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STUDY OF LONG-TERM CLINICAL AND PATHOGENETIC EFFECTS OF FAVIPIRAVIR-BASED ANTI-VIRAL DRUG IN PATIENTS WITH METABOLIC SYNDROME IN POST-COVID PERIOD

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The article presents modern scientific data on long-term clinical and pathogenetic effects of the antiviral drug Areplivir (Favipiravir) in patients with metabolic syndrome in the post-COVID period.

The aim of the article is to study long-term cytokine-mediated (IL-6/sIL6r and LIF/sLIFr) pathogenetic effects of the favipiravir (Areplivir®) based drug on the incidence of complications in patients with metabolic syndrome in the post-COVID period.

Material and methods. With the approval of the local ethics committee at the N.P. Ogarevs Mordovia State University (Protocol No. 5 dated May 17, 2020) "An open prospective comparative study of the Areplivir® (Favipiravir) drug effectiveness in reducing the risk of complications in the post-COVID period in patients with metabolic syndrome" in the Republic of Mordovia was carried out.

The study included 190 metabolic syndrome patients who received the outpatient treatment for COVID-19 at Saransk polyclinics from February 2021 to March 2021. The case of COVID-19 was diagnosed in accordance with the current Temporary Guidelines for the prevention, diagnosis and treatment of the new coronavirus infection.

Results. The analysis of the metabolic syndrome patients' follow-up within 1 year after undergoing COVID-19, revealed significant differences in the incidence of complications depending on the intake of the favipiravir based drug. The patients who were administrated with favipiravir at the early stage of infection, were characterized by lower serum levels of four members of the interleukin 6 family – IL-6 (IL-6, sIL6r and LIF, sLIFr) 10, 30 and 180 days after a clinical and laboratory recovery ($p<0.001$). The average statistical changes in the IL-6 /sIL6r system of the group administrated with favipiravir, were 90%, and they were higher than in the group not administrated with antiviral drugs. In the group of the patients administrated with favipiravir, there was a significant ($p<0.001$) positive dynamic of the sLIFr indicator, while in the comparison group, there was an increase in this indicator.

A protective effect of the early favipiravir use was characterized by a decrease in the frequency of cardiovascular complications, a 2.66-fold decrease in the risk of a stroke and the ACS in the post-COVID period.

Conclusion. The areplivir therapy in the acute period of coronavirus infection made it possible to timely reduce the viral load. It helps to correct the pro-inflammatory vector of the immune response at the post-COVID stage and, accordingly, reduces the risk of progression of atherosclerosis, transient cerebrovascular accidents with a cognitive decline, an endothelial dysfunction, and can be considered a secondary prevention of life-threatening cardiovascular complications.

Keywords: Areplivir; favipiravir; COVID-19; postcovid syndrome; metabolic syndrome

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Abbreviations: MS – metabolic syndrome; AH – arterial hypertension; DM – diabetes mellitus; ACVE – Acute Cerebrovascular Event; ACS – acute coronary syndrome; MI – Miocardial Infarction; ALT – Alanine transaminase; AST – aspartate aminotransferase; BMI – body mass index; PCR – polymerase chain reaction; ECG – electrocardiogram; VED – vital essential drugs; RNA – ribonucleic acid; ELISA – enzyme-linked immunoelectrodiffusion essay; CI – confidence interval; IL-6 – interleukin 6; sIL-6R – soluble interleukin 6 receptor; sLIFr – leukemia inhibiting factor soluble receptor; LIF – Leukemia inhibitory factor (leukemia inhibitory factor); iNOS – Nitric oxide synthase; inducible (inducible nitric oxide synthase); eNOS – endothelial nitric oxide synthase (endothelial nitric oxide synthase); ADMA – asymmetric dimethylarginine (asymmetric dimethylarginine); SDMA – symmetric dimethylarginine (symmetrical dimethylarginine); NO – nitric oxide; PWVcf – carotid to femoral artery pulse wave velocity; EchoCG – echo-cardiography; PVR – peripheral vascular resistance; GFR – glomerular filtrate rate; gp – glycoprotein; STAT3 – signaling protein and transcription activator of signal transducers and activators of transcription (STAT).

ИЗУЧЕНИЕ ОТДАЛЕННЫХ КЛИНИКО-ПАТОГЕНЕТИЧЕСКИХ ЭФФЕКТОВ ПРОТИВОВИРУСНОГО ЛЕКАРСТВЕННОГО ПРЕПАРАТА НА ОСНОВЕ ФАВИПИРАВИРА В ПОСТКОВИДНОМ ПЕРИОДЕ У ПАЦИЕНТОВ С МЕТАБОЛИЧЕСКИМ СИНДРОМОМ

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В статье представлены современные научные данные в отношении отдаленных клинико-патогенетических эффектов противовирусного препарата Арепливир (фавипиравир) в постковидном периоде у пациентов с метаболическим синдромом.

Цель. Изучить отдаленные цитокин-опосредованные (IL-6/sIL6r и LIF/sLIFr) патогенетические эффекты применения препарата на основе фавипиравира («Арепливир®») на частоту развития осложнений у пациентов с метаболическим синдромом в постковидном периоде.

Материал и методы. С одобрения локального этического комитета при ФГБОУ ВО «МГУ им. Н.П. Огарева» (протокол № 5 от 17 мая 2020) проведено «Открытое проспективное сравнительное исследование эффективности применения препарата «Арепливир®» (фавипиравир) в отношении снижения риска развития осложнений в постковидном периоде у пациентов с метаболическим синдромом» в Республике Мордовия.

