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Approaches to Etiotropic Therapy of Covid-19 in Outpatient Patients

Mukhtorova Sh. A. [1], **Jalilova A. S.** [2]

[1, 2] Bukhara State Medical Institute named after Abu Ali ibn Sino, Bukhara, Uzbekistan
shohida.muxtorova@mail.ru

Abstract: The article presents the results of a post-registration observational study to evaluate the results of early initiation of antiviral therapy in patients with COVID-19 receiving treatment at home.

Goal- to evaluate the efficacy and safety of antiviral therapy for the treatment of outpatient patients with coronavirus infection caused by SARS-COV-2.

Materials and methods. The study included 200 outpatient patients with COVID-19. According to etiotropic therapy, patients were divided into 3 groups: those who received favipiravir, hydroxychloroquine and those who did not receive antiviral agents.

Results. The average time to virus elimination while taking favipiravir was 3 (3.0-5.0) days, among those receiving hydroxychloroquine – 5 (4.0-6.0) days, without antiviral therapy – 8.5 (7.0-10.0) days. Normalization of body temperature occurred faster with favipiravir therapy.

Conclusions. Antiviral therapy in outpatient patients with COVID-19 is effective and safe. . Taking favipiravir promotes earlier elimination of the virus, faster normalization of body temperature and a favorable outcome of the disease. Hydroxychloroquine may be prescribed as an alternative antiviral drug to outpatient patients in the absence of a risk of severe course..

Keywords: COVID-19, SARS-CoV-2, coronavirus infection, hydroxychloroquine, favipiravir, virus elimination.

Introduction

For the third year in our world, the pandemic caused by the SARS-CoV-2 virus continues. Despite active vaccination and clinical studies that have confirmed the effectiveness of a large number of drugs for the treatment of COVID-19, coronavirus infection remains one of the main health problems in all countries of the world. The search for optimal therapy regimens continues. One of the main properties of SARS-CoV-2, contributing to further spread, was a pronounced ability to change the genetic structure, leading to a decrease in the effectiveness of vaccination, repeated episodes of COVID-19 with new features of symptoms. Already according to the first estimates of the epidemic in 2020, a high susceptibility to the pathogen was noted in all population groups and a pronounced tendency to severe course, which prompted an active search for therapeutic agents [1-6]. The course of the new COVID 19 coronavirus infection caused by SARS CoV 2 in adults varies from asymptomatic and mild symptoms of respiratory tract disease to severe pneumonia with acute respiratory distress syndrome (ARDS) and multiple organ dysfunction.

Studies conducted at the beginning of the pandemic showed that the main approach to the treatment of COVID-19 should be the proactive appointment at the early stages of an effective therapeutic regimen that prevents the development of life-threatening conditions such as pneumonia, acute respiratory distress syndrome (ARDS), cytokine storm, COVID-associated coagulopathy, sepsis [7-10]. Currently, there are several drugs that can be used in the treatment of COVID-19. These include

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favipiravir, remdesivir, interferon-alpha intranasally in combination with umifenovir, molnupiravir, as well as antiviral monoclonal antibodies [11,14].

The course of the new COVID 19 coronavirus infection caused by SARS CoV 2 in adults varies from asymptomatic and mild symptoms of respiratory tract disease to severe pneumonia with acute respiratory distress syndrome (ARDS) and multiple organ dysfunction.

According to the current protocols, favipiravir and remdesivir, as well as kasirivimab-imdevimab - a cocktail of monoclonal antibodies are used in the Republic of Uzbekistan for the treatment of patients with a new coronavirus infection. In many countries, the need for the use of etiotropic therapy is still being discussed.

Favipiravir was the first drug that passed all stages of clinical trials involving patients with COVID-19. It is an antiviral drug, a selective inhibitor of RNA polymerase, active against RNA-containing viruses. The original drug favipiravira Avigan was developed by the Japanese company Toyama Chemical / Fuji Film in 1998. According to the results of the conducted studies, clinical improvement in patients with COVID-19, according to the WHO scale (namely, recovery or the presence of symptoms that do not limit the usual loads), when taking favipiravir was achieved significantly faster (on average, after 6.0 days) than when using umifenovir in combination with intranasal interferon alpha-2b or hydroxychloroquine (on average, in 10 days) [11,12,15]. The frequency of clinical improvement on day 7 in the favipiravir group was 1.5 times higher compared to the control group: 52.7% vs. 35.8% ($p = 0.020$). In the course of post-registration observational studies, the reasons for the absence in some cases of a positive result from the use of this drug were revealed, consisting in violation of recommendations on dosages and regimens of its administration [11,13].

Currently, favipiravir and hydroxychloroquine are recommended in Rep -19.

Given the variability of the virus, it is obvious that a post-registration evaluation of the Republic of Uzbekistan for outpatient use in the treatment of COVID is necessary to assess the effectiveness and safety of the use of basic antiviral drugs.

The purpose of the study- to evaluate the efficacy and safety of antiviral therapy for the treatment of outpatient patients with coronavirus infection caused by SARS-COV-2.

