



STUDY OF CLINICAL AND PATHOGENETIC EFFECTS OF ANTI-VIRAL DRUG BASED ON FAVIPIRAVIR IN COMORBID PATIENTS WITH COVID-19 AT THE OUTPATIENT STAGE OF TREATMENT

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In many ways, arterial hypertension and obesity determine the likelihood of a severe course and lethal outcomes in COVID-19. This fact justifies the expediency of an early use of drugs with a direct antiviral action, the analysis of their efficacy not only in the acute, but also in the postcovid period.

The aim of the research was to analyze the outpatient cards and case histories of the COVID-19 patients to study the effect of the early (up to the 5th day after the onset of the first symptoms of the disease) use of the drug based on favipiravir, on the frequency of patients' hospitalizations with arterial hypertension and obesity, as well as to determine the cytokine status characteristics of this patient category in the postcovid period.

Materials and methods. "An open prospective comparative study of the "Areplivir" (favipiravir) efficacy in the debut of COVID-19 in comorbid patients" was carried out in the Republic of Mordovia (the analysis of the hospitalizations frequency and blood levels of M-CSF, EPO in 218 patients, in terms of the use of the antiviral preparation).

Results. According to the results of the analysis, it was found out that, despite the presence of comorbid conditions that increase the risk of developing a severe course of COVID-19, i.e. obesity and essential arterial hypertension, in the group of patients taking favipiravir, the need for hospitalization was twice as low ($p < 0.05$), in relation to the comparison group. The analysis of the cytokine status revealed that in the postcovid period, in the group that took the drug based on favipiravir at the outpatient stage, the average level of M-CSF was significantly lower ($p > 0.05$), and EPO was higher ($p > 0.05$) than in the patients from the group "without antiviral drugs at the outpatient stage". Indirectly, according to the previously obtained data, that acts as a potential marker for reducing the risk of long-term cardiovascular complications of COVID-19.

Conclusion. This study showed that an early prescription of favipiravir contributes to a decrease in the rate of COVID-19 patients' hospitalization even against the background of concomitant hypertension and obesity, due to a decrease in the likelihood of moderate and severe courses of the disease, and also leads to an earlier objective and subjective recovery. The results demonstrated a high potential benefit of an early favipiravir use in the novel coronavirus infection and in the prevention of postcovid complications.

Keywords: favipiravir; COVID-19; novel coronavirus infection; Areplivir

Abbreviations: AH – arterial hypertension; DM – diabetes mellitus; ACA – Acute Cerebrovascular Accident; TCA – Transient Cerebrovascular Accident; MI – myocardial infarction; ALT – alanine aminotransferase; AspAT – aspartate aminotransferase; BMI – body mass index; CT – computerized tomography; PCR – polymerase chain reaction; ECG – electrocardiogram; VED – Vital and Essential Drugs; EAH – essential arterial hypertension; MCSF – macrophage colony stimulating factor; RNA – ribonucleic acid; enzyme-linked immunosorbent assay; ELISA – enzyme immunoassay; CI – confidence interval; GCS(s) – glucocorticosteroids; WHO – World Health Organization; TNF- α – tumor necrosis factor alpha; 1 β -IL β – interleukin.

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ИЗУЧЕНИЕ КЛИНИКО-ПАТОГЕНЕТИЧЕСКИХ ЭФФЕКТОВ ПРОТИВОВИРУСНОГО ПРЕПАРАТА НА ОСНОВЕ ФАВИПИРАВИРА У КОМОРБИДНЫХ ПАЦИЕНТОВ С COVID-19 НА АМБУЛАТОРНОМ ЭТАПЕ ЛЕЧЕНИЯ

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Артериальная гипертензия и ожирение, во многом, определяют вероятность тяжелого течения и летальных исходов при COVID-19. Этот факт обосновывает целесообразность раннего применения лекарственных средств прямого противовирусного действия с анализом эффективности не только в остром, но и постковидном периоде.

Цель. Провести анализ амбулаторных карт и историй болезни пациентов с COVID-19 для изучения влияния раннего (до 5-го дня от момента появления первых симптомов болезни) применения препарата на основе фавипиравира на частоту госпитализаций у пациентов с артериальной гипертензией и ожирением, а также определить особенности цитокинового статуса пациентов данной категории в постковидном периоде.

Материалы и методы. Проведено «Открытое проспективное сравнительное исследование эффективности применения препарата «Арепливир®» (фавипиравир) в дебюте COVID-19 у коморбидных пациентов» в Республике Мордовия (анализ частоты госпитализации и содержания в крови М-CSF, EPO у 218-ти больных в зависимости от применения противовирусного препарата).

