



## EFFICACY AND SAFETY OF SOME ETIOTROPIC THERAPEUTIC SCHEMES FOR TREATING PATIENTS WITH NOVEL CORONAVIRUS INFECTION (COVID-19)

L.A. Balykova, V.F. Pavelkina, N.V. Shmyreva, N.A. Pyataev, N.M. Selezneva, O.I. Shepeleva, R.Z. Almyasheva

National Research Ogarev Mordovia State University  
26 (Bld.A), Ulyanov St., Saransk, Republic of Mordovia, Russian Federation

E-mail: [larisabalykova@yandex.ru](mailto:larisabalykova@yandex.ru)

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**The aim of the study** is to assess the efficacy and safety of the Favipiravir (Areplivir) drug, compared to the standard etiotropic therapy in the patients hospitalized with COVID-19.

**Material and methods.** The research was conducted as a part of an open, randomized, multicenter comparative study of the efficacy and safety of Areplivir, 200 mg film-coated tablets ("PROMOMED RUS" LLC, Russia), in the patients hospitalized with COVID-19. The dosing regimen of Favipiravir was 1600 mg twice a day on the 1<sup>st</sup> day and 600 mg twice a day on days 2–14. Thirty nine patients were enrolled into the study with a laboratory-established diagnosis of a new type of Coronavirus infection caused by SARS-CoV-2 (confirmed) of moderate severity, with pneumonia. The group of comparison (22 patients) received standard etiotropic therapy, prescribed in accordance with the current version of the temporary guidelines for the diagnosis and treatment of COVID-19, represented mainly by Hydroxychloroquine with the dosage regimen of 800 mg on the 1<sup>st</sup> day, then 400 mg on days 2–7, and Azithromycin 500 mg once a day for 5 days. The main group (17 patients) received Favipiravir (Areplivir) as etiotropic therapy.

**Results.** In the main group, the time period until fever disappeared was found to be 1.36 days shorter than in the group of comparison ( $p < 0.05$ ); there was a higher rate of the reduction of inflammatory changes in the lungs according to the computer tomography data (38.4% vs 14.9%,  $p < 0.05$ ). By the end of the treatment, there was also a lower lactate level in the blood (27.1%,  $p < 0.05$ ) than in the patients of the group of comparison. The evaluation of the drug efficacy according to the Categorical Ordinal Scale of Clinical Improvement and measurements of oxygen saturation in the blood, manifested similar positive dynamics in the patients treated according to various etiotropic therapy regimens. By the end of the treatment, the RNA SARS-CoV-2 tests were also negative in all the patients. As for the overall frequency of adverse events (AEs), no relevant distinctions were found between the groups. A greater part of AEs was related to hepatotoxicity, with a predominantly clinically relevant increase in alanine aminotransferase (ALT). A clinically relevant prolongation of the corrected QT interval on the standard ECG was found to occur in the standard-therapy group on day 5, while no serious AEs were registered in the main group. No serious adverse reactions were registered in patients of the main group.

**Conclusion.** The efficacy of the Favipiravir (Areplivir) therapy for the novel coronavirus infection has proved to be superior to the efficacy of the standard etiotropic therapy in a number of aspects. Basing on the obtained findings, Favipiravir (Areplivir) drug can be recommended for treating patients with the novel coronavirus infection of moderate severity.

**Keywords:** novel coronavirus infection, COVID-19, etiotropic therapy, Areplivir, computer tomography, corrected QT-interval

**Abbreviations:** activated partial thromboplastin time (APTT); alanine aminotransferase (ALT); aspartate aminotransferase (AST); blood pressure (BP); upper limits of the norm (UHN); Temporary guidelines (TMR); a categorical ordinal scale of clinical improvement (CPSA); computed tomography (CT); corrected QT interval (QTc); creatine phosphokinase (CPK); adverse event (AE); polymerase chain reaction (PCR); prothrombin time (PTT); blood oxygen saturation ( $SpO_2$ ); serious adverse events (SAEs); C-reactive protein (CRP); respiratory rate (RR); heart rate (HR); electrocardiogram (ECG).

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## СРАВНИТЕЛЬНАЯ ЭФФЕКТИВНОСТЬ И БЕЗОПАСНОСТЬ РАЗЛИЧНЫХ СХЕМ ЭТИОТРОПНОЙ ТЕРАПИИ У ПАЦИЕНТОВ С НОВОЙ КОРОНАВИРУСНОЙ ИНФЕКЦИЕЙ (COVID-19)

Л.А. Балыкова, В.Ф. Павелкина, Н.В. Шмырева, Н.А. Пятаев, Н.М. Селезнева,  
О.И. Шепелева, Р.З. Альмяшева

Национальный исследовательский Мордовский государственный университет им. Н.П. Огарёва  
Российская Федерация, республика Мордовия, г. Саранск, ул. Ульянова, д. 26а

E-mail: larisabalykova@yandex.ru

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**Цель.** Оценка эффективности и безопасности препарата Фавипиравир («Арепливир») в сравнении со стандартной этиотропной терапией у пациентов, госпитализированных с COVID-19.