В исследование включены 190 пациентов с метаболическим синдромом, получавших амбулаторное лечение в связи с COVID-19 на базе поликлиник г. Саранска в период с февраля 2021 по март 2021. Диагноз COVID-19 был выставлен в соответствие с актуальными временными методическими рекомендациями по профилактике, диагностике и лечению новой коронавирусной инфекции.

Результаты. Анализ наблюдения пациентов с метаболическим синдромом в течение 1 года после перенесенного COVID-19 определил достоверные отличия в частоте осложнений в зависимости от приема лекарственного препарата на основе фавипиравира. Пациенты, получавшие фавипиравир на раннем этапе заражения, характеризовались более низким уровнем содержания в сыворотке крови четырех представителей семейства интерлейкина 6-IL-6 (IL-6, sIL6r и LIF, sLIFr) через 10, 30 и 180 дней после клинико-лабораторного выздоровления ($p<0,001$). Среднестатистические изменения в системе IL-6/sIL6r группы, принимающих фавипиравир, составляли 90% и были выше, чем у группы без приема противовирусных препаратов. В группе пациентов, принимавших фавипиравир, наблюдалась значимая ($p<0,001$) положительная динамика показателя sLIFr, тогда как в группе сравнения наблюдался рост данного показателя.

Протективное действие при раннем использовании фавипиравира характеризовалось уменьшением частоты сердечно-сосудистых осложнений, снижением риска развития ОНМК и ОКС в 2,66 раза в постковидном периоде.

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Заключение. Терапия арепливиром в остром периоде коронавирусной инфекции позволила своевременно снизить вирусную нагрузку, что способствует корректировке провоспалительного вектора иммунного реагирования на постковидном этапе и, соответственно, снижает риск прогрессирования атеросклероза, транзиторных нарушений мозгового кровообращения со снижением когнитивных функций, эндотелиальной дисфункции и может рассматриваться в качестве вторичной профилактики жизнеугрожающих сердечно-сосудистых осложнений.
Ключевые слова: Арепливир; фавипиравир; COVID-19; постковидный синдром; метаболический синдром
Список сокращений: МС-метаболический синдром; АГ – артериальная гипертензия; СД – сахарный диабет; ОНМК – острое нарушение мозгового кровообращение; ОКС – острый коронарный синдром; ИМ – инфаркт миокарда; АлТ – аланинаминотрансфераза; АсТ – аспартатаминотрансфераза; ИМТ – индекс массы тела; ПЦР – полимеразная цепная реакция; ЭКГ – электрокардиограмма; ЖНВЛП – жизненно необходимые важнейшие лекарственные препараты; РНК – рибонуклеиновая кислота; ИФА – иммуноферментный анализ; ДИ – доверительный интервал; IL-6 – интерлейкин 6; sIL-6R – растворимый рецептор интерлейкина 6; sLIFr – растворимый рецептор лейкемия-ингибирующего фактора; LIF – лейкемия-ингибирующий фактор; iNOS –индуцибильная синтаза оксида азота; eNOS – эндотелиальная синтаза оксида азота; ADMA – асимметричный диметиларгинин; SDMA – симметричный диметиларгинин; NO – оксид азота; СПВкф – скорости пульсовой волны на каротидно-феморальном сегменте; ЭХО-КГ – эхокардиография; ОПСС – общее периферическое сопротивление сосудов; СКФ – скорость клубочковой фильтрации; gp – гликопротеин; STAT3 – сигнальный белок и активатор транскрипции из семейства белков STAT.

INTRODUCTION

A significant proportion of people who have had COVID-19, suffer from persistent pathological symptoms that reduce the quality of life and increase the risk of disability. In a number of sources, it is referred to as post-COVID syndrome [1–3]. Herewith, the term “post-COVID syndrome” has a number of limitations that do not allow to unambiguously consider the progression of concomitant diseases after SARS-CoV-2 infection, in particular, arterial hypertension, increased glucose levels, etc., as components of post-COVID syndrome [4]. The data from the studies analyzing cytokine-mediated mechanisms of non-communicable diseases immunopathogenesis (including essential arterial hypertension (EAH) and metabolic syndrome (MS) in the post-COVID period, demonstrating the relevance of the problem, have already been published [5]. The changes in the cytokine regulation associated with complications in the post-COVID period, are studied by many international scientific groups [6]. The data on the “unexpected” increase in the levels of pro-inflammatory markers after 7–8 months in the patients who have undergone the SARS-CoV-2 infection asymptomatically, have been presented [7]. In the severity of post-infection changes, heterogeneity may be also associated with differences in therapy during the acute period of COVID-19. It is known that the earliest possible use of etiotropic therapy is the most important therapeutic tactics for the timely relief of an increasing viral load and reducing the risk of developing a complicated course of the disease. Blocking the virus vital activity in the body due to the drugs of a direct antiviral action allows, in its turn, to reduce the pathological effect of the virus and, accordingly, will help to reduce the severity of post-infection complications [8].