Результаты. По результатам проведенного анализа установлено, что, не смотря на наличие коморбидных состояний, повышающих риск развития тяжелого течения COVID-19, а именно ожирения и эссенциальной артериальной гипертензии, в группе пациентов, принимавших фавипиравир, необходимость в госпитализации была в 2 раза ниже ($p < 0,05$), по отношению к группе сравнения. Анализ цитокинового статуса выявил, что в группе, принимавшей препарат на основе фавипиравира на амбулаторном этапе, средний уровень М-CSF в постковидном периоде был достоверно ниже ($p > 0,05$), а EPO – выше ($p > 0,05$), чем у пациентов из группы «без противовирусных препаратов на амбулаторном этапе», что косвенно, по полученным ранее данным, выступает потенциальным маркером снижения риска отдаленных сердечно-сосудистых осложнений COVID-19.

Заключение. Раннее назначение фавипиравира способствует снижению частоты госпитализации пациентов с COVID-19 даже на фоне сопутствующих АГ и ожирения из-за уменьшения вероятности среднетяжелого и тяжелого течения заболевания, а также приводит к более раннему объективному и субъективному выздоровлению. Показана высокая потенциальная польза раннего применения фавипиравира при новой коронавирусной инфекции и в отношении профилактики постковидных осложнений.

Ключевые слова: фавипиравир; COVID-19; новая коронавирусная инфекция; Арепливир

Список сокращений: АГ – артериальная гипертензия; СД – сахарный диабет; ОНМК – острое нарушение мозгового кровообращения; ТНМК – транзиторное нарушение мозгового кровообращения; ИМ – инфаркт миокарда; АЛТ – аланинаминотрансфераза; АСТ – аспартатаминотрансфераза; ИМТ – индекс массы тела; КТ – компьютерная томография; ПЦР – полимеразная цепная реакция; ЭКГ – электрокардиограмма; ЖНВЛП – жизненно необходимые важнейшие лекарственные препараты; ЭАГ – эссенциальная артериальная гипертензия; М-CSF – макрофагальный колониестимулирующий фактор; РНК – рибонуклеиновая кислота; ИФА – иммуноферментный анализ; ДИ – доверительный интервал; ГКС – глюкокортикостероиды; ВОЗ – Всемирная организация здравоохранения; TNF- α – фактор некроза опухоли альфа; 1 β -ИЛ – интерлейкин.

INTRODUCTION

The pandemic of the novel coronavirus infection continues to pose new challenges to the health care system. The issues of diagnosis and prevention of COVID-19 have been mainly determined, but the treatment strategies continue to be developed [1]. The latest six versions of the domestic temporary guidelines emphasize the need for early specific etiotropic therapy (including

favipiravir) at the outpatient stage of the disease (Temporary guidelines version 7–13¹).

Arterial hypertension and obesity (the most frequent comorbidities in coronavirus patients) mainly determine the likelihood of a severe course and lethal outcomes in COVID-19 [2]. This fact justifies the expediency

¹ Temporary guidelines "Prevention, diagnosis and treatment of new coronavirus infection (COVID-19)" of the Ministry of Health of Russia (version 13.1 of 11/09/2021). Russian

of an early use of drugs with a direct antiviral action, followed by the analysis of their efficacy not only in the acute, but also in the postcovid periods [3, 4].

Previously, the efficacy of favipiravir preparations had been established in terms of the rate of the virus elimination, positive dynamics of the lung tissue state according to the computerized tomography (CT) data during SARS-CoV-2 infection [5]. However, the published data demonstrating a decrease in the incidence of a severe course and lethal outcomes of the coronavirus infection while taking favipiravir drugs, are insufficient [6], especially in high-risk comorbid patients (with arterial hypertension, obesity, and diabetes mellitus). When carrying out a comparative analysis of the favipiravir and arbidol efficacy for the treatment of COVID-19, Chen S. et al. found out the following. In the patients with concomitant hypertension and/or diabetes mellitus in a moderate course of disease, the time period before the normalization of the body temperature and the disappearance of cough was significantly shorter in the group using favipiravir, compared with group using arbidol ($p < 0.001$) [7].

The published results demonstrate the maximum efficacy of antiviral therapy [8, 9] when carried out in the first 5 days of the disease, which actualizes the use of the drug and the analysis of its efficacy starting from the outpatient stage of treatment, especially in the patients at risk. That is why, by order of the Government of the Russian Federation dated October 14, 2021 No.2626-r², favipiravir was included in the List of Vital and Essential Drugs (VED), which made it possible to compensate for the costs of purchasing drugs from the compulsory medical insurance fund and start the treatment as soon as possible.