**Материалы и методы.** Исследование проводилось в рамках открытого рандомизированного многоцентрового сравнительного исследования эффективности и безопасности препарата «Арепливир», таблетки 200 мг, покрытые пленочной оболочкой, (ООО «ПРОМОМЕД РУС», Россия), у пациентов, госпитализированных с COVID-19. Режим дозирования фавипиравира: 1600 мг 2 р/сут в 1-й день и 600 мг 2 р/сут в 2–14 дни. В исследование включено 39 пациентов, госпитализированных в стационар по поводу лабораторно подтвержденной новой коронавирусной инфекции, среднетяжелого течения с развитием пневмонии. Группа сравнения (22 больных) получала стандартную этиотропную терапию, назначенную в соответствии с действующей версией временных методических рекомендаций по диагностике и лечению COVID-19, представленную преимущественно Гидроксихлорохином (режим дозирования по 800 мг в 1-й день, далее по 400 мг в 2–7 дни) и Азитромицином по 500 мг 1 раз в день в течение 5 дней. Основная группа (17 пациентов) получала в качестве этиотропной терапии препарат Фавипиравир («Арепливир»).

**Результаты.** В основной группе было отмечено сокращение времени исчезновения лихорадки (на 1,36 дней  $p < 0,05$ ), более высокая скорость редукции воспалительных изменений в легких по данным компьютерной томографии (38,4% против 14,9%,  $p < 0,05$ ) и более низкий уровень лактата (на 27,1%,  $p < 0,05$ ) крови к концу курса лечения по отношению к группе сравнения. Оценка эффективности терапии по категориальной порядковой шкале клинического улучшения и уровня сатурации кислорода крови выявили сходную положительную динамику у пациентов, получавших различные схемы этиотропной терапии. Также у всех пациентов тесты на наличие SARS-CoV-2 по завершению курса лечения показали отрицательные результаты. Значимые различия между группами терапии по общей частоте нежелательных явлений отсутствовали. Большая часть нежелательных явлений касалась гепатотоксичности, при этом преимущественно отмечалось клинически значимое повышение аланинаминотрансферазы. Кардиотоксическое действие в виде клинически значимого удлинения скорректированного интервала QT (QTc) на стандартной электрокардиограмме имело место на 5-ый день лечения в группе стандартной терапии, тогда как в основной группе подобных нежелательных реакций отмечено не было. Серьезных нежелательных реакций у пациентов основной группы не зарегистрировано.

**Заключение.** Эффективность препарата Фавипиравир («Арепливир») в терапии новой коронавирусной инфекции по ряду изучаемых показателей превосходит эффективность стандартной этиотропной терапии. Учитывая полученные результаты, препарат Фавипиравир («Арепливир») может быть рекомендован для лечения больных новой коронавирусной инфекцией средней степени тяжести.

**Ключевые слова:** новая коронавирусная инфекция, COVID-19, этиотропная терапия, Фавипиравир («Арепливир»), компьютерная томография, скорректированный интервал QT

**Список сокращений:** активированное частичное тромбопластиновое время (АЧТВ); аланинаминотрансфераза (АЛТ); аспартатаминотрансфераза (АСТ); артериальное давление (АД); верхние границы нормы (ВГН); Временные методические рекомендации (ВМР); категориальная порядковая шкала клинического улучшения (КПШКУ); компьютерная томография (КТ); скорректированный интервал QT (QTc); креатинфосфокиназа (КФК); нежелательные явления (НЯ); полимеразная цепная реакция (ПЦР); протромбиновое время (ПТВ); сатурации кислорода крови (SpO<sub>2</sub>); серьезные нежелательные явления (СНЯ); С-реактивный белок (СРБ); частота дыхания (ЧД); частота сердечных сокращений (ЧСС); электрокардиограмма (ЭКГ).

### INTRODUCTION

Three epidemics marked the beginning of the 21<sup>st</sup> century. They were appearing one after the other: a severe acute respiratory distress syndrome caused by SARS-CoV (atypical pneumonia), a Middle-East respiratory syndrome caused by MERS-CoV and, finally, a severe acute respiratory syndrome caused by SARS-CoV-2,

the so-called novel coronavirus infection, or COVID-19 [1].

COVID-19 is greatly ahead of the former epidemics of coronavirus infection by the number of infected individuals. Currently, while vaccination against COVID-19 has not become available en masse and its long-term effects have not been evaluated, the effectiveness of

various etiotropic therapy regimens, as well as drugs for pathogenetic treatment, the action of which is aimed at suppressing the secondary effects of the cytokine storm and/or modulating the body's immune system or blocking some specific links in the pathogenesis of a new coronavirus infection (in particular, hypercoagulation), is widely studied [2].

It is known, that in most patients, COVID-19 has mild or moderately forms; however, about 5 to 10 percent of patients encounter serious, potentially life-threatening manifestations and complications. This creates an urgent need to develop and put into practice efficient etiotropic drugs [5, 6]. Despite several hundred already performed and on-going clinical trials assessing the efficacy and safety of various antiviral and immune-modulating medications, the World Health Organization states that at present, there are no drugs with unambiguously proven efficacy against the novel coronavirus infection.

