Practical Experience of Using Riamilovir in Treatment of Patients with Moderate COVID-19

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The article evaluates the results of Riamilovir use in treatment of patients with a moderate form of the disease caused by a new strain of the SARS-CoV-2 virus. It was found that the average time required to complete resolution of symptoms during treatment with the drug was 6–7 days. The first negative result of PCR analysis for the SARS-CoV-2 virus was registered on the 10–11th day of therapy; two consecutive negative PCR results for the SARS-CoV-2 virus were registered in the majority of patients by day 14–19 of treatment in 63±4.28 %. The body temperature of the majority of patients (75 %) returned to normal by the 4th day of treatment. CT scan showed improvement in the lungs of patients: a repeated CT scan performed on average on day 19 from the start of therapy showed no lung damage or no progression in 10±3.0 % of patients following therapy. The CT scan of the lungs performed in 1–2 months after the treatment showed that the number of patients with no lung damage increased to 27±4.44 %. As a result of treatment, a decrease in the C-reactive protein index was observed in patients. The tolerability level of the drug was assessed as good: no adverse events or significant deviations in laboratory parameters were detected.

Keywords: Riamilovir, COVID-19, SARS-CoV-2, antiviral activity.

Introduction

Viral infections are one of the most common infectious pathologies in the world. Acute respiratory viral infections (ARVI) occupy the leading position in the overall structure [1, 2]. Most diseases are caused by pathogens such as paramyxoviruses, orthomyxoviruses, picornaviruses, adenoviruses, and coronaviruses [3].

The family of coronaviruses, discovered back in 1931, currently includes 7 species that can cause disease in humans [4]. Initially, it was believed that coronaviruses do not pose a particular danger to humans, but in 2002, an epidemic of severe acute respiratory syndrome caused by the SARS-CoV coronavirus was registered in the Guangdong province of China. The epidemic spread to 29 countries, about 10 % of patients with confirmed diagnosis died [4, 5]. The outbreak of infection gave rise to study and discovery of new types of coronaviruses, including two viruses that cause human diseases — NL63 and HKU1 [4].

In 2014, there was an outbreak of Middle East Respiratory Syndrome (caused by a MERS-CoV virus) [4]. About 2.5 thousand cases of the disease were registered in 23 countries, while outbreaks from single to several dozen cases continue to be registered [4, 6].

In 2019, the world faced a new epidemic of coronavirus infection, which received the status of a pandemic [7]. An outbreak of the disease caused by the SARS-CoV-2 virus, type 2 acute respiratory syndrome virus, has now been registered in more than 118 countries [4, 7, 8].

Against the background of the spread of coronavirus infection, there is an active search and development of antiviral chemotherapy drugs that guarantee the efficacy of etiotropic therapy [2].

One of the drugs showing direct antiviral activity against RNA-containing viruses is riamilovir (Triazavirin®), registered in the Russian Federation since 2014 as a drug for the treatment of influenza. However, a number of clinical studies have shown the efficacy and safety of the drug not only for patients diagnosed with influenza, but also with ARVI of non-influenza etiology [9–13]. In our opinion, in connection with the above, it is advisable to study the potency and safety of the drug riamilovir in the treatment of infection caused by the new type of coronavirus.

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Materials and Methods

An open-label, cohort study of the clinical efficacy and safety of the antiviral drug riamilovir (Triazavirin®) in patients over 18 years of age with a confirmed diagnosis of moderate severity of COVID-19 was carried out. Treatment and observation of patients was carried out on the basis of the Federal State Budgetary Institution Polyclinic No. 3 of the Administrative Department of the President of the Russian Federation (Moscow), the municipal autonomous healthcare institution City Clinical Hospital No. 40 (Ekaterinburg), Krai Government-Owned Publicly Funded Health Care Institution Krasnoyarsk Interdistrict Clinical Hospital of Emergency Medical Care named after N. S. Karpovich (Krasnoyarsk). The severity was assessed on the basis of the criteria set out in the interim recommendations of the Ministry of Health of the Russian Federation "Prevention, diagnosis and treatment of new coronavirus infection Covid-19".

Laboratory verification of the diagnosis was carried out by polymerase chain reaction (PCR) methods using nasopharyngeal and oropharyngeal swabs.

The patients received the drug riamilovir (Triazavirin®, manufactured by OOO Zavod Medsintez, Russia) at a dose of 250 mg/TID as antiviral monotherapy. The duration of the course was 10 days. The prescription of the drug was carried out in accordance with the Decree of the Government of the Russian Federation No. 441 "On the peculiarities of the circulation of medicinal products for medical use, which are intended for use in conditions of a threat of occurrence, occurrence and elimination of an emergency and for organizing the provision of medical care to persons affected by emergencies, warning emergencies, prevention and treatment of diseases that pose a danger to others, diseases and injuries resulting from exposure to adverse chemical, biological, radiation factors." In parallel, patients were prescribed pathogenetic and symptomatic therapy. The patient's body temperature was measured daily. The primary endpoints for assessing the dynamics of body temperature were determined on the 3rd and 7th days of observation. Separately, the day of therapy was recorded, on which the body temperature reached the level of normalization.

The following parameters were used to assess the efficacy and safety of treatment: the number of days until two consecutive negative results of PCR analysis were obtained; the number of days until the patient's condition improves (based on the absence of complaints); the number of days before the normalization of body temperature (normalization of body temperature means a temperature value < 37 °C); the number of days until the improve of patient's results of lungs computed tomography (CT); change in the results of the analysis for C-reactive protein; drug tolerance.