In the Republic of Mordovia, since September 2021, a complication of the situation with the novel coronavirus infection has been notified. So, in October 2021, according to recent reports of the autonomous public health care institution "Medical Information and Analytical Center for the Republic of Mordovia"*³, 13,414 cases³ of the novel coronavirus infection COVID-19 have been registered (1722.0 per 100 thousand population), which is 7098 cases more than in September 2021 (6316 cases – 810.8 per 100 thousand population). In other words, the increase in the incidence was 112.4%, and the features of the course of the coronavirus infection caused by the delta strain, are the rapid progression of the disease and a tendency to a severe course. In this situation, the Executive Board of the republic took a number of organizational measures in the form of an increase in the additional bed fund of the infectious profile by 185% (from 1503 to 2780 beds). Nevertheless, even in this situation, inpatient beds worked at full capacity, which actualized the need for a more active treatment of COVID-19 at the outpatient

stage to potentially reduce the number of patients requiring hospitalization. As a part of the charitable program, on 01.10.2021 and 12.10.2021, the Ministry of Health of the Republic of Mordovia received 16,038 packages of the drug "Favipiravir" (Areplivir®) (film-coated tablets, 200 mg No. 40) for the outpatient treatment of the novel coronavirus infection, which made it possible to determine the aim of the study.

THE AIM of the research was to analyze the outpatient cards and case histories of the COVID-19 patients to study the effect of the early (up to the 5th day after the onset of the first symptoms of the disease) use of the drug based on favipiravir, on the frequency of patients' hospitalizations with arterial hypertension and obesity, as well as to determine the cytokine status characteristics of this patient category in the postcovid period.

MATERIALS AND METHODS

Approval by the local ethics committee at National Research Ogarev Mordovia State University (Protocol No. 5 dated May 17, 2020) "An open prospective comparative study of the efficacy of the drug "Areplivir®" (favipiravir) in the debut of COVID-19 in comorbid patients" was conducted in the Republic of Mordovia. The study included 1200 patients who received outpatient treatment at the outpatient clinics of Saransk. For 340 hospitalized patients of them, the data from the case histories from March to May 2021, as well as during October 2021 (the time of the maximum use of favipiravir at the outpatient stage), were analyzed. The COVID-19 diagnosis was aligned with the current interim guidelines for the prevention, diagnosis and treatment of the novel coronavirus infection⁴.

The study included patients of both sexes with laboratory and / or clinically confirmed new mild and moderate kinds of coronavirus infection. They were aged 48-80 years, suffered from the combination of obesity and essential arterial hypertension (EAH), stage II, established before getting infected with SARS-CoV-2 and controlled by antihypertensive drugs. Herewith, a duration of COVID-19 before treatment was to be no longer than 5 days. 2 groups of patients were formed. The comparison group consisted of the patients who received basic anti-inflammatory, anticoagulant, symptomatic (according to the indications – antibacterial) therapy for the coronavirus infection, according to temporary guidelines⁵, and the ones who did not receive, for various reasons, antiviral drugs. The second group consisted of the patients selected according to the case-control type, who, alongside with anti-inflammatory, anticoagulant and symptomatic therapy, received the antiviral drug Areplivir® already at the outpatient stage.

In accordance with the instructions for the use of a medicinal product, the drug based on favipiravir, was to be administered orally 30 minutes before meals, accord-

² Order of the Government of the Russian Federation dated 12.10.2020 No.2626-r. Available from: <http://publication.pravo.gov.ru/Document/View/0001202010140014>. (Date of access 24 Nov 2021). Russian

³ GAUZ of the Republic of Mordovia "Medical Information and Analytical Center". Available from: <http://miacrm.ru>.

⁴ Temporary guidelines "Prevention, diagnosis and treatment of new coronavirus infection (COVID-19)" of the Ministry of Health of Russia (version 13.1 of 11/09/2021). Russian

⁵ Ibid.

ing to the following scheme: the patients weighing less than 75 kg were to be administrated with 1600 mg (8 tablets) twice on the 1st day of therapy, then, from the 2nd to the 10th day – 600 mg (3 tablets) twice/day; the patients weighing more than 75 kg were to be administrated with 1800 mg (9 tablets) twice on the 1st day of therapy, then (from the 2nd to the 10th day of therapy) – 800 mg (4 tablets) twice/day)⁶.

The exclusion criteria were: the history of associated clinical conditions – acute cerebrovascular accidents (ACVs), myocardial infarction (MI), angina pectoris, coronary revascularization, renal failure, type 1 diabetes mellitus, autoimmune, allergic diseases, symptomatic hypertension, the use of glucocorticosteroids, hydroxyl-chloroquine, the use of other antiviral drugs (except “Areplivir®”) and/or immunomodulators at the outpatient stage, vaccination for the prevention of COVID-19 in history, a patient’s refusal from a long-term participation in the study. At the postcovid stage, for 4 months (once every 2 months), a survey of 218 patients of the indicated groups was carried out, with the registration of the features of the postcovid period according to the developed questionnaire and the verification of the changes based on the analysis of the outpatient records. The indicator of “the number of days before the subjective recovery” was assessed according to the period, which was named by the patient during the telephone survey, subjectively notifying the restoration to working condition. From the 1st day of health encounter, after signing a written informed consent, a blood sample was taken with the release of serum, which was frozen for storage and subsequent determination of the level of cytokines. There were 48 patients (out of 91) whose treatment had been completed without hospitalization and who were taking favipiravir on the outpatient basis, and 42 patients (out of 53) who were not taking any antiviral drugs. During the period of therapy, the analysis of the outpatient records focused on the levels of ALT, AST, and blood creatinine with the calculation of the glomerular filtration rate, as well as the control of dyspeptic complaints of all the patients, was carried out. The characteristics of the patients included in the study, are presented in Table 1.