In most conducted trials, only one group was enrolled for medical interference, with a control group absent, some medical drugs are being used up till now on the basis of either in vitro studies or on the basis of extrapolated data, or observational studies [7–9].

The following drugs have been better studied: the efficacy and safety of Hydroxychloroquine, Chloroquine, and Mefloquine both in monotherapy and in combination with Azithromycin, Umifenovir, Remdesivir, Lopinavir/Ritonavir with Interferon-1b, Favipiravir. Some of them have been studied in randomized clinical trials [10–16].

However, only Remdesivir and Favipiravir have not only a high efficiency, but also a selectivity of action, blocking the RNA-dependent RNA polymerase of the SARS-CoV-2 virus. However, Favipiravir has a dual mechanism of action, inducing lethal mutations of viral RNA, helping to reduce the viral load [17–19].

**THE AIM** of the study was to assess the therapeutic efficacy and safety of Favipiravir (Areplivir, film-coated tablets, OOO "PROMOMED RUS", Russia) compared to those of the standard etiotropic therapy administered in compliance with Temporary Methodological Recommendations of the Ministry of Health of RF aimed at the prevention, diagnostics and treatment of the novel coronavirus infection COVID-19 (version 6 of 28.04.2020 and version 7 dated 03/06/2020). Favipiravir is known to block RNA-dependent RNA-polymerase of SARS-CoV-2 virus [17–19].

### MATERIAL AND METHODS

The study was conducted during the pandemic rise of COVID-19 in the Republic of Mordovia (in the period from 01.06.2020 to 01.08.2020) in the research center of "National Research Ogarev Mordovia State University" as part of an open randomized multicenter comparative study of the efficacy and safety of Areplivir, 200 mg film-coated tablets (PROMOMED RUS LLC, Russia), in patients hospitalized with COVID-19.

This article presents the data on the patients admitted only at the above-mentioned center. Thirty-nine patients, aged 21 to 73 years, were enrolled in the study, with a laboratory-confirmed diagnosis "Coronavirus infection, caused by SARS-CoV-2 (confirmed), of moderate severity, with the presence of bilateral pneumonia". The study was approved by the Local Ethics Committee at Ogarev Mordovia State University (Protocol No. 85 dated 27.05.2020), and was also reviewed in the international register of clinical trials (clinicaltrials.gov (NCT04542694)). The diagnosis was confirmed by PCR tests; RNA SARS CoV-2 was identified in the biomaterial of all the patients from the swabs taken in the nasopharynx and/or oropharynx. The diagnosis was established in compliance with the TMR. The patients were admitted at hospitals in Saransk and Ruzaevka.

**The criteria of enrollment** into the study were: signing and dating an Informed Consent Form of the Patient Information Sheet; male or female gender; the age from 18 to 80; a patient's hospitalization not exceeding 48 hrs prior to administering etiotropic therapy; a positive PCR test result for the presence of RNA SARS-CoV-2; a patient's consent to use reliable preventive measures during the study and for 3 weeks after their completion.

**The exclusion criteria** were: unavailability of a computed tomography(CT) procedure for some reason (for example, a plaster cast or metal constructions at the site under study); a need for a patient to be treated at the resuscitation and intensive therapy departments; an impaired liver function (AST and/or ALT $\geq$ 2 upper limits of the norm (ULN) and/or the total bilirubin  $\geq$  1.5 of ULN) an impaired kidney function (creatinine clearance  $<$  45ml/min); a positive test for HIV, syphilis, hepatitis B and /or C; a chronic heart failure of functional classes III-IV; the syndrome of malabsorption or some other clinically relevant disease of the gastrointestinal tract, which may affect the absorption of the studied drug; the patient's history of malignant neoplasms; alcohol, pharmacologic and/or drug (narcotic) addiction; mental pathology in the history or suspected pathology; severe decompensated or unstable somatic diseases that were life-threatening or deteriorated the patient's prognosis; pregnancy or its planning, breast-feeding.

All the patients were randomized into 2 groups. Group 1 (a group of comparison, n=22) received standard etiotropic therapy, administered in compliance with the treatment regimens stated in the TMR. Twelve patients (54.5%) received a combination of Hydroxychloroquine and Azithromycin as an antiviral therapy, 8 patients (36.4%) – Hydroxychloroquine (monotherapy), 2 patients (9.1%) – Lopinavir/Ritohavir (Calidavir). The dosage regimen was the following: for Hydroxychloroquine it was 800 mg on the first day (400 mg twice a day), then 400 mg/day (200 mg twice a day) for 2–7 days; for Azithromycin: 500 mg once a day for 5 days; for Lopinavir/Ritonavir: 400 mg+100 mg orally every 12 hours for 14 days. The patients were aged from 21 to 73

(the average age was  $47.5 \pm 1.99$  yrs). Group 2 (the main group), 17 patients, aged from 34 to 63 yrs (the average age was  $47.12 \pm 2.26$  yrs), received Favipiravir (Areplivir) as an etiotropic therapy: on day 1 – 1600 mg (8 tablets) twice a day; on days 2–14 of the therapy – 600 mg (3 tablets) twice a day. The main-group patients who received the drug under study, were not allowed to take other medications of the standard etiotropic therapy for COVID-19, in compliance with the TMR or any other antiviral therapeutic medicines.