Results and Discussion

A sample of 214 patients was randomized in the study with a moderate form of the disease, confirmed by PCR, with a diagnosis of COVID-19. Mean age was 52.69 ± 1.29 CI [50.13–55.25] years (Table 1).

Table 1. **Age data of patients included in the study**

Age range, years	%	Mean age
18–35	7±2.55	28.7±28.7 CI [23.77–33.66]
35–55	50±5.00	45.9±0.83 CI [44.30–47.54]
More than 55	43±4.95	64.5±1.16 CI [62.14–66.79]

Most of the patients (67 ± 4.7 %) had no concomitant diseases, while for the rest of the patients the following concomitant diseases were recorded:

- respiratory diseases (chronic obstructive pulmonary disease, bronchial asthma – 11 ± 3.13 %);
- diseases of the endocrine system, nutritional disorders and metabolic disorders (diabetes mellitus and obesity – 17 ± 3.76%);
- diseases of the respiratory system and diseases of the endocrine system, eating disorders and metabolic disorders at the same time (5 ± 2.18 %).

By the end of the first week of treatment (6–7 days), an improvement in the general condition was noted in 57 ± 4.95 % of patients. Moreover, according to some studies, the condition of patients who did not receive specific antiviral therapy, on average, improved only by the third or fourth week of therapy [14–16].

The first negative result (PCR analysis) for the SARS-CoV-2 virus in most patients was obtained before the 13th day of treatment (improvement was 59 ± 4.92 %, Fisher's exact test $p = 0.00001$, compared with the first PCR result). The largest number of patients with the first negative PCR result was on the 10th (42.37 ± 3.8 % of patients) and 11th (35.59 ± 3.68 % of patients) days of observation.

During the study, it was found that two consecutive negative PCR results for the SARS-CoV-2 virus were registered in most patients (63 ± 4.28 %) by 14–19 days of treatment.

The dynamics of the temperature, taking into account the endpoints, was as follows: upon admission, 100 % of patients had a body temperature higher than normal, on the third day of therapy, 18 ± 3.84 % of

patients had a normal body temperature (Fisher's exact test $p = 0.00001$), and on the 7th day of therapy, the temperature returned to normal in 100 % of patients (Fisher's exact test $p = 0.00001$). At the same time, in 75 ± 4.33 % of patients, the temperature returned to normal by the 4th day of treatment.

During the observation, an improvement in the results of lungs CT of patients was noted. Upon admission, 69 ± 4.63 % of patients had lung lesions from 25 to 50 %, 29.0 ± 4.54 % of patients had lung lesions up to 25 %, and 2.0 ± 1.4 % of patients had a degree of lung lesion over 50 %. There were no patients without lung involvement.

After treatment, a repeated CT scan (performed on average on the 19th day from the start of therapy) showed that 10 ± 3.0 % of patients had no lung lesions ($p = 0.0008$). The third CT result (1–2 months after patient's discharge showed that the number of patients with no lung lesions increased to 27 ± 4.44 % ($\chi^2 = 9.58$, $p = 0.002$) (Table 2).

Table 2. **Comparative analysis of lung lesions based on CT results — at admission, repeated CT after therapy, and CT after 1–2 months after discharge**

Lung damage	CT at admission, %	Repeated CT, %	Testing the hypothesis about differences significance	CT after 1–2 months, %	Pearson's test (χ^2, p)
No lung damage	0	10	Fisher's exact test p=0,0008	27	χ^2=9,58, p=0,002
Less than 25 %	29	22	Pearson's test χ^2=1,29, p=0,2561	54	χ^2=21,73, p=0,00001
25–50 %	69	67	Pearson's test χ^2=0,09, p=0,7618	19	χ^2=47,0, p=0,00001
More than 50 %	2	1	Fisher's exact test p=0,5	0	Fisher's exact test p=0,5

At the same time, some foreign studies have shown that in the absence of specific therapy, the condition of patients may worsen [17].

The result of the analysis of C-reactive protein in patients at baseline was lower than 10 mg/L in 33 ± 4.7 % of patients, and higher than 10 mg/L in 67 ± 4.7 % of patients.

As a result of treatment, on the 14th day of observation, in most patients (90 ± 3.0 %, $\chi^2 = 68.61$ $p = 0.00001$), C-reactive protein level was lower than 10 mg/L. At the same time, in studies where patients did not receive specific antiviral therapy, the number of patients with this indicator outside the normal range increased during therapy [17].

During the observation, no undesirable effects were revealed, manifested clinically or as significant deviations in laboratory parameters, which indicates a good tolerability of the drug. The absence of adverse events is comparable to the data on the number of adverse events in patients who did not receive specific antiviral therapy in other studies [14, 17, 18].

Study Discussion

During the observation of patients with a moderate form of Covid-19 treated with riamilovir as an etiotropic antiviral monotherapy, empirical results were obtained that are encouraging in terms of continuing study to evaluate the efficacy of the drug in the new coronavirus infection treatment. The suppression of viral activity can explain the obtained such clinical effect as the timing of general symptoms disappearance, including the relief of fever and laboratory signs of systemic inflammation, the absence of progression and the pneumonia involution, according to CT data, finally, negative PCR results for 10, 11, 14th days of illness. At the same time, in previously conducted foreign studies, it was shown that a negative result of PCR analysis was obtained by the 23rd day of observation [14].

Conclusions

1. Clinical, laboratory, and radiological data on the efficacy of the antiviral drug riamilovir in the treatment of new coronavirus infection have been obtained, requiring continuation of clinical studies.

2. The absence of adverse events in treatment with riamilovir in patients with Covid-19 indicates its good tolerance.

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