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EFFICACY AND SAFETY OF ANTIVIRAL THERAPY IN PATIENTS HOSPITALIZED WITH COVID-19

1. **Oblokulov A.R.**
2. **Elmurodova A.A.**
3. **Mukhtorova Sh.A.**
4. **Nurova O.K.**

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[1,2,3,4] Bukhara State Medical Institute named after Abu Ali ibn Sino
[1] a.obloqulov59@gmail.com

Annotation: The article presents the data of a post-registration observational study to evaluate the results of the use of remdesivir and favipiravir in an infectious hospital.
The aim is to evaluate the efficacy and safety of the use of the drugs remdesivir and favipiravir in hospitalized patients with pneumonia caused by the SARS-CoV-2 virus.
Materials and methods. The study included 150 patients aged 18 to 98 years hospitalized with COVID-19, confirmed by PCR and complicated by pneumonia. 60 patients received remdesivir, and 90 - favipiravir of these.
Results. The average period before reaching a satisfactory condition and discharge from the hospital was significantly less in the group receiving remdesivir than when using favipiravir. There is less need to replace therapy, there have been no cases of its cancellation due to poor tolerability when using remdesivir.
Conclusion. Remdesivir is a more effective and safer drug for the treatment of COVID-19 in patients with pneumonia.

Keywords: coronavirus infection, COVID-19, favipiravir, remdesivir, SARS-CoV-2, viral pneumonia.

Relevance of the topic

COVID-19 is an acute viral disease with predominant respiratory tract involvement caused by the RNA genomic virus SARS-CoV-2. The main source of infection is a sick person with characteristic respiratory symptoms. Studies have shown that the virus can be transmitted from a sick person both in the prodromal and incubation periods, when there are no characteristic clinical symptoms, which significantly reduces the effectiveness of anti-epidemic measures. Already the first estimates of the epidemic in 2020 showed high susceptibility to the pathogen in all population groups and a pronounced tendency to a severe course, which prompted an active search for therapies [1-6].

The course of the new coronavirus infection COVID 19, caused by SARS CoV 2, in adults ranges from asymptomatic and mild respiratory tract symptoms 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 COVID-19 treatment should be the proactive prescription of an effective therapeutic regimen early on, preventing the development of life-threatening conditions such as pneumonia, acute respiratory distress syndrome (ARDS), cytokine storm, COVID-associated coagulopathy, sepsis [7-10]. Currently, several drugs that can be used in the treatment of COVID-19 should be distinguished. These include favipiravir, remdesivir, interferon-alpha intranasally in combination with umifenovir, molnupiravir, and antiviral monoclonal antibodies [11,12].

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

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

The first drug to undergo all stages of clinical trials with COVID-19 patients was favipiravir. It is an antiviral drug, a selective RNA polymerase inhibitor active against RNA-containing viruses. The original favipiraviravir drug Avigan was developed by the Japanese company Toyama Chemical / Fuji Film in 1998. According to the results of these studies, clinical improvement in patients with COVID-19, according to the WHO scale (namely, recovery or the presence of symptoms not limiting habitual activities), was achieved significantly faster (on average, in 6.0 days) when taking favipiravir than when using umifenovir in combination with intranasal interferon alfa-2b or hydroxychloroquine (on average, in 10 days) [11, 12]. The frequency of clinical improvement at day 7 was 1.5 times higher in the favipiravir group compared with the control group: 52.7% vs. 35.8% ($p = 0.020$). In the course of post-registration observational studies, the reasons for the lack of positive results from the use of this drug in some cases were identified, consisting in violation of the recommendations on the dosage and regimen of its administration [11]. The need for an active antiviral drug for therapy in cases of individual intolerance or inability to take it orally led to the rapid emergence in clinical practice of an agent for infusion - remdesivir.

Remdesivir is an FDA-approved medication that inhibits COVID-19 replication. It can help speed recovery from COVID-19 and reduce the risk of severe COVID-19. [1,2].

Remdesivir is a nucleoside analog and is a prodrug. On entering the cell it is metabolized to active triphosphate, which binds to the RNA polymerase of the virus, incorporates into the growing chain of viral RNA and leads to its termination, thus stopping replication. In a series of scientific works it was shown that remdesivir binds to one of the conserved domains of RNA-dependent RNA polymerase of coronaviruses, which enables its application not only against human, but also against a wide range of different zoonotic coronaviruses [13]. The efficacy and safety of remdesivir have been studied in a number of clinical trials [14-16]. Analysis of the results shows that the efficacy of therapy may be influenced by features of the circulating variant of coronavirus, symptomatology of coronavirus infection, severity of course, duration of prescription from onset, concomitant therapy, and age and ethnic characteristics of the population being evaluated, which requires new studies. Publications cite the cost-effectiveness of remdesivir for hospitalized patients with COVID-19 and identify key value factors to help guide future pricing and reimbursement efforts [17].

The objective was to evaluate the efficacy and safety of remdesivir and favipiravir in hospitalized patients with SARS-CoV-2 pneumonia.

Materials and Methods

An observational post-registration study included 120 patients aged 18 to 98 years hospitalized with COVID-19-associated pneumonia. Coronavirus infection caused by SARS-CoV-2 was confirmed by PCR. Pneumonia was diagnosed on the basis of complaints, auscultation findings, and chest radiography or multispiral computed tomography (MSCT) findings.