One of the most studied modern molecules used in the treatment of COVID-19 and able of suppressing the reproduction of RNA viruses is favipiravir (6-fluoro-3-hydroxy-2-pyrazinecarboxamide). The effectiveness of this compound has been proven against various RNA viruses (influenza, including strains H1N1, H5N1, H7N9, arenaviruses, flaviviruses, alphaviruses, etc.), which has been demonstrated in clinical and experimental studies [9–11, 13]. The active form of favipiravir selectively interacts with RdRp, is included in the emerging viral RNA chain, or binds to preserved polymerase domains, blocking the viral RNA replication, which leads to the utilization of the “defective” RNA and disappearance of the viral genome. The drug-induced “fatal” mutagenesis in widespread coronaviruses, as well as a selective inhibition of RdRp, allows us to consider favipiravir as a universal inhibitor of epidemiologically significant RNA-containing viruses – the main causative agents of seasonal ARVI [14, 15].

According to the clinical trials, in COVID-19 patients, the favipiravir-based direct antiviral drug Areplivir, registered in Russia and widely used, has manifested a high efficacy and safety in comparison with the standard therapy [16]. The use of favipiravir for the treatment of the infection caused by the SARS-CoV-2 coronavirus, reduces the clinical improvement period by an average of 4 days compared with the standard therapy, reaches, according to the computer tomography (CT) data, the lungs state improvement and eliminates the virus in more than 90% of patients. All these factors contribute to the acceleration of recovery. Timely initiation of therapy with favipiravir (Areplivir) improves the prognosis of the disease and reduces the global socio-economic burden of the current pandemic [8, 9].

The scheme of the early and effective direct etiotropic favipiravir therapy at the outpatient stage, preserved in the Interim Guidelines[1] for the Prevention, Diagnosis and Treatment of a New Coronavirus Infection, Version 15, takes priority and prevents the development of severe forms of infection.

The etiotropic therapy of acute respiratory viral infections in a pandemic, even with a negative polymerase chain reaction (PCR) test for COVID-19, is reasonable in comorbid patients in the context of preventing the pro-

[1] Interim guidelines “Prevention, diagnosis and treatment of a new coronavirus infection (COVID-19)”. Version No. 15 of 22 Feb 2022. Available from: https://static-0.minzdrav.gov.ru/system/attachments/attaches/000/059/392/original/BMP_COVID-19_V15.pdf. Russian

gression of the disease to a more severe form and the development of life-threatening conditions, minimizes the risk of post-infectious complications and improves the quality of patients' life [10, 12, 16].

It is important to study the long-term effects of favipiravir not only in terms of registering clinical differences (complication rates, etc.), but also through the analysis of immune-regulatory mechanisms, and, most significantly, in the group of patients with mild and moderate COVID-19 forms. Having pantropism and a proven importance in the COVID-19 pathogenesis, cytokines are relevant candidate molecules that determine post-COVID complications. The IL-6 family is being paid additional attention: a number of researchers argue that IL-6 is an independent predictor of severity and mortality from COVID-19 [17].

THE AIM of the article is to study long-term cytokine-mediated (IL-6/sIL6r and LIF/sLIFr) pathogenetic effects of the favipiravir (Areplivir®) based drug on the incidence of complications in patients with metabolic syndrome in the post-COVID period.

MATERIALS AND METHODS

With the approval of the local ethics committee at the National Research Ogarev Mordovia State University (Protocol No. 5 dated May 17, 2020) "An open prospective comparative study of the Areplivir (Favipiravir) drug effectiveness in reducing the risk of complications in the post-COVID period in patients with metabolic syndrome" in the Republic of Mordovia was carried out. The study included 190 metabolic syndrome patients who received the outpatient treatment for COVID-19 at Saransk polyclinics from February 2021 to March 2021. The case of COVID-19 was diagnosed in accordance with the current Temporary Guidelines for the prevention, diagnosis and treatment of the new coronavirus infection[2].

The study included patients of both sexes aged 50-65 years with laboratory and clinically confirmed mild and moderate forms of the novel coronavirus infection, in combination with metabolic syndrome (AH, the increased body mass index), established before the SARS-CoV-2 infection. Previously, the blood pressure control had been reached with antihypertensive drugs and low-density lipoproteins (LDL) levels – with drugs from the statin group, in case the duration of COVID-19 before the prescription of treatment had lasted no more than 5 days. Two groups were formed as follows: the patients who, along with the anti-inflammatory, anticoagulant and symptomatic therapy, were administrated with the antiviral drug Areplivir® at the outpatient stage during the acute course of COVID-19; and a comparison group – the patients who, according to the Temporary Guidelines[3], were administrated with the basic anti-inflammatory, anticoagulant, symptomatic (antibacterial) therapy for the coronavirus infection, and did not receive, for various reasons, antiviral drugs.

The favipiravir based drug was administered 30 minutes before meals p. o., according to the following scheme. For the patients weighing less than 75 kg – 1600 mg (8 tablets) twice on the 1st day of therapy, then 600 mg (3 tablets) twice per day from the 2nd to the 10th day; for the patients weighing more than 75 kg – 1800 mg (9 tablets) twice on the 1st day of therapy, then, in accordance with the instructions for use of the medicinal product, 800 mg (4 tablets) twice per day from the 2nd to the 10th day of therapy)[4].

The exclusion criteria were: associated clinical conditions in past medical history – acute cerebrovascular accident (CVA), myocardial infarction (MI), angina pectoris, coronary revascularization, renal failure, type 1 diabetes mellitus, autoimmune, allergic diseases, symptomatic hypertension, use of glucocorticosteroids, hydroxychloroquine, other antiviral drugs (except Areplivir®) and / or immunomodulators at the outpatient stage, a history of vaccination for the prevention of COVID-19, a patient's refusal to a long-term participation in the study.