### Parameters under study

According to the study protocol, the following parameters were assessed: clinical status according to the Categorical Ordinal Scale of Clinical Improvement proposed by the World Health Organization (Table 1); test results for the presence of SARS-CoV-2 RNA; body temperature; assessment of changes in the lungs according to “Empirical” Visual Scale (Table 2); (the CT data); a need for the patients to be treated at the Resuscitation and Intensive therapy department; a need for non-invasive ventilation of the lungs; a need for artificial lung ventilation; an incidence of fatal cases; occurrence of undesirable phenomena (UP)/of serious undesirable phenomena (SUP); vital indices (BP, heart rate, respiration rate), the findings of the physical examination; a clinical blood test, a biochemical blood test (alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein, creatinine, urea, total bilirubin, glucose, C-reactive protein, creatine phosphokinase (CPK), ferritin, lactate); a coagulogram (activated partial thromboplastin time, thromboplastin time (PT), prothrombin time, fibrinogen, D-dimer): data on pulse oximetry with SpO<sub>2</sub> measurement; general urinalysis (pH, specific weight, protein, erythrocytes, leukocytes); a test for pregnancy for women capable of childbearing, the ECG (with estimated corrected QT interval (QTc) by Bazett formula; by Framingham formula estimated HR below 60 or over 100 beats per minute); blood test data for HIV, syphilis, hepatitis B and C. The following equipment was used to perform the studies: clinical blood analysis – hematological analyzer Micros ES 60, Horiba ABX (France), biochemical analysis – biochemical analyzer HUMASTAR 600, Human GmbH (Germany), coagulogram – analyzer-coagulometer KS 1 Delta, Tcoag (Ireland), urine analysis – uroanalyzer Combilyzer 13, Human GmbH (Germany). The analyses were performed using certified reagent kits according to the manufacturer’s protocols. Coagulogram and lung CT data were analyzed at the patient’s admission at the hospital and on the 15th day of therapy, the duration of the QT interval and laboratory parameters were evaluated on the day of admission at the hospital, on the 5th and 15th day of therapy, virus elimination was judged by the absence of SARS-CoV-2 RNA on the 10th and 11th day from the start of treatment.

### Statistical processing of results

Statistical processing of the findings was conducted

on a personal computer with the help of Statistica 6.0 and Microsoft Excel programs. Processing of the descriptive statistical data was conducted by estimating the mean arithmetic value (M) and an error to the mean arithmetic value ( $\pm m$ ). The average values were compared using the t-Student criterion (for normal distribution of the trait) or the nonparametric Wilcoxon criteria (for paired samples) and Mann-Whitney criteria (for unpaired samples). The selection of the criterion (parametric or nonparametric) was carried out after checking the type of the data distribution for compliance with the normal distribution law using the Shapiro-Wilk criterion. The relevance and significance of the differences for qualitative signs between the compared groups, were determined by the analysis of contingency tables, with computation of exact  $\chi^2$  criterion according to Pearson. The results at  $p < 0.05$  were considered significant.

### RESULTS OF THE STUDY AND THEIR DISCUSSION

A comparative evaluation of time periods (in days) had been made until fever disappeared. A criterion for this indicator was the body temperature lower than 37.2 for 3 days in succession, without an intake of antipyretic drugs. In the group of comparison, a period until fever disappeared was  $6.36 \pm 0.56$  days; in the main group it was  $5.00 \pm 0.34$  days. The distinction between the opposed groups was statistically significant ( $p < 0.05$ ). This is an evidence of a higher therapeutic effect of Favipiravir (Areplivir) on fever in the patients who were receiving this drug.

The efficacy of the conducted therapy was also assessed by Categorical Ordinal Scale for Clinical Improvement (COSCI), its parameters are presented in Table 1. The assessment by this scale was conducted daily.

The assessment of the treatment efficacy by COSCI showed that the condition of the comparison-group patients on admission to the in – patient department corresponded to  $3.36 \pm 0.10$  category; on day of the surveillance to  $1.95 \pm 0.15$  category ( $p < 0.001$ ). Similar positive dynamics in patient condition, evaluated by COSMI was recorded in the main group. At the beginning of the surveillance the condition of the patients was evaluated as  $3.24 \pm 0.11$  category, on day 15 as  $1.59 \pm 0.17$  ( $p < 0.001$ ). The conducted therapy was similarly effective in the studied groups ( $p > 0.05$ ).

On the 15th day of the observation in the main group, the condition of the patients was assessed at  $1.59 \pm 0.17$  points (categories) according to the Categorical Ordinal Scale of Clinical Improvement (COSCI), versus  $3.24 \pm 0.11$  categories at the admission to hospital ( $p < 0.001$ ). In the comparison group, a similar positive dynamic was observed. On the 15th day of therapy, the condition of the patients according to COSCI, was assessed in  $1.95 \pm 0.15$  categories versus  $3.36 \pm 0.10$  at the beginning of the observation ( $p < 0.001$ ). There were no significant differences between the groups ( $p > 0.05$ ).