Patients in extremely severe condition with acute respiratory distress syndrome, shock, multiple organ failure, in severe forms with indications for invasive AV (with SpO2 oxygen saturation < 92% on noninvasive AV) were not included in the study.

Inclusion criteria also included pregnancy or breastfeeding, and drug dependence.

All patients received local antiseptics, parenteral anticoagulant drugs (heparin or enoxaparin) and antiaggregants, and anti-inflammatory, antibacterial and metabolic therapy as indicated. Of the etiotropic antiviral agents, 60 patients received Remdess (remdesivir) (the main group), and 60 patients received favipiravir (comparison group).

Comparison groups were comparable in terms of age, gender composition, time from the beginning of the disease to the prescription of etiotropic therapy.

The mean age of patients in the main group was 60.2 (±12.3) years, in the comparison group - 59.4 (±12.9) years. Co-morbidities were observed in the vast majority in both groups: 75% of patients receiving remdesivir and 71% of patients receiving favipiravir. Hypertension and CHD were the most common.

The mean duration of illness from the onset of the first symptoms was 8.9±3.7 days.

We evaluated the time from the start of antiviral therapy until the patient reached a satisfactory condition and was discharged from the hospital, the frequency of need to change therapy, the number of patients who recovered on days 5-7 and 14, the dynamics of C-reactive protein level and leukocyte number on days 4-7 of treatment. Transaminase levels (aspartate aminotransferase and alanine aminotransferase), and creatinine were additionally analyzed.

Statistical data processing was performed using R programming language. The choice of statistical analysis method was determined by the type of initial data, type of distribution. To estimate the primary endpoint - time to satisfactory condition and possibility of patient's discharge from hospital we calculated the difference of median (Me) and arithmetic mean (M) times, taking into account standard deviation (SD) with 95% confidence interval (CI). Results were analyzed using log-rank criterion, Kaplan-Meier method. Hazard Ratio (HR) with confidence intervals and Cox proportional hazards model was used for frequency analysis. Categorical data were also processed using frequency tables, Fisher's exact test, and Pearson's criterion. Categorical data were described using percentages or fractions. Comparison of clinical and laboratory parameters was performed using Student's t-test, Mann-Whitney U-test (nonparametric criterion for two independent samples), Wilcoxon T-test (nonparametric criterion for two dependent samples). The choice of criterion (parametric or nonparametric) was made after checking the type of data distribution for compliance with the normal distribution law using the Shapiro-Wilk criterion.

Results and Discussion

The mean period until satisfactory progression to discharge was significantly shorter (4.3±2.1 days) in the Remsivir group than in the Favipiravir group (6.1±2.8 days). When using remdesivir, the need to correct the therapy was detected less frequently (in 8% - in 5 patients), and against the background of taking favipiravir - in 20% (18 patients). In most cases, favipiravir was replaced by remdesivir, and additional anti-

inflammatory therapy (corticosteroids) and/or antibacterial drugs were prescribed. There were no cases in which remdesivir had to be withdrawn due to poor tolerance.

It should be noted that the proportion of cases of clinical recovery on days 5-7 and 14 showed no significant differences between the groups: on days 5-7 - in 45% (27) patients when prescribed remdesivir and in 44% (40) patients when given favipiravir. On the 14th day recovery was noted in 90% (54) patients in the main group and 84% (50 patients) in the comparison group, indicating the high effectiveness of both drugs compared.

No lethal outcomes were registered. The mean time to fever relief was very short: 2.51±1.27 days in patients receiving remdesivir and 3.02±2.41 days with favipiravir. This period was significantly shorter than with other drugs or without the use of etiotropic therapy [18,19].

Among the biochemical markers evaluated, the level of C-reactive protein - the main indicator of inflammatory process activity on days 5-7 remained elevated significantly less frequently when using remdesivir: in 57% (in 34 patients), and when using favipiravir - in 87.0% (in 52 patients). This testifies to more active suppression of inflammation in the main group and confirms higher effectiveness of remdesivir for prevention of disease progression. The increased level of C-reactive protein correlates with the volume of lung tissue damage and the risk of developing life-threatening conditions.

Transaminase levels were significantly higher on days 5-7 in the group treated with favipiravir, but no difference was detected on day 14. The average creatinine values on days 5-7 of therapy in both groups were comparable.

Thus, remdesivir and favipiravir are effective drugs for the treatment of COVID-19. With the ongoing pandemic and the emergence of new strains of the virus, it is imperative to have a choice of drugs. It is obvious that parenteral - intravenous administration will increase the effectiveness of the drug in severe and extremely severe course, in the development of multiple organ failure, in vomiting, various gastrointestinal tract diseases, abdominal blood supply disorders. Therefore, remdesivir, which is available in a dosage form for infusion, is required primarily in the group of patients with pronounced progressive symptoms, as well as in case of individual intolerance to favipiravir and liver diseases.

Conclusion. Antiviral therapy prevents progression of symptoms and shortens the duration of illness in patients hospitalized with SARS-CoV-2 pneumonia. Remdesivir is more effective and safer to treat COVID-19 than favipiravir.

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