Within one year (once every 2 months), at the post-COVID stage, 170 patients of these groups were interviewed with the registration of the post-COVID period features according to the developed questionnaire and the verification of the changes based on the outpatient records analysis. Within one year on days 10, 30 and 180 after a clinical and laboratory recovery (2 negative PCR test results for coronavirus RNA), all patients underwent blood sampling with the entry into the outpatient cards to determine the levels of ALT, AST, blood creatinine to calculate glomerular filtration, as well as the LDL control. The patients' characteristics at the time of the acute period of COVID-19 are presented in Table 1. The mean age of patients was 59 (95% CI [50–65]) years.

Obtaining biological material (blood) for the study, was carried out taking into account the provisions of World Medical Association's Declaration of Helsinki[5] (2013) and the protocol of the Convention of the Council of Europe on Human Rights and Biomedicine (1999), taking into account the additional protocol to the Convention on Human Rights and Biomedicine in the field of biomedical testing[6] (2005). Additional blood sampling in this category of patients was carried out after two negative PCR results on the presence of SARS CoV-2 virus RNA on days 10, 60, 180 in the morning on an empty stomach

[2] Interim guidelines "Prevention, diagnosis and treatment of a new coronavirus infection (COVID-19)". Version No.13.1 of 09 Nov 2021). Available from: https://static-0.minzdrav.gov.ru/system/attachments/attaches/000/058/211/original/BMP-13.pdf. Russian

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(12 hours without eating). The blood was centrifuged, followed by separation of the serum and storage in labeled test tubes at -30°C for no more than 45 days. Then, the parameters were analyzed, their choice had been justified by the data of the previously conducted study of their own, including 32 cytokines and 5 vasoactive substances (NO, SDMA, ADMA, iNOS, eNOS). They demonstrated the significance of the blood levels role of IL-6 family members in the pathogenesis of cardiovascular complications [5], as well as the literature data on the pathogenetic role of representatives of the IL-6 family in the pathogenesis of COVID-19 [18].

The levels of cytokines (IL-6, sIL-6r, LIF, sLIFr), as well as vasoactive substances (NO, SDMA, ADMA, iNOS, eNOS) were determined by the enzyme-linked immunoelectrodiffusion essay (ELISA) in the laboratory of the Department of Immunology, Microbiology, Virology with a course of clinical immunology and Allergology at the National Research Ogarev Mordovia State University on the enzyme immunoassay analyzer "Personal Lab TM" (Adaltis, Italy). The following test systems were used: LIF (eBioscience (Bender MedSystems, Austria) – the analytical sensitivity of the test system: 0.66 pg/ml, the Detection interval: 0.66–200 pg/ml; sLIF-R/gp190 (eBioscience (Bender MedSystems, Austria) Austria) – the analytical sensitivity of the test system: 0.052 ng/ml, the detection interval: 0.052–5 ng/ml; IL-6 (eBioscience (Bender MedSystems, Austria) – the detection interval: 0.92–100 pg/ml, the analytical sensitivity test system: 0.92 pg/ml; sIL-6R (eBioscience (Bender MedSystems, Austria) – the analytical sensitivity of the test system: 0.01 ng/ml, the detection interval: 0.01–5 ng/ml; NO (R&D Systems, USA) – the detection interval: 0.78–200 µmol/L, the analytical sensitivity of the test system: 0.78-200 µmol/L; iNOS (USCN Life Science, Malaysia) – the detection interval: 0.064–10 ng/L ml, the analytical sensitivity of the test system: 0.064 ng/ml; eNOS (USCN Life Science, Malaysia) – the detection interval: 5.5–1000 pg/ml, the analytical sensitivity of the test system: 5.5 pg/ml; ADMA (Imm undiagnostik, Germany) – the detection interval: 0.0–2 µmol/l, the analytical sensitivity of the test system: 0.04 µmol/l; SDMA (Immundiagnostik, Germany) – the detection interval: 0.05-4 µmol/l, the sensitivity: 0.05 µmol/l.

Based on the results of non-invasive arteriography, the following indicators were analyzed: SPVkf, as well as calculated hemodynamic parameters with the introduction of the EchoCG data: PVR (DIN * sec / ml) = 1332 * Mean BP / Minute blood volume[7].

Statistical processing of results

Statistical processing of the obtained data was carried out using Stat Soft Statistica 13.5. Results are shown with median (Me) and percentiles (Q 0.25–Q 0.75). The distribution of the indicators differed from the normal distribution of Gauss – Laplace, therefore, when comparing the dependent samples, the Wilcoxon test was used; for the unrelated samples, it was the Mann-Whitney U-test, the Spearman's correlation coefficient (significant at $p<0.05$). The absolute and relative risks were calculated with the determination of 95% confidence interval (CI), the sensitivity and specificity (χ^2). A multivariate correlation analysis was carried out based on the construction of the Cox regression model.

RESULTS

Within a year after suffering COVID-19, the observational analysis of patients with MS (AH, an increased body mass index) revealed significant differences in the incidence of complications depending on the intake of the drug from the favipiravir group. Thus, the patients whose therapy regimens included favipiravir at the outpatient stage were characterized by a decrease in the incidence of ACVE and ACS by 2.66 times (Table 2). Despite the risks of concomitant diseases complications due to timely viral load relief, in a greater number of cases, the patients in this group compared with the group without antiviral therapy, retained glucose tolerance without taking hypoglycemic drugs and control of blood pressure levels without changing antihypertensive drug regimens. The results obtained were statically confirmed based on the calculation of Pearson's coefficient and the assessment of the strength of the revealed correlations. The maximum strength of the correlation was determined between taking favipiravir and a decrease in the frequency of an increase in the LDL blood level when compared with the period before the SARS-CoV-2 infection (Table 2). That indicates a positive protective effect of favipiravir therapy on the patients' lipid profile. Herewith, there were no significant differences in the frequency analysis of the decrease in GFR and an increase in ALT, AST and bilirubin ($p>0.05$) in the patients of both groups. That confirms the available data on a favorable safety profile of the therapy even in comorbid patients.