Table 1 – Categorical Ordinal Scale for Clinical Improvement [20]

Patient condition	Description	Category
Uninfected	Clinical and virological signs of infection are absent	0
Out-patient	Restrictions on human activity are absent	1
	Restriction on human activity are present	2
In-patient	Hospitalized. oxygen therapy	3
Moderate course of disease	Absent	4
	Oxygenation with a mask or nasal cannula	
Severe course of disease	Non-invasive ventilation or high – flow oxygenation	5
	Intubation or mechanical ventilation	6
	Ventilation + an additional support of organs: vasopressors. replacement therapy for kidneys. extracorporeal membrane oxygenation (ECMO)	7
Deceased	Death	8

Table 2 – “Empirical” Visual Scale for assessing pronounced changes in the lungs by the CT data [21]

Description	Value
Absence of characteristic manifestations	CT-0
Minimal volume/prevalence. <25% of lung volume	CT-1
Medium volume/prevalence. 25–50% of lung volume	CT-2
Considerable volume/prevalence. 50–75% of lung volume	CT-3
Crucial volume/prevalence. >75% of lung volume	CT-4

Table 3 – Assessment of changes in the lungs by CT data

CT data	Group of comparison M±m (n=22)		Main group M±m (n=17)		P
	On admission	On day 15 of therapy	On admission	On day 15 of therapy	
Area of lung damage. %	31.41±2.27	26.73±3.11	26.62±2.59	16.4±1.98*	<0.05
Area of lung damage by EVS	1.73±0.097	1.59±0.14	1.65±0.12	1.24±0.11	<0.05

Notes: p – statistical significance of differences in the indices of the main and groups on day 15 of therapy; \* – significance of the differences in the indices associated with the dynamics of the disease during the treatment.

Table 4 – Undesirable phenomena recorded in the study

Undesirable phenomena (UPs)	Group of comparison. m (n. %)	Main group. m (n. %)	P
Total number of UPs	31 (16, 72.7%)	23 (11, 64.7%)	>0.05
UPs probably associated with etiotropic drug intake	5 (5, 22.7%)	0 (0, 0%)	<0.05
UPs possibly associated with etiotropic drug intake	27 (15, 68.2%)	23 (11, 64.7%)	>0.05
Clinically relevant ALT elevation	11 (11, 50%)	10 (10, 58.8%)	>0.05
Clinically relevant AST elevation	5 (5, 22.7%)	5 (5, 22.7%)	>0.05
Skin rash	5 (5, 22.7%)	5 (5, 22.7%)	>0.05
Clinically relevant prolongation of QTc	5 (5, 22.7%)	0 (0, 0%)	<0.05
Clinically relevant hyperglycemia	4 (4, 18.2%)	2 (2, 11.8%)	>0.05
Clinically relevant elevation of creatine phosphokinase	1 (1, 4.5%)	0 (0, 0%)	>0.05
Clinically relevant leukocyturia	1 (1, 4.5%)	0 (0, 0%)	>0.05
Clinically relevant erythrocyturia	1 (1, 4.5%)	1 (1, 5.9%)	>0.05

Notes: m – the number of UPs; n – the number of patients with UPs in the group (percentage is estimated to the total number of patients in the group); P – statistical significance of differences in comparison – group indices and main – group indices

**Table 5 – Assessment of the QTc duration against the background of different therapeutic options**

Study timing	QTc duration. ms		P
	Group of comparison. M±m (n=22)	Main group. M±m (n=17)	
On admission	394.65±3.99	400.71±6.41	>0.05
On day 5 of treatment	411.08±6.71*	392.33±5.19	<0.05
On day 15 of treatment	396.44±4.37	398.26±5.49	>0.05

Notes: p – statistical significance of differences in indices in the group of comparison and the main group; \* – significance of differences compared to the values at admission

**Table 6 – Coagulogram indices against the background of various treatment methods**

Indices (reference intervals)	Group of comparison. M±m (n=22)		Main group. M±m (n=17)		p
	At admission	On day 15 of therapy	At admission	On day 15 of therapy	
APTT (24–34 sec)	28.78±1.71	27.45±1.73	30.31±1.66	26.029±1.27	>0.05
PTT (9–16 sec)	13.90±0.32	13.49±0.37	13.67±0.32	13.02±0.30	>0.05
Fibrinogen (200–400 mg/dl)	342.52±24.87	337.69±16.02	330.51±23.95	372.29±25.49	>0.05
D-dimer (0–386 ng/ml)	484.59±135.30	422.95±118.38	471.35±156.30	409.47±131.92	>0.05

Note: p – significance of differences between the indicators of the main and comparison groups on day 15th of therapy