Materials and methods. The observational post-registration study included 200 outpatient patients aged 18 to 90 years with a confirmed PCR method of COVID-19. Patients had a mild (26%) or moderate - severe (74%) course of the disease. Among the symptoms of coronavirus infection in all cases, the body temperature was above 37.3 ° C, weakness, muscle pain were recorded, there was a slight or moderate hyperemia of the pharynx, as well as signs of viral pneumonia with lung damage by the type of frosted glass, according to computed tomography, with a prevalence of 5 to 50%. The study included patients who had no more than 10 days from the onset of the disease to the appointment of therapy.

According to etiotropic therapy, the patients were divided into 3 groups: 112 of them received favipiravir (group 1), 32 - hydroxychloroquine (group 2), 56 - did not take any antiviral drugs.

In group 1, favipiravir was administered orally 30 minutes before meals according to the standard recommended regimen: at a weight of 75 kg or more – 1800 mg 2 times a day for the first day, then 800 mg 2 times a day. In group 2, patients took hydroxychloroquine orally on the first day for 200 mg twice a day, after one tablet for 6 days. The recommended course of treatment with favipiravir was 10 days with the possibility of discontinuation of the drug upon recovery, but not earlier than 6 days from the start of taking the prescribed medication. The deterioration of the condition with the need to replace drugs was taken into account when analyzing the results of observation. Patients of all groups received pathogenetic and symptomatic therapy in accordance with the temporary guidelines for the treatment, diagnosis and prevention of COVID-19 of the Ministry of Health of the Republic of Uzbekistan in force at the time of the study. Most patients received oral anticoagulants, paracetamol at a body temperature of more than 38 ° C, local antiseptics for irrigation of the nasal cavity and throat, mucolytic and antibacterial therapy. Anti–inflammatory drugs (from the group of

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corticosteroids and / or janus kinase inhibitors) were prescribed, if necessary, in situations with no effect from the therapy, no earlier than 3 days after the start of taking the antiviral drug (in 47% of patients).

All groups were completely comparable in gender, age, severity of the disease, clinical manifestations, time from the start of therapy, concomitant pathology. The time from the start of therapy to the elimination of the virus, the number of patients with normalization of body temperature by day 7 and 14, the frequency of cases of deterioration with the need for hospitalization were evaluated.

During statistical processing, the average values of M and the confidence interval were calculated. A two-way Z-test was used to determine the statistical significance of the differences. The differences were considered significant at $p<0.05$.

Results and discussion. The average time to virus elimination between the groups significantly differed, amounting to 3 (3.0-5.0) days against the background of taking favipiravir, 5 (4.0–6.0) days among those receiving hydroxychloroquine, 8.5 (7.0-10.0) days without antiviral therapy. Normalization of body temperature also occurred significantly faster with favipiravir therapy than in the absence of antiviral therapy: after 3.3 (1.5-6.5) days. There were no significant differences compared to group 2. In group 3, the period before fever relief was 8.6 (3.5-13.2) days. In most cases, if the fever persisted, it was necessary to adjust the therapy regimen 2-3 or more times. Among these patients, hospitalization was required in 45% (25 patients). In the group receiving favipiravir, the proportion of hospitalized patients was significantly less: 23% (36 patients). There were no significant differences compared to group 2 (28% - 9 patients were hospitalized). Among the patients receiving Favipiravir, there was not a single case of hospitalization in the intensive care unit, there were no deaths.

It is obvious that the direct antiviral effect of drugs contributes to faster elimination of the virus. A longer stay of the virus in the body is the cause not only of a prolonged course, but also of significant complications. An earlier normalization of temperature correlates with the timing of recovery. The study showed that favipiravir acts more actively than hydroxychloroquine. The effectiveness of both drugs is reliably visible when comparing the results of therapy in the absence of antiviral agents.

Not all patients are justified in prescribing the most effective drug. In the absence of risks of infection progression and severe course, the appointment of hydroxychloroquine with a possible transition to a more active favipiravir while maintaining symptoms is justified.

In addition, the study showed that with COVID-19, sustained improvement with subsequent recovery can be achieved only with the use of complex therapy regimens.

In addition to systemic antiviral therapy, outpatient patients need to prescribe antiseptics for irrigation of the nasal cavity and throat, prevention of thrombosis and thromboembolism, if indicated (shock, pronounced increase in C-reactive protein and interleukin-6) – anti-inflammatory therapy (janus kinase inhibitors, corticosteroids). It is important to supplement the treatment regimen with antibacterial drugs in time with the development of bacterial infection or sepsis. In many cases, it is necessary to add probiotics and/or antifungal drugs. Additionally, detoxification therapy, metabolic and oxygen therapy can be used in the treatment.

Conclusions. Antiviral therapy in outpatient patients with COVID-19 is effective and safe. Taking favipiravir promotes earlier elimination of the virus, faster normalization of body temperature and a favorable outcome of the disease. Hydroxychloroquine may be prescribed as an alternative antiviral drug to outpatient patients in the absence of a risk of severe course.

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