Obtaining biological material (blood) for research was carried out taking into account the provisions of the Helsinki Declaration of the World Medical Association (WMA) (2013)⁷ and the Protocol of the Council of Europe Convention 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 research (2005)⁸. In this cate-

gory of patients, additional blood sampling was carried out 10, 60, 180 days after two negative results of the polymerase chain reaction (PCR) for the presence of SARS CoV-2 RNA in the morning on an empty stomach (12 hours without food). The blood was centrifuged, followed by separation of serum and storage in labeled tubes at –30°C for no longer than 45 days. The levels of erythropoietin (EPO) and the macrophage colony-stimulating factor (MCSF) were determined by ELISA in the laboratory of the Department of Immunology, Microbiology, Virology of National Research Ogarev Mordovia State University on an enzyme immunoassay analyzer “Personal Lab TM” (Adaltis, Italy). The choice of the above-listed cytokines is based on the data of the authors’ earlier studies, which included 32 cytokines. The research is devoted to the study of the cytokine-dependent mechanisms of the essential arterial hypertension progression (10 years of 480 patients’ dynamic follow-up), with the inclusion of the analysis in the period after the coronavirus infection (1.5 years of the dynamics). This made it possible to identify the prognostic significance of an increase in MCSF (above 389 pg/ml) [4] and a decrease in EPO as risk factors for cardiovascular complications in patients with EAH in the postcovid period, and the markers of the efficacy of the outpatient use of favipiravir in relation to isolated COVID-19 related complications.

The average age of patients was 59 (75% CI [48–80]) years.

Statistical processing of results

Statistical processing of the data obtained was carried out using Stat Soft Statistica 13.5. The results are shown with the indication of the median (Me) and percentiles (Q 0.25–Q 0.75). The distribution of indicators differed from the normal Gaussian-Laplace distribution, therefore, when comparing dependent samples, the Wilcoxon test was used; for unconnected samples, the Mann-Whitney U-test. Absolute and relative risks were calculated with determination of 95% confidence interval (CI), sensitivity and specificity, χ^2 with Yates correction.

RESULTS

According to the results of the analysis, it was found out that, despite the presence of comorbid conditions that increase the risk of developing a severe course of COVID-19 – obesity and essential hypertension, in the group of patients taking favipiravir, the need for hospitalization was twice as low ($p < 0.05$), in relation to the comparison group (in the group “favipiravir” – 29 people were hospitalized (24.2%), in the group “without antiviral drugs” – 45 people (45.9%), including the decrease ($p < 0.01$) in the number of people with severe COVID-19 (hospitalization was carried out according to the criteria described in the recommendations⁹. As follows from the

⁶ State Register of Medicines of the Russian Federation. Areplivir®. Available from: <https://grls.rosminzdrav.ru/LP-007609-171121>. Russian

⁷ Association WM. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. JAMA. 2013;310(20):2191-4.

⁸ Kholodova EI, Turshuk LD. Bioethics and Human Rights: International Legal Regulation and Ways of its Implementation. Actual Problems of Russian Law. 2017;(3):193–198. Russian. DOI: 10.17803/1994-1471.2017.76.3.193-198.

⁹ Temporary guidelines “Prevention, diagnosis and treatment of new coronavirus infection (COVID-19)” of the Ministry of Health of Russia (version 13.1 of 11/09/2021). Russian

data presented in Table 2, during hospitalization against the background of the disease progression in patients who had not received antiviral drugs, the risk of a severe course of the disease was 3.36 times higher (95% CI [1.57–7.23]%). The sensitivity was 0.86; the specificity was 0.6, χ^2 with Yates' correction equal to 10 ($p=0.002$); Pearson's coefficient was 0.31 (the relationship was more moderate than in the patients receiving the drug based on favipiravir).

The early antiviral therapy based on favipiravir, reduces the length of a hospital stay: the number of bed-days without antiviral therapy at the outpatient stage is 21.7 days (18–31), with antiviral therapy (favipiravir) – 14.3 (9.7–17.1, $p<0.01$). It also increases the frequency of significant improvements in the lung tissue state according to the CT data on the 10th day of treatment. Positive dynamics in CT at discharge (by 2 or more points on the WHO scale) without antiviral therapy at the outpatient stage comprises 23 people (51.1%), with antiviral therapy (favipiravir) – 21 people (72.4%), $p<0.01$.