**Table 7 – Biochemical data of blood analysis against the background of different therapeutic options**

Indices (reference intervals)	Group of comparison. M±m (n=22)			Main group. M±m (n=17)			p
	At admission	On day 5 of therapy	On day 15 of therapy	At admission	On day 5 of therapy	On day 15 of therapy	
Bilirubin (2.7–21 mcmol/l)	9.90±0.98	10.93±0.93	12.10±1.19*	10.52±0.97	10.73±1.24	11.50±1.39	>0.05
ALT (5–41 units/l)	32.85±3.57	49.77±6.93*	91.57±26.81*	33.58±4.01	70.88±11.89*	102.2±20.0*	>0.05
AST (3–35 units/l)	31.82±2.68	33.61±2.50	36.76±4.17	33.94±2.83	38.88±5.99	50.06±9.27	>0.05
Urea (3.5–8.3 mmol/l)	5.68±0.40	6.07±0.38	5.92±0.45	5.15±0.31	5.46±0.46	5.62±0.54	>0.05
Creatinine (51–115 mcmol/l)	85.50±4.12	86.41±4.84	90.36±3.97	98.65±14.75	90.81±5.11	91.06±5.54	>0.05
Lactate (0.5–2.2 mmol/l)	3.57±0.46	5.12±0.54*	5.42±0.60*	3.20±0.24	3.99±0.47	3.95±0.37	<0.05
CRP (0–6 mg/l)	22.90±4.75	15.93±3.89*	11.19±3.56*	25.43±6.28	10.38±2.16*	12.51±2.51*	>0.05
Ferritin (20–250 mcg/l)	150.0±18.66	155.1±24.58	192.9±28.06	220.3±30.93	265.1±37.76	242.6±32.84	>0.05
Uric acid (200–420 mmol/l)	243.0±17.64	240.9±13.46	280.1±14.71*	250.3±13.99	243.1±12.62	322.4±28.8*	>0.05
CPK (24–171 unit/l)	95.0±38.68	87.64±31.82	54.68±8.66	80.76±26.87	47.88±8.95	38.24±6.07	>0.05
Glucose (3.5–6.4 mmol/l)	6.16±0.65	7.12±0.85	7.47±1.06	5.80±0.37	6.52±0.59	5.79±0.66	>0.05
Total protein (64–87 g/l)	69.68±1.07	68.64±1.11	67.18±1.27	70.41±0.86	68.18±1.37	66.76±1.92	>0.05

Note: p – significance of difference between the indices of the main and comparison groups on day 15 of the treatment; \* – significance of differences in disease dynamics during the conducted therapy. It is important to note that not a single patient has been transferred to the departments of resuscitation and intensive therapy. There have been no cases of non-invasive or artificial ventilation of the lungs. and no deaths either

The study of the indicator “blood oxygen saturation” is very important. To assess an intensity of hypoxemia and reveal respiratory failure distress, pulse oximetry was conducted to all the patients with measurements of blood oxygen saturation ( $SpO_2$ ). Positive dynamics of blood oxygen saturation was notified in both groups.

In the main group, this index was  $94.47 \pm 0.47\%$  at the initiation of the therapy for infection, significantly rising during the ongoing therapy up to  $97.88 \pm 0.26\%$  ( $p < 0.001$ ). At the admission to the hospital,  $SpO_2$  value in patients of the comparison group was  $94.68 \pm 0.31\%$ ; by day 15 of the surveillance a significant increase in  $SpO_2$  had risen up to  $97.86 \pm 0.20\%$  ( $p < 0.001$ ).

A computed tomography, as a highly sensitive device for detecting COVID-19 characteristic changes in the lungs, was used in the study to assess such changes. The use of the CT is reasonable for an initial evaluation of the state of the chest organs in patients with severely progressing forms of the disease and, for both differential diagnostics of detected changes and assessment of dynamics of the process, too. The CT makes it possible to reveal characteristic lung changes in COVID-19 patients prior to the availability of positive laboratory tests for infection done with nucleic acid amplification technique. To unify the rapid visual assessment of the volume of the lung tissue compaction according to the CT data, WHO has proposed an “empirical” visual scale [21], which makes it possible to determine the degree of lung damage (Table 2).

The study of the CT data by “Empirical” Visual Scale showed the following. The scale indices for the comparison group were  $1.73 \pm 0.097$  and  $1.59 \pm 0.14$  against the background of treatment. In the main group they were significantly lower:  $1.61 \pm 0.12$  and  $1.24 \pm 0.11$ , respectively ( $p < 0.05$ ). This is another proof of a high efficacy of the therapy if it includes Favipiravir (Areplivir) as an antiviral drug.

At admission to hospital, there were no significant differences in lung lesions between the main group and the comparison group. By the 15th day of treatment with Favipiravir (Areplivir), a decrease in the area of lesion of the pulmonary parenchyma by 38.4% ( $p < 0.05$ ) had been notified, and in the group of traditional therapy – by 14.9% from the initial level ( $p > 0.05$ ). In the main group of patients at the end of the course of treatment, a smaller area of lung tissue damage was found in relation to the comparison group ( $16.4 \pm 1.98$  and  $26.73 \pm 3.11$ , respectively,  $p < 0.05$ ), indicating the superiority of treatment with Favipiravir (Areplivir) compared to the recommended etiotropic therapy.

In all the patients, the percentage of virus elimination during the treatment was assessed. The elimination of the virus was determined by two negative lab tests for the presence of RNA SARS-CoV-2 done with an interval of 24 hrs on days 10 and 11 of hospital therapy. On the

completion of the therapy, the test results were negative in the both studied groups, which points to the elimination of the virus and the efficacy of the conducted etiotropic therapy.