In the authors' previous studies, a significant effect of changes in the level of cytokines on the pathogenesis of cardiovascular complications (ACVE, transient cerebrovascular accidents with a cognitive decline, acute coronary syndrome) in AH patients at stage II in the post-COVID period, was shown [5]. The recent publications also describe the role of members of the IL-6 family in the pathogenesis of COVID-19 [18]. To understand the immunopathogenesis of the above listed complications and reduce the risk of their development when using a favipiravir based drug in the patients in the acute stage of COVID-19, the content dynamics of IL-6 /sIL6r and LIF/sLIFr in the peripheral blood serum, was analyzed (Table 3).

[7] Savitsky NN. Biofizicheskie osnovy krovoobrashcheniya i klinicheskie metody izucheniya gemodinamiki [Biophysical bases of blood circulation and clinical methods for studying hemodynamics]. Medical Sciences Academy of the USSR. 3rd ed., rev. and addit. Leningrad: Medicine. Leningrad. dept. 1974: 311 p. Russian

Table 1 – Characteristics of COVID-19 patients (Me [$Q_{25\%}$–$Q_{75\%}$]) included in the study

Parameters of patients' anamnesis and conditions	Without taking antiviral drugs at the outpatient stage (n=64)	Taking favipiravir at the outpatient stage (n=68)
Illness-term before therapy (days)	4.16 [2.17–5.22]	4.17 [2.91–4.56]
Maximum percentage of lungs damage during disease period (%)	12.7 [6–28.2]	8.12 [5.24–27.2]
Presence of comorbid diseases	–	–
AH	100%	100%
Past medical history of type 2 diabetes mellitus	40%	100%
Obesity	100%	100%
BMI	37.4 [35.2–40.4]	38.9 [36.3–42.7]
SpO_2, %	97.98 [96.4–98.6]	98.1 [96.3–99]
C-, mg/l	6.43 [6.65–9.13]	5.46 [4.05–8.54]
D-dimer, ng/ml	238 [196–435]	223 [187–305]
Glucose, mmol/l	4.41 [2.8–5.2]	4.23 [2.72–5.92]
Hemoglobin, g/l	125 [112–137]	122 [117–141]

Table 2 – Analysis of correlation between complications development depending on the use of favipiravir based drug for COVID-19 (Me [$Q_{5\%}$–$Q_{95\%}$]) in MS patients, in post-COVID period

Indicators	Favipiravir (n=68)	No antivirals (n=64)
Numbers of ACVEs and ACSs	3	12
Relative Risk	2.66 [1.23–14.1] * (Se-0.8, Sp-0,55), χ^2=6.73 (p=0.01), medium correlation	
First recorded increase in blood glucose above 10 against the background of diet and / or use of hypoglycemic agents	5	13
Relative Risk	2.72 [1.03–7.2] * (Se-0.72, Sp-0.54) χ^2=4.7 (p=0.031), medium correlation	
Changing antihypertensive therapy regimen due to its inefficiency	9	27
Relative Risk	3.19 [1.63–6.25]* (Se-0.75, Sp-0.61) χ^2=13.9 (p<0.001), relatively strong correlation	
Increase in LDL levels	9	24
Relative Risk	2.83 [1.43–5.62]* (Se-0.73, Sp-0.6) χ^2=10.3 (p=0.002), medium correlation	
Increase in ALT, AST, bilirubin	6	5
Relative Risk	0.88 [0.28–2.76] (Se-0.45, Sp-0.51) χ^2=0.044 (p=0.83), insignificant correlation	
Decrease in GFR	6	4
Relative risk	0.7 [0.21–2.39] (Se-0.4, Sp-0.51) χ^2=0.31 (p=0.58), insignificant correlation	

Note: * – significant difference in the analysis of risk ratios.

Table 3 – Dynamics of changes in the content of IL-6 family cytokines depending on the intake of favipiravir based drug for COVID-19 Me [$Q_{25\%}$–$Q_{75\%}$], in MS patients in post-COVID period

Therapy	Favipiravir (n=68)			No antivirals (n=64)		
Period	In 10 days	In 30 days	In 180 days	In 10 days	In 30 days	In 180 days
IL-6, pg/ml	24.2 [22.8–27.3]	16.8*[1] [14.1–21.4]	13.1*[1,2] [10.7–16.3]	34.2 *[1] [28.5–36.7]	25.9*[2,4] [23.8–31.2]	25.1 *[3,4] [22.9–31.1]
sIL-6r, pg/ml	2160 [1548–2430]	1850'[1] [1240–2060]	1615*[1]^[2] [1470–1820]	3100 *[1] [2330–3470]	3620 *[2,4] [2980–4634]	2971 *[3,5] [2156–3365]
LIF, pg/ml	9.17 [8.23–11.3]	7.22 [6.2–9.24]*[1]	7.47 [6.15–9.12]*[1]	12.3 [10.3–14.8]*[1]	15.7*[2,4] [12.7–19.5]	15.5*[3,4] [11.2–18.7]
sLIFr, pg/ml	3520 [2980–4260]	4100'[1] [3420–4900]	2800 *[1,2] [2170–3120]	4810*[1] [3970–5530]	6200*[2,4] [4500–7610]	7460 *[3,4,5] [6120–9400]

Note: * – p<0.001, ^ – p<0.01, '– p<0.05 – significance level in accordance with the specified group based on the Wilcoxon test for related populations and the Mann-Whitney U-test for unrelated populations.