During the recovery period (2 and 4 months after the illness), the analysis of the telephone survey data determined a 2-fold decrease in the number of days before the subjective recovery in COVID-19 convalescents with hypertension and obesity, when starting antiviral therapy, no later than the 5th day of illness compared to the group without early antiviral therapy ($p<0.001$). In the group of patients who did not take antiviral drugs, in a greater number of cases (34 people (75.5%) versus 10 people (34.5%)), in the group with the early use of favipiravir at the stage of inpatient treatment, antibacterial drugs were prescribed due to the secondary bacterial infection.

The analysis of the cytokine status revealed that in the group who took the drug based on favipiravir at the outpatient stage, the average level of MCSF in the post-covid period was significantly lower ($p>0.05$), and EPO was higher ($p>0.05$) than in the patients from the group "without antiviral drugs at the outpatient stage" (Table 3). At the same time, at the onset of the disease, the patients of both groups were comparable in terms of the content of these cytokines.

The patients with COVID-19, concomitant EAH and obesity, who had not required hospitalization and had not taken outpatient antiviral drugs, had lower average serum EPO levels on days 10, 30 and 180 after clinical and laboratory recovery than the patients who had been treated with a drug based on favipiravir ($p<0.001$), at the outpatient stage. The opposite trend was revealed when analyzing the content of MCSF in blood serum: higher average levels of this cytokine were recorded in the patients "without antiviral therapy" with the progression of negative dynamics in the postcovid period.

Thus, even in patients with hypertension and obesity, at an early start of taking Areplivir®, there was no

imbalance in the production of the cytokines EPO and M-CSF, which indirectly, according to previously obtained data, may be a marker for reducing the risk of cardiovascular COVID-19 complications.

The results of the questionnaire (survey) of the coronavirus infection convalescents in hypertension and obesity patients who had received treatment on an outpatient basis without hospitalization 180 days after the recovery showed that at an early start of the antiviral therapy with a drug from the favipiravir group, the crisis course of hypertension was observed less frequently than in the control group. Moreover, in the considered group, there was no need to change the regimen and dose of antihypertensive drugs, less often symptoms of asthenia were observed: increased fatigue, weakness, dizziness, emotional lability, pain in joints and muscles (Table 4).

It is important to notify that in the group of COVID-19 and EAH convalescents who had not taken antiviral drugs at the outpatient stage of treatment (98 people) within 180 days of the observation after the clinical and laboratory recovery, 5 cases of cardiovascular complications (5.1%) were recorded: 3 cases were transient cerebrovascular accidents, 1 case was an acute cerebrovascular accident, 1 case was myocardial infarction. Of these, 4 patients were characterized by a significant (twice or more times) individual increase in the M-CSF content in the blood during the observation period against the background of a 35% decrease in EPO. In the group treated with favipiravir at the outpatient stage, there were no cases of cardiovascular complications during the convalescence period after COVID-19 (the patients with an individual increase in M-CSF blood by 100% or more were not identified).

Thus, on the one hand, an early initiation of favipiravir therapy reduced the risk of hospitalization and aggravation of the condition, and, on the other hand, it was beneficial in a faster recovery from the coronavirus infection and reduced risk of the associated cardiovascular complications.

According to the analysis of the outpatient records during the treatment of the acute phase of the coronavirus infection, an increase in the level of ALT and/or AST was detected in 4 patients out of 91 (4.39%) in the group taking the drug based on favipiravir and in 1 out of 53 (1, 88%) in the group "without antiviral drugs". Subjective complaints of nausea, heaviness in the right hypochondrium in the favipiravir group were notified in 8 people (8.79%), in the group "without antiviral drugs" – in 4 patients (7.55%). No increase in the level of creatinine (a glomerular filtration rate), and of urea above the reference values, was recorded. The data obtained, confirm the predictable favorable safety profile of the investigational drug based on favipiravir (Areplivir®) and are consistent with the data of the international studies [5, 7, 10, 11].

Table 1 – Characteristics of patients with COVID-19, included in the study

Patient history and condition parameters	Without anti-viral medication at the outpatient stage (n=98)	With anti-viral medication (favipiravir) at the outpatient stage (n=120)
Duration of illness before starting therapy (days)	3.12 [1.28–4.73]	3.17 [1.33–4.47]
Percentage of lung damage on the 5 th day of illness (%)	6.82 [0-10.7]	8.12 [0–13.2]
Presence of comorbid diseases	–	–
AH	100%	100%
Type 2 diabetes mellitus	31.6% (31 persons)	51.6% (62 persons)
Obesity	100%	100%
BMI	36.2 [34.2–39.6]	37.6 [35.4–40.5]
SpO ₂ , %	98.4 [97.6–99.8]	97.9 [96.3–99]
C-reactive protein, mg/l	6.3 [6.76–8.9]	5.7 [4.17–8.33]
D-dimer, ng/ml	242 [180–430]	310 [287–402]
Glucose, μ/L	5.41 [4.8–11.2]	6.22 [4.66–10.9]
Hematoglobin, g/l	125 [112–137]	122 [117–141]