An important indicator of an emerging pathological process associated with oxygen deficiency (for instance, in pneumonia), is accumulation of lactate due to hypoxia. With a reduced oxygen delivery to the cells, lactate production rises, thus making blood lactate level elevated [22]. It is known that blood lactate level helps to monitor an extent of tissue hypoxia. An elevated lactate level is an early sensitive indicator of imbalance between oxygen demand and its delivery to the tissues. Elevation of blood lactate level may pose a risk of complications [23].

At the onset of the surveillance, the lactate level was notified to elevate in both-group patients: up to  $3.57 \pm 0.46$  mmol/L in the comparison group and up to  $3.20 \pm 0.24$  mmol/L in the main group (Table 7). However, during the treatment, lactate accumulation was found to occur in patients of standard – therapy group ( $5.42 \pm 0.61$  mmol/L). Meanwhile, in Favipiravir (Areplivir) group its level did not change ( $3.95 \pm 0.37$  mmol/L;  $p < 0.05$ ) but it was lower than in the group of comparison.

Thus, no correlation was found between the lactate concentration and the degree of lung tissue damage in patients with moderate COVID-19. This may be due to the extrapulmonary mechanisms of hypoxia development and progression in patients with COVID-19 and the peculiarities of the mechanism of action of Favipiravir and Hydroxychloroquine, which prevent the interaction of the virus with hemoglobin hemoxyprophyrin and the development of hemic hypoxia [24]. In addition, hyperlactatemia in this case may be associated with the production of lactate in the lung tissue itself [25].

In the course of the study, all the data were collected on the undesirable phenomena (UPs) associated with an intake of the standard-therapy drugs and Favipiravir (Areplivir) (Table 4). On the whole, 54 undesirable phenomena were recorded in both groups: 31UPs in 16 patients (72.7%) in the comparison group and 23 UPs in 11 patients (64.7%) of the main group. All the recorded UPs were mild in form. The association with the intake of etiotropic drugs was suggested in 5 cases of UPs as probable (in the comparison group), in 48 cases as possible (26 UPs in the comparison group and 23 in the main group).

It is important to note, that there has not been a single case of a serious undesirable phenomenon (SUP) recorded, and not a single case of an early termination of participation in the study due to UPs or to SUPs associated with an intake of the studied drugs or drugs of comparison. None of the recorded cases of UPs have led to the withdrawal of any etiotropic drug or to a change in the dosage of the administered drugs, either.

Associated with an intake of etiotropic drugs, undesirable phenomena of this type were recorded in five

comparison-group patients (22.7%). These phenomena were manifested as a significant prolongation of the corrected QT interval (QTc) on the ECG. Similar UPs were not notified in the main group ( $p < 0.05$ ).

Most of the undesirable phenomena were associated with hepatotoxicity, manifested mainly as elevated ALT and ACT, to a lesser degree: in 11 patients of the comparison group (50%) and in 5 (22.7%); in 10 (58.8%) and in 8 (47.1%) main-group patients, respectively. The following undesirable phenomena were observed less frequently: skin rash, a clinically relevant increase in creatine phosphokinase (CPK), hyperglycemia, leukocyturia, erythrocyturia. However, no statistically significant intergroup differences were noted in incidence of above-mentioned undesirable phenomena ( $p > 0.05$ ).

It is well known that Hydroxychloroquine and Azithromycin, when used in monotherapy or in a combination, prolong the QT interval. Their use may cause drug-induced ventricular «pirouette» – a type of Tachycardia (torsades de pointes, Td P). Although Td P occurs only in a small proportion of patients with a prolonged QTc interval (longer than 500 ms), the drug QT prolongation may increase a risk of death from arrhythmic or non-arrhythmic causes. For this reason, this indicator is very important for sachet of drugs [26, 27]. The analysis of the Multinational Register conducted in late May 2020 with enrollment of patients with severe COVID-19 showed that Hydroxychloroquine use is associated with an increased tick of intrahospital mortality. The association of the use of Hydroxychloroquine (including its combination with Macrolide) with occurrence of ventricular arrhythmias during hospitalization, was also confirmed [19].

Taking the above into account, the lack of Favipiravir (Areplivir) effect on the duration of the corrected QTc interval observed in our study, is of vital importance. The QTc value in a standard-therapy group averaged  $394.65 \pm 3.99$  ms on the admission. 54.4% patients received a combination of Hydroxychloroquine and Azithromycin, 36.4% – only Hydroxychloroquine. On day 5 of the treatment, the QTc duration went up, amounting to  $411.08 \pm 6.71$  ms ( $p < 0.05$ ). While in the Favipiravir (Areplivir) group the value of the corrected QTc interval did not change ( $400.71 \pm 6.41$  ms on admission and  $392.33 \pm 5.19$  by day 5 of the therapy ( $p > 0.05$ )). Hence, an observed difference between the groups turned out to be statically significant ( $p > 0.05$ ), which is an evidence of a safer use of Favipiravir (Areplivir) with regard to the heart.