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Table 4 – Influence analysis of IL-6, sIL-6, LIF, LIFr contents in patients with stage II MS on the incidence of complications (95% CI) within 1 year after suffering COVID-19

Variables	Beta	Standard	t-value	Exponent Beta	Wald	P
IL-6 (>23.8 pg/ml)	1.07	0.63	1.69	2.17	2.73	0.062
sIL-6r (>2212 pg/ml)	1.17	0.67	1.77	1.38	2.34	0.072
LIF (>9.78 pg/ml)	1.12	0.79	1.95	2.04	1.6	0.093
sLIFr (>5074 pg/ml)	2.29	0.33	6.93	4.75	13.3	0.009

Note: Cox regression model and multivariate analysis are presented.

Table 5 – Correlation matrix of cytokine content in peripheral blood serum and hemodynamic parameters in MS patients in post-COVID period

Interleukine / Indicators	IL-6	sIL-6r	LIF	sLIFr
NO	0.64. p<0.05	0.46 p>0.05	0.49 p<0.05	–0.47 p<0.05
ADMA	0.52. p>0.05	0.4 p>0.05	0.58 p<0.05	0.86 p<0.001
SDMA	0.34. p>0.05	0.29 p>0.05	0.16 p>0.05	0.88 p<0.001
eNOS	–0.62 p<0.05	–0.67 p<0.05	–0.12 p>0.05	–0.72 p <0.001
iNOS	0.78 p<0.001	0.49 p>0.05	0.51 p<0.05	0.36 p>0.05
PVR	0.55 p<0.05	0.39 p>0.05	0.89 p<0.001	0.81 p<0.001
PWVcf	0.51 p<0.05	0.34 p>0.05	0.51 p<0.05	0.87 p<0.001

The table shows that the patients administrated with Areplivir at the early stage of infection, were characterized by lower serum levels of the four members of the IL-6 family (IL-6, sIL6r and LIF, sLIFr) 10 days after their clinical and laboratory recovery (p<0.001). This pattern persisted 30 and 180 days after COVID-19. Significant differences in the dynamics of cytokine parameters were revealed. In the patients administrated with Areplivir in past medical history, a dynamic decrease in IL-6 and its soluble receptor is recorded both in the interval from day 10 to day 30 (by 31 and 25%, respectively) and from day 30 to day 180 (by 19 and 23%, respectively) after suffering COVID-19. In the persons not administrated with antiviral drugs, the dynamics was different: a decrease in IL-6 from day 10 to day 30 by 24% (p<0.01), but there was no dynamics from day 30 to day 180 (p>0.05). The concentration of sIL-6r in the blood was characterized by an increase by 24% in the interval from day 10 to day 30 (p<0.001) and a decrease up to the level of day 10 in the period from day 30 to day 180 (Table 3). The presented average statistical patterns of changes in the IL-6 /sIL6r system are typical for 90% (77 people out of 86) from the group taking the favipiravir based drug during the COVID-19 period, and 85% (54 people out of 64) from the group not taking antiviral drugs. The differences were statistically significant (p<0.01).

Thus, the advisability of the early etiotropic favipiravir based therapy was also shown in terms of reducing the risk of developing long-term consequences of the coronavirus infection.

In the comparison of groups, the indicators analysis of the LIF system and its soluble receptor revealed multidirectional dynamics of changes. The patients taking the favipiravir-based drug are characterized by a decrease in serum LIF from day 10 to day 30 by 22% (p<0.001), but there was no further decrease from day 30 to day 180. The patients without taking antiviral drugs in past medical history were characterized by an increase in peripheral serum LIF content in the period from day 10 to day 30 by 22% (p<0.001), without dynamics – from day 30 to day 180. In the favipiravir group, there was a slight increase in the sLIFr levels from day 10 to day 30 by 24%, with a pronounced decrease by 32% (p<0.001) from day 30 to day 180. In the group without favipiravir in past medical history, there was an increase in the content of sLIF in the blood serum from day 10 to day 30 by 23% and from day 30 to day 180 by 17%, (p<0.001). It is important to note the importance of the analysis of patients' individual indicators. Thus, in the group with an official favipiravir intake in past medical history, 4 out of 68 patients were characterized by individual dynamics corresponding to the patients without antiviral drugs. There was an increase in the sLIFr serum by 23% from day 10 to day 30 and by 21% from day 30 to day 180; 3 of them suffered a stroke during the next 6 months of the observation. Herewith, in 10 patients from the group without favipiravir in past medical history, there was an increase in sLIFr by 54% from day 10 to day 30 and by 48% from day 30 to day 180; 8 of them suffered ACVE and ACS in the subsequent observation period. The data obtained confirm the hypothesis of a negative impact of the growth of the above listed indicators on the prognosis, and serve as a rationale for the positive pathogenetic effect of the early favipiravir therapy on reducing the risk of ACVE and ACS in the post-COVID period even in the patients with comorbid conditions.