Table 2 – Use of favipiravir group drugs at the outpatient stage and features of the COVID-19 course in patients with EAH and obesity (Me [Q_{25%}–Q_{75%}])

Groups considered	Group number	Number of disabled days	Time until temperature returns to normal (days)	Period to subjective recovery (days)*	Severity of the course, pers (%)
Patients without hospitalization during the period	–	–	Without GCS	–	–
Without antiviral therapy at the outpatient stage, n = 53 people	1	15.3 [12.4–18.8]	5.47 [4.32–7.45]	61 [32–95]	Mild course – 42 pers. (79.2%) Moderate course – 11 pers. (20.8%)
Use of Favipiravir at the outpatient stage, n = 91 people	2	12,7 [10.1–14.3]	3.78 [2.16–4.22]	31 [16–49]	Mild course – 84 pers. (92.3%) Moderate course – 7 pers. (7.7%)
Statistical significance	–	p ¹⁻² <0.05	p ¹⁻² <0,05	p ¹⁻² <0,001	p ¹⁻² <0.05
The hospitalized after the 5 th day of outpatient therapy	–	–	With GCS	–	–
Without antiviral therapy at the outpatient stage, n=45 people	3	34,7 [21.5–42.1]	3,97 [2.45–4.23]	74 [41–120]	Moderate course – 21 (46.7%) Severe course – 22 (48.8%) CT-2 (4.5%)
Use of favipiravir at the outpatient stage, n=29 people	4	25.9 [15.2–28.4]	4.12 [2.66–4.68]	35 [29–58]	Moderate course – 20 (68.9%) Severe course – 8 (27.6%) CT-1 (3.5%)
Statistical significance	–	p ³⁻⁴ <0.01 p ¹⁻³ <0.001 p ²⁻⁴ <0.01	p ³⁻⁴ >0.05 p ¹⁻³ <0.05 p ²⁻⁴ >0.05	p ³⁻⁴ <0.01	p ³⁻⁴ <0.01

Note: * – according to the survey data after the laboratory recovery, the Mann-Whitney test was used for related aggregates; when specifying the degree of confidence.

Table 3 – Comparative characteristics of EPO and MCSF levels (pg/ml) in the blood serum of patients with hypertension and obesity 10, 30 and 180 days after COVID-19 (Me [Q_{25%}–Q_{75%}])

Without antiviral therapy, n=42 people	EPO	M-CSF
Initiation of therapy	98.3 [89,9–107]	287 [254–327]
10 days after recovery	102 [95.5–108]	587 [538–702]
30 days after recovery	105 [97.1–126]	724 [623–810]
180 days after recovery	127 [98.8–140]	742 [669–856]
Statistical significance	p>0.05 ^{1–2, 2–3, 3–4} p<0.05 ^{1–4}	p<0.001 ^{1–2, 1–3, 1–4, 2–3, 2–4} p>0.05 ^{3–4}
Favipiravir, n = 48 persons	EPO	M–CSF
Initiation of therapy	95.4 [91,7–121]	307 [269–336]
10 days after recovery	148 [110–169]	297 [248–410]
30 days after recovery	162 [155–176]	307 [204–416]
180 days after recovery	177 [159–202]	299 [242–457]
Statistical significance	p>0.05 ^{1–5} p<0.05 ^{6–7, 7–8} p<0.001 ^{5–6, 5–7, 5–8, 2–6, 3–7, 4–8}	p>0.05 ^{1–5, 5–6, 5–7, 5–8, 6–7, 7–8, 6–8} p<0.001 ^{2–6, 3–7, 4–8}

Note: the confidence level in accordance with the specified group based on the Wilcoxon criterion for related aggregates and the Mann-Whitney U-test for unrelated aggregates).

Table 4 – Analysis of subjective and objective characteristics of patients with hypertension and obesity 180 days after suffering COVID-19 (without hospitalization)

Estimated characteristics	Without antiviral therapy, n=53 pers.	Favipiravir, n=91 pers.
Crisis course of AH	26 pers. (49%)	8 pers. (8.79%)
Changing antihypertensive therapy regimen	21 pers. (39.6%)	12 pers. (13.2%)
Fatigue	42 pers. (79.2%)	32 pers. (35.1%)
Dizziness	7 pers. (13.2%)	2 pers. (2.2 %)
Muscle and joint pain	24 pers. (45.3%)	14 pers. (15.4%)

Taking into account the ongoing charity event (16,672 packages of the drug were distributed among 8,336 sick patients), the analysis of the pharmaco-economic effect of increasing the frequency of the early prescription of Areplivir® in the Republic of Mordovia in the period from October 1, 2021 to November 1, 2021, revealed a decrease in the hospitalization rate by 1757 people for 1 month when compared with September 2021. So, according to the Ministry of Health of the Republic of Mordovia, despite the fact that the number of infected people during the period under review had increased by more than three times, the total number of patients in the need for the inpatient treatment (24/7 beds of an infectious profile), decreased from 49.3% to 36.2%. Taking into account the average cost of treating one patient in hospital under the compulsory medical insurance system in the Republic of Mordovia, this made it possible to reduce budgetary costs by more than 260 million rubles.

