was registered in 59.4%, and subfebrile was noted in 40.6% of cases. Comorbid conditions in the group of patients receiving the complex therapy with baricitinib were more common than in the comprehensive therapy group with dexamethasone and the comparison group. The baseline values of CRP, ferritin, CPK, and LDH activity were higher in group 1 patients than in group 2 and group 3 patients. The levels of fibrinogen and D-dimer in all groups were approximately equal. Therefore, all patients with COVID-19 should be prescribed anticoagulant therapy due to the pathogenetically proven formation of microthrombosis in different caliber vessels with a predominant microvasculature lesion [9–12]. The number of patients with grade III–IV lung tissue changes on CT was higher in percentage terms in group 1 (54.7%) than in group 2 (42.4%) and group 3 (20%).

During treatment, RF was resolved in all patients, oxygen saturation reached optimal values, the oxygen therapy requirement was eliminated, body temperature returned to normal, the cough was stopped, patients' nausea/vomiting/diarrhea subsided, and the sense of smell and taste returned. In all groups, during treatment, general asthenia symptoms persisted, namely in 23 (36%) patients using baricitinib, in 14 (42.4%) patients using dexamethasone, and in nine (36%) in the comparison group. The decrease in inflammation markers was more pronounced during baricitinib use (ferritin level 791.23 ± 342.75 μg/l). However, the indicators did not reach the reference values, which can be due to this patient group's very high ferritin level values (1609.48 ± 816.29) before starting treatment. In patients who received dexamethasone in combination therapy and patients of the comparison group, ferritin indices returned to normal in almost all cases (180.8 ± 72.55 and 496.47 ± 271.23 μg/l, respectively), except for cases of deterioration, according to clinical manifestations and CT. A decrease in the CRP level was noticeable in all groups and at the end of the therapy cycle. The values of this CRP amounted to 10.63 ± 4.84 mg/l in the baricitinib group, 12.51 ± 6.22 mg/l in the dexamethasone group, and 3.7 ± 2.59 mg/l in the comparison group. In all cases, fibrinogen and D-dimer levels returned to normal during treatment. In patients of all groups, ALT activity increased over time, which may be associated with drug hepatotoxicity. However, there were no cases of drug withdrawal (baricitinib, dexamethasone) due to adverse events.

During the comprehensive therapy with baricitinib, an improvement on CT was determined in 48.4% of cases, and deterioration was registered in 4.7% of cases. Positive changes on CT scans in patients receiving dexamethasone in complex therapy were determined in 18.2% of cases, and deterioration was registered in 15.2% of cases.

Conclusions

1. The patients with the greatest amount of comorbid pathology and severe course of COVID-19 were predominantly in group 1. As a result of comprehensive treatment, which included baricitinib, the clinical and laboratory parameters normalized, and improvement according to CT was registered in 48.4% of patients. The treatment duration for patients in this group was 22.9 ± 7.5 days.
2. The course of COVID-19 in group 2 patients was more severe than in the comparison group, but the disease course was milder than in group 1. As a result of comprehensive therapy, which included dexamethasone, clinical and laboratory parameters returned to normal, and 18.2% of patients showed improvement according to CT data. The treatment duration of patients in this group was 18.3 ± 7.4 days.
3. In the comparison group, comorbid conditions and the course of COVID-19 were less pronounced compared with the patient groups whose comprehensive therapy included baricitinib and dexamethasone. As a result of the standard complex therapy, clinical and laboratory parameters returned to normal, and 56% of patients improved according to CT data. The treatment duration of patients in this group was 15.4 ± 2.5 days.

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