Taking into account the identified potential correllations between the degree of increase in the content of IL-6 family cytokines in the blood serum and the risk of complications in the post-COVID period, a multivariate correlation analysis was carried out in order to identify the most significant marker for the development of cardiovascular complications of the coronavirus infection. The critical levels for entering the analyses system were determined based on the interquartile analysis data (Table 4). The obtained results demonstrate an increase in the blood serum of MS patients in the post-COVID period of the sLIFr level, which has the greatest influence (among the IL-6representatives) on the increase in the risk of developing cardiovascular complications during a year after COVID-19. The above-described pathological processes are observed in the group of patients without taking antiviral drugs in past medical history. In order to construct a potential pathogenetic scheme, taking into account MS as a symptom complex on the basis of which, after COVID-19, cardiovascular complications developed in some patients, an analysis of the correlations of the analyzed cytokines with vasoactive substances (NO ADMA, SDMA, eNOS, iNOS) and indicators, reflecting peripheral vascular resistance – OPSS and PWVcf, was made (Table 5). ADMA and SDMA are markers of the endothelial dysfunction and blockers of the NO synthesis by reducing the eNOS formation [19]. ADMA acts as an oxidative stress mediator by downregulating eNOS and uncoupling NO synthesis pathways [20], increasing the expression of inflammatory genes. It was fouare nd out that in MS patients in the post-COVID period, the most pronounced ($p<0.001$) relationships are between an increase of sLIF in the peripheral blood serum and the levels of conditioned vasopressors ADMA and SDMA with a secondary decrease in the vasorelaxant eNOS, as well as an increase in the functional parameters of TPVR and PWVcf. Symmetrical correlation lines but of lesser strength ($p<0.05$) were registered for LIF. It is important to note that IL-6 blood levels are directly associated with an increase in iNOS ($p<0.001$) without correlation with ADMA and SDMA ($p>0.05$). The presented data demonstrate the potential of the early antiviral therapy in terms of blocking the post-COVID immunopathogenetic vector – "COVID-19 in anamnesis-growth of IL-6 family members-increase in vasopressors-decrease in-eNOS induced nitric oxide."

DISCUSSION

The problem of complications development in comorbid patients in the post-COVID period is becoming increasingly relevant [21]. At the same time, persistent endotheliopathy during recovery is not limited to those who have experienced severe COVID-19 [21], which updates the information obtained in the present study. An important aspect is the analysis aimed at identifying the factors of the acute infectious period, such as components of therapy and / or the use of additional methods for assessing the laboratory / functional characteristics of the pathological process, which are associated with a change in the incidence of complications after suffering COVID-19. A dynamic observation of patients for 1 year in the post-COVID period, demonstrates a decrease in the frequency of both cardiovascular complications (ACVE, transient cerebrovascular accidents with a cognitive decline, acute coronary syndrome), and the risk of increased blood glucose and LDL levels, the growth of which is a prognostic marker for the development of cardiovascular complications. These effects are undoubtedly pathogenetically associated with a decrease in the viral replication and viral load [22–26] with a secondary blocking of the components of a potentially excessive cytokine response, which was demonstrated in this study using representatives of the IL-6 family as an example.

It is important to note that the study included only MS patients under clinically comparable COVID-19 medical treatment, regardless of taking an antiviral drug. But a deeper study of a cytokine regulation of the post-COVID period revealed fundamental differences in this group. Higher peripheral blood serum levels of both IL-6 and its soluble receptor (sIL-6r), which expands the spectrum of cells sensitive to this cytokine (endothelial cells are a significant component in the development of hypertension), express gp130 and not IL-6R. Therefore, these cells can respond to IL-6 only in the presence of sIL-6R [27], which is pathogenetically associated with a decrease in a significant NO vasorelaxant that determines the progression of atherosclerosis and an endothelial dysfunction with changes in the vascular tone (the study revealed the relationship of this cytokine with PVR and PWVcf). At the same time, it is important to note the change in the dynamic characteristics of IL-6: in the patients taking favipiravir during the acute infection period, a decrease in this cytokine in the blood is observed from day 10 to day 180 in the post-COVID period. At the same time, in the group without antiviral drugs, despite a decrease in the concentration of IL-6 in the first 30 days, a "plateau" is subsequently recorded, and the decrease in the level of the "dangerous" cytokine stops at the values that exceed those in the group with favipiravir. Moreover, persistent elevated levels of IL-6 are accompanied by an increase in soluble IL-6 receptor up to day 30 in the post-COVID period. Thus, the absence of the etiotropic therapy in the acute period of an infectious disease increases the risk of the components progression of the metabolic syndrome (AH, dyslipidemia, etc.).

The data on a long-term increase in IL-6 (3 or more months) in the post-COVID period and the association of this imbalance with symptoms of chronic fatigue, headaches, and changes in the metabolic processes of the brain indicating a greater degree of severity in women, have been published [28]. So, in the study by Durstenfeld M.S. et al., a hypothesis about the significance of the drugs aimed at blocking IL-6 in the post-

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COVID period and indicating the importance of studying all immunopathophysiological processes associated with the IL-6 family, is expressed [29]. In particular, IL-6 itself promotes myocardial hypertrophy through the gp130 stimulation, activates the transcription through STAT3, causing adverse effects on the progression of a heart failure [30, 31] and hypertension as an MS component. A long-term pronounced physiological decrease in IL-6 observed in the patients taking Areplivir at the early stages of a COVID infection, indicates a decrease in the risk of developing not only life-threatening diseases (a heart failure, ACVE, etc.), but also the conditions that sharply worsen the quality of patients' life (chronic fatigue, headaches, etc.).