By day 15 of the treatment, the QTc duration in the comparison group had returned to the initial one, making  $396.44 \pm 4.37$  ms. No changes in the QTc value were observed in the main group ( $398.26 \pm 5.49$  ms). Eventually, statistically significant intergroup difference recorded on day 5 of the Surveillance was leveled out by day 15 ( $p > 0.05$ ). This may be apparently explained

by quite a long period of withdrawal of Hydroxychloroquine and Azithromycin by that time (the duration of Hydroxychloroquine intake was 7 days, of Azithromycin – 5 days).

Evaluation of the indicators of the general blood test, coagulogram and simple urine test in the moderate course of COVID-19, did not reveal statistically significant dynamics during the study and intergroup differences. The coagulation parameters were presented in Table 6. No difference in the number of clinically significant deviations of these indicators from the norm, has been notified either.

The data on biochemical blood analyses of both group patients, are presented in Table 7. As previously mentioned, our observation showed an extensive involvement of the liver into the pathological process. The syndrome of hepatocyte cytolysis was recorded on day 5 of the surveillance: the enzymatic ALT activity in a group of comparison equaled to  $49.77 \pm 6.93$  units/L, in the main group to  $70.88 \pm 19.89$  units/L. By day 15 of the treatment, a significant rise of ALT activity had been observant in both groups, up to  $91.57 \pm 26.81$  and  $102.2 \pm 20.0$  units/L, respectively. However, no difference in hepatotoxicity was found in the drugs user in the studied groups ( $p < 0.05$ ).

## CONCLUSION

The results obtained in our study, have shown that the efficacy of Favipiravir (Areplivir) drug for the treatment of the novel coronavirus infection is superior to the efficacy of standard etiotropic therapy in a number of aspects (indices). The time period until fever disappeared, had been shorter in the group with administered Favipiravir (Areplivir) (the body temperature  $< 37,2$  within 3 days in succession, without any antipyretic drugs). The lactate level in the blood of this group of patients, was lower than in the patients who received standard antiviral therapy prescribed in accordance with temporary guidelines. The greater effectiveness of therapy in the main group is also indicated by CT data, which showed a more significant reduction in the area of pulmonary parenchyma lesion on the 15th day of therapy, in relation to the comparison group.

The conducted study also bears evidence that, the safety of Favipiravir (Areplivir) use for treating patients with novel coronavirus infection of moderate severity, is comparable to the safety of standard therapy. Of vital importance is the fact, that by its effect on the corrected QTc interval, Favipiravir (Areplivir) is safer than standard therapy represented mostly by Hydroxychloroquine and Azithromycin.

On the basis of the results obtained in the study, Favipiravir (Areplivir) can be recommended for the treatment of patients with the novel coronavirus infection of moderate severity.



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## AUTHOR'S CONTRIBUTIONS

All authors have contributed to the research equally.

## CONFLICT OF INTERESTS

The authors declare no conflicts of interests.

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### AUTHORS

**Larisa A. Balykova** – Doctor of Sciences (Medicine), Professor, the Head of the Department of pediatrics; corresponding member of the Russian Academy of Sciences. Director of the National Research Ogarev Mordovia State University. ORCID ID: 0000-0002-2290-0013. E-mail: larisabalykova@yandex.ru

**Vera F. Pavelkina** – Doctor of Sciences (Medicine), Professor, the Head of the Department of infectious diseases with courses in epidemiology, phthisiology, skin and venereal diseases. National Research Ogarev Mordovia State University. ORCID ID: 0000-0001-9582-9986. E-mail: pavelkina@rambler.ru

**Natalya V. Shmyreva** – Candidate of Sciences (Medicine), Associate Professor of the Department of Pharmacology and Clinical Pharmacology with a course in pharmaceutical technology. National Research Ogarev Mordovia State University. ORCID ID: 0000-0001-9331-7979. E-mail: shmyrevanv@yandex.ru

**Nikolay A. Pyataev** – Doctor of Sciences (Medicine), Associate Professor and the Head of the Department of

Anesthesiology and Reanimatology. National Research Ogarev Mordovia State University. ORCID ID: 0000-0002-9688-7640. E-mail: pyataevna@mail.ru

**Natalya M. Selezneva** – Candidate of Sciences (Medicine), Associate Professor of the Department of Hospital Therapy. National Research Ogarev Mordovia State University. E-mail: nata\_rm@mail.ru. ORCID ID: 0000-0002-3004-2063

**Olga I. Shepeleva** – Candidate of Sciences (Medicine), Associate Professor of the Department of Faculty therapy with courses of physiotherapy, physiotherapy exercises. National Research Ogarev Mordovia State University. ORCID ID: 0000-0001-8307-2787. E-mail: shepeleva-oi@rambler.ru

**Rimma Z. Almyasheva** – Candidate of Sciences (Medicine), Associate Professor of the Department of infectious diseases with courses in epidemiology, phthisiology, skin and venereal diseases. National Research Ogarev Mordovia State University. ORCID ID: 0000-0001-6727-9083. E-mail: almyasheva.rimma@yandex.ru