The tariff agreement in the system of compulsory health insurance of the Republic of Mordovia was validated on 02/14/2021 (as amended on 09/30/2021)]¹⁰.

¹⁰ Tariff agreement in the compulsory health insurance system of the Republic of Mordovia dated 02.14.2021 (as amended on 09.30.2021). Available from: <https://docs.cntd.ru/document/571071803>. Russian

Moreover, according to the presented study, the use of the drug based on favipiravir, made it possible to reduce the duration of hospital stay by more than 1.5 times compared to the group of the patients who had not received antiviral therapy at the outpatient stage, which provided additional budget savings. It is also worth noting a decrease in the burden on the social security system of citizens due to a decrease in the number of days of disability in the patients receiving favipiravir at the onset of the disease compared with patients without antiviral therapy.

DISCUSSION

To date, the results of more than 1,000 studies devoted to the research of the anticovid activity of drugs based on favipiravir, are available. At the same time, the data on the effect of the drug on such check points as mortality, duration of respiratory support, as well as the duration of virus elimination based on PCR results vary widely, which is confirmed by the results of published systematic reviews [12, 13].

By reference to the immunopathogenesis of COVID-19, a number of researchers emphasize the need to study the efficacy of drugs from the favipiravir group

for the early outpatient prescription [14,15], followed by the study of its effect on the frequency of hospitalizations. According to the data obtained, it was the early (up to 5 days from the onset of the first symptoms) use of favipiravir that twice reduced the frequency of hospitalizations in the group of comorbid COVID-19 patients against the background of hypertension and obesity as the conditions that increased the risk of a severe course and unfavorable outcomes of the coronavirus infection. This fact has undoubted clinical and social and medico-economic significance, given the difference in the costs of treating an outpatient and an inpatient. It is worth noting that, according to the instructions for medical use, the prescription of favipiravir is possible for both confirmed SARS-CoV-2, and for a probable case of the disease diagnosed on the basis of characteristic clinical symptoms, which is associated with the direct antiviral effect of the drug against a wide range of RNA-containing viruses.

The immunopathogenetic and clinical effects of a drug based on favipiravir proved in this study, are most likely mediated by the suppression of viral replications and a decrease in the peak viral load [16] due to the selective blockade of the key replication enzyme SARS-CoV-2, RNA-dependent RNA polymerase [17–20]), which increases the likelihood of an effective immune response without a hyperinflammatory phase. However, even in case of hospitalization with the progression of the disease in the group of patients with an early start of COVID-19 treatment using the drug favipiravir compared with the group without antiviral therapy, a decrease in the likelihood of a severe course of COVID-19 was determined. That emphasizes the beneficial effect of an early start of therapy on the characteristics of the inpatient stage. In addition, within the framework of this study, based on routine biochemical tests, the safety of using the drug based on favipiravir, has been confirmed once again.

A serious consequence of SARS-CoV-2 infection is an imbalance in the system of pro- and anti-inflammatory immunoregulatory peptides (cytokines), which can persist after the recovery and determine the progression of existing chronic diseases and pathological conditions, such as hypertension and atherosclerosis, as well as be a component of a postcoid syndrome.

The previously published data on the role of the M-CSF family members [22] in the progression of hypertension in the postvoid period, can explain the effect of antiviral drugs based on favipiravir not only on reducing the risk of severe COVID-19, but also in the aspect of preventing the progression of chronic diseases in the postcovid period, in particular the development of fatal and non-fatal cardiovascular complications. The relationship between the use of a drug based on favipiravir and the absence of a decrease in EPO in the period after COVID-19, opens up prospects for a new direction of scientific research: the effect of a therapy regimen on the characteris-

tics of the postcovid period in patients with hypertension and obesity. It is important to note that the data on a decrease in serum EPO levels were obtained in the group of patients who did not need hospitalization and were mainly characterized by a higher percentage of cases of a mild COVID-19 course despite the concomitant pathology. EPO is a factor that regulates not only erythropoiesis, but also a number of immune mechanisms due to the wide presentation of its receptors on the cells of the body. Tissue hypoxia, typical for patients with COVID-19, should activate the synthesis of this cytokine [23], but, as it has been established in the course of this study, in the patients receiving antiviral therapy at the onset of the disease, the dynamics notified was opposite.