The data on changes in the LIF/sLIFr system due to their multidirectional dynamics in the post-COVID period in MS patients, depending on the past medical history of taking a favipiravir-based drug, are of great interest. LIF is a pleiotropic cytokine of the IL-6 family, the effect of which depends on the localization of the target cells [29]. The role of LIF in the regulation of the cardiovascular system has been described [29]. In the first month after COVID-19, an increase in the LIF and sLIFr peripheral blood serum is blocked in the group of patients taking a favipiravir-based drug, while in MS patients who did not undergo the antiviral therapy; an increase in the level of the above-mentioned indicators is recorded. At the same time, the data on the LIF effect on the vascular wall in AH are controversial [32,33], since against the background of the increased blood pressure, the LIF effects are distorted with the abolition of protection against the myocardium and endothelium. According to the data presented in the article, LIF correlates with the NO, SDMA level, thereby confirming the previously put forward hypothesis about the negative effect of this cytokine growth in the blood serum of patients with hypertension, including the ones within MS.

When analyzing the relationships between the studied cytokines and the frequency of cardiovascular complications, a multivariate correlation analysis revealed the priority of an increase in sLIFr in the peripheral blood serum as a risk marker of the developing ACVE and MI. sLIFr is a factor with a potentially antagonistic effect on LIF [34]. At the same time, in the earlier studies, there were the data on potential intrinsic sLIFr effects which have been undeservedly not studied [35,36] though their search is relevant. Previously, the research group published the data [37] demonstrating negative dose-dependent sLIF effects (at the level of more than 4800 pg/ml) on the AH progression, including the ones through positive correlations with SDMA and ADMA. That has also been confirmed in MS patients in the post-COVID period. In the patients without the antiviral therapy, the quantitative characteristics of the sLIF content in the post-COVID period correspond to a pathogenetically critical level (more than 4800 pg/ml) with a further increase and a correlation with an increase in SDMA and ADMA against the background of a decrease in NO and eNOS. That was clinically accompanied by a deterioration in the severity of the metabolic syndrome components.

It should be noted that an important component of the study was the analysis of hepatorenal complications. Their frequency did not differ in the groups of patients who received and the ones who did not receive favipiravir, which indicates a high safety profile of the therapy.

The most important protective effect of the early etiotropic therapy based on favipiravir is a significant reduction in the incidence of cardiovascular complications (ACS, ACVE) in the post-COVID period, which can be explained by blocking the components of the analyzed vector: "the iNO-dependent progression of the endothelial dysfunction – tissue remodeling of the cardiovascular complex – cardiovascular complications". According to Merkler A.E. et al. [38], the frequency of cerebral strokes in the post-COVID period reaches 1.6% and is 8 times higher than the frequency of similar complications in patients with influenza. It is assumed that this is due to the development of the acute endothelial dysfunction and a shift of hemostasis to the procoagulant side in COVID-19. Taking into account the number of patients who have survived a novel coronavirus infection, and the cost of one completed case of treating a patient with an ischemic stroke[8], the economic burden of ACVE alone associated with the suffered COVID-19 may be more than 20 billion rubles over the past pandemic period. Taking into account the above-mentioned results of the present study, the earlier administration of the favipiravir-based etiotropic therapy is appropriate not only clinically, but also pharmacoeconomically, by minimizing the risks of post-COVID complications, especially in comorbid patients.

CONCLUSION

It is important that the COVID-19 therapy regimen determines not only the risk of a severe and an extremely severe course of an infectious disease, but can directly affect the risk of both the progression of the patient's concomitant diseases and the development of new pathological conditions in the post-COVID period.

The Areplivir therapy in the acute period of the coronavirus infection allows a timely reduction of the viral load, which contributes to the correction of the pro-inflammatory vector of the immune response at the post-COVID stage. Accordingly, it reduces the risk of the atherosclerosis progression, transient cerebrovascular accidents with a cognitive decline, an endothelial dysfunction, and can be considered as a secondary prevention of cardiovascular complications.

The study provides valuable information on the complication patterns seen in after COVID-19 patients in

[8] Decree of the Government of the Russian Federation of December 7, 2019 No.1610 "On the Program of State Guarantees of Free Provision of Medical Care to Citizens for 2020 and for the Planning Period of 2021 and 2022" (with amendments and additions). Available from: https://base.gar. Russian

clinical practice, and strengthens the evidence that the favipiravir-based drug can be considered in the context of a positive effect on minimizing the symptoms in the post-COVID period.

Taking into account the frequency of decrease in IL-6 levels in the study drug group, it can be concluded that etiotropic therapy in the early stages helps to reduce the risk of life-threatening conditions and postcovid complications by 82% during the first year after COVID-19 in comorbid patients.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS CONTRIBUTION

Olga A. Radaeva – development and implementation of research design, research, aim setting, results analysis, text writing; Larisa A. Balykova – development and implementation of research design, text writing and editing; Kira Ya. Zaslavskaya – results analysis, text writing; Aleksey V. Taganov – results analysis, text editing; Petr A. Bely – results analysis; Yuliya A. Kostina – statistical processing of the experiment results; Elena V. Negodnova – statistical processing of the experiment results, study aim setting, results analysis; Svetlana V. Mashnina – statistical results processing, study aim setting, results analysis, Denis D. Bessheinov – statistical results processing, study aim setting, results analysis; Maria S. Iskandyarova – results analysis, text writing; Vitaliy V. Eremeev – control of material intake; Nikita M. Chumakov – statistical data processing.

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