A pathophysiological regulation of EPO and proinflammatory TNF- α , IL-1 β cytokines obeys the principle of a negative feedback [24]. Consequently, the revealed decrease in EPO in the patients who did not receive early antiviral therapy is associated with a decrease in the anti-inflammatory effect of this cytokine, which, possibly, determines a wider spectrum and frequency of manifestations of a postcovid syndrome identified in this category of patients. It is necessary to identify the problem of false clinical well-being of such patients, since, according to the data presented, they remain at risk of developing cardiovascular complications.

The data reflecting the dynamics of the M-CSF content in the blood of convalescents of the coronavirus infection are of scientific interest. An increase in its content within 180 days of the post-infectious period may be associated with the progression of endothelial dysfunction or, possibly, an increase in the pro-inflammatory activity of adipocytes, which can maintain a viral replication for a long time and determine an additional release of pro-inflammatory cytokines into circulation [25]. As established in this study, an early prescription of an antiviral drug based on favipiravir in the treatment regimen for comorbid patients with COVID-19, reduced the incidence of ACA, TCA, MI, compared with the patients who did not receive antiviral drugs. Of course, the data obtained require a further study on an expanded sample of patients.

The relevance of the further feature analysis of the drugs based on favipiravir, is indisputable. According to the doctors' data, the prescription of a drug is not accompanied by a significant increase in the frequency of undesirable effects (increased ALT, AST, dyspeptic phenomena). That can be associated with the use of a drug from the favipiravir group: a comparison was made with the group without any use of antiviral therapy in the patients with COVID-19 against the background of hypertension and obesity. Previously, the review data on the potential risk of mutagenic effects of the drugs based on favipiravir against SARS-CoV-2 have been published [26]. It is important to note that the authors confirm the effectiveness of the drug in blocking SARS-CoV-2 viral replication, but there is a problem, which, first of all, is

relevant if the manufacturer's recommended doses and duration of the drug use are not followed. At the same time, fundamental studies of the action mechanism of the drug show [27–31] those abnormalities in nucleotide sequences that determine violations of RNA virus replications, cause processes of lethal mutagenesis, which lead to the destruction of virus particles, rather than its variability. The resulting fragments of RNA do not even represent subgenomic fragments and cannot biologically represent mutations. The issue of the relevance of its modification in order to maintain its high efficacy in subsequent years requires additional research.

CONCLUSION

This study showed that an early prescription of favipiravir contributes to a decrease in the rate of COVID-19 patients' hospitalization even against the

background of concomitant hypertension and obesity, due to a decrease in the likelihood of moderate and severe courses of the disease, and also leads to an earlier objective and subjective recovery. The results demonstrated a high potential benefit of an early favipiravir use in the novel coronavirus infection and in the prevention of postcovid complications. The results obtained open up prospects for further studies analyzing individual cytokine-mediated variants of a post-covid syndrome in patients with a high risk of cardiovascular complications against the background of the use of drugs with molecular-targeted antiviral effects. The demonstrated effect of the Areplivir® drug on reducing the socio-economic burden of the coronavirus infection, which has been shown off, emphasizes the advisability of an early prescription of antiviral therapy in high-risk comorbid COVID-19 patients.

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CONFLICT OF INTEREST

The clinical study was organized by the National Research Mordovia State University. Promomed DM LLC is a member of the group of companies JSC Promomed. Promomed RUS LLC is a part of the group of companies JSC Promomed. Promomed RUS LLC is the holder of the registration certificate for the drug "Areplivir" LP-006288 dated 23 June 2020. The manufacturer of the drug "Areplivir" is JSC Biokhimik, which is part of the group of companies JSC Promomed. Promomed RUS LLC is the initiator of a charitable program to provide the population of the Republic of Mordovia with favipiravir. Administration of the Head of the Republic of Mordovia is the coordinator of the charitable program. Promomed RUS LLC is the rightholder of a patent for an antiviral composition - Patent for invention No. 2751108 (application No.2020119747, priority 15 June 2021; date of state registration 07 Aug 2021). Zaslavskaya K.Ya. – director for new products of Promomed DM LLC.

AUTHORS' CONTRIBUTION

Larisa A. Balykova – development and implementation of research design, text writing and editing; Olga A. Radaeva – setting the study aim, study goal setting, results analysis, text writing; Kira Ya. Zaslavskaya – text writing and editing; Yulia A. Kostina – statistical processing of the experimental results; Maria S. Iskandarova – statistical processing of the experiment results, setting the aim of the study, Elena V. Negodnova – statistical processing of the experiment results, setting the aim of the study, results analysis; Vitaly V. Ereemeev – statistical processing of the experiment results, setting the aim of the study, results analysis; Lenar F. Sabirov – control of material sampling; Elena V. Semeleva – development and implementation of research design.

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