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Early Onset of Favipiravir Saves Lives-Expert Review

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Introduction

SARS-CoV-2 is an enveloped, positive-polarity, and single-stranded RNA virus that belongs to the beta-coronavirus group. SARS-CoV-2 is a zoonotic pathogen and can cause symptoms ranging from mild clinical course to severe lower respiratory tract infection, Acute Respiratory Distress Syndrome (ARDS), when it infects humans [1]. SARS-CoV-2 has a genetic similarity of 79% to SARS-CoV, 50% to MERS-CoV, and ~96% to coronaviruses found in bats. The main feature of SARS-CoV-2, which appears to have been formed as a result of a new mutation, is that it easily binds to the ACE2 receptor, especially lung type 2 alveoli cells in humans, and uses the ACE2 receptor as the entry gate to the cells [2]. Replication of the virus, which enters the cell by binding to ACE2, begins, and the inflammatory reaction chain is triggered. Depending on the age of the host and the immune system, the severity of the inflammatory reaction occurs. It mainly affects the natural immune system and leads to the release of cytokines. They are viruses with positive polarity. They do not contain RdRP enzymes but the genetic structure to code. They produce this enzyme in the host cells they enter. In the presence of an effective RNA-dependent RNA polymerase inhibitor, it is thought that this drug may be effective against the replication of the virus and possible mutations that the virus may pass through. SARS-CoV-2 is mainly spread through droplets and direct contact. The contagious rate is high. The average incubation period of COVID-19 infection is 5.5 days. However, it was reported that it could extend up to 14 days [3]. The most common symptoms are fever, fatigue, muscle pain, sore throat and dry cough, dyspnea, less commonly nausea, vomiting, and diarrhea [4]. In 80% of the cases, the symptoms are mild-moderate [5]. In mild cases, there may be complaints similar to upper respiratory tract infection, mild fever, and muscle pain that do not affect daily life, and there may not be any symptoms during the contagious period. Another characteristic of patients who develop severe COVID-19 infection is a high viral load and prolonged virus excretion [7]. The main cause of hospital admissions is pneumonia. Causes of death are respiratory failure, circulatory failure due to myocardial damage, and respiratory and circulatory failure [6]. Although various protocols have been tried in the treatment of COVID- 19, there is still no standard treatment option established by traditional evidence-based methods. 200 mg hydroxychloroquine sulfate twice a day for 5 days and oseltamivir in cases in which influenza cannot be excluded, azithromycin, and/or hydroxychloroquine sulfate for 5 days in patients diagnosed with uncomplicated probable/definite COVID-19, age (>50), risk factors or low prognosis indicators and oseltamivir in cases in which influenza cannot be excluded, azithromycin, hydroxychloroquine sulfate and/or Favipiravir for 5 days in cases with severe pneumonia and oseltamivir in cases where influenza cannot be excluded, and Favipiravir or lopinavir 200 mg/ritonavir 50 mg tablets for 10-14 days in addition to hydroxychloroquine in patients whose clinical condition became severe or whose pneumonia symptoms progressed while receiving hydroxychloroquine treatment were recommended for treatment. As a support treatment, antibiotic administration is recommended in ARDS cases, including 1-2 mg/kg/day, methylprednisolone for 5-7 days with a "poor level of evidence," and in severe pneumonia by including atypical pneumonia. Anti-cytokine/anti-inflammatory treatments such as Tocilizumab and Anakinra can be tried in patients with macrophage activation syndrome (MAS) characterized by a cytokine storm. Coronavirus can lead to thromboembolic complications as a result of vascular micro thrombotic disease in patients who develop stasis or sepsis directly associated with endothelial damage, inactivity, or hospitalization. Therefore, low molecular weight heparin (enoxaparin 40 mg/day) prophylaxis should be administered to all COVID-19 patients [8].

Methods

Patients

This study was carried out in Tuzla State Hospital with the approval of the Marmara University Faculty of Medicine Ethics Committee after obtaining permission from the Scientific Research Unit of the Ministry of Health and with the permission of Istanbul Provincial Health Directorate. Patients with severe COVID-19 pneumonia who were admitted to Tuzla State Hospital between 20/3/2020 and 30/5/2020 and treated with Favipiravir at any stage of their treatment were examined retrospectively. The study included patients aged over 18, non- pregnant (for women), with or without comorbid, and those who have severe pneumonia (respiratory rate > 30/min) and/or severe respiratory distress (dyspnea or use of extra respiratory muscles) and/or fingertip oxygen saturation <90% (PaO2/FiO2<300 in patients receiving oxygen) and were treated with Favipiravir at any stage of their treatment and have bilateral multi-lobar ground glass densities in computed tomography (CT).

Data collection and analysis

The research data were collected retrospectively through the Tuzla State Hospital registration system. Descriptive statistics, categorical variables, and mean ± SD or median and interquartile range for continuous variables. Comparisons were determined by t-test. The SPSS 22.0 statistics method was used.

Results

We examined 180 patients hospitalized in Istanbul Tuzla State Hospital and treated with Favipiravir between 20/3/2020 and 30/5/2020. The mean age of the patients is 59±17.4. The number of patients aged ≤ 65 years is 108, and ≤ 65 years old mortality rate is 12%. 15 of 108 patients died. The average age of the patients who died was 71.0±14.7, and the average age of the recovered patients was 54.7±16.3

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($p<0.001$). The number of patients aged >65 years is 72 patients, and the mortality rate is 45%. 32 of 72 patients died. This means that the mortality rate increases as age increases. While the mortality rate was 64% in males and 36% in females (17 of the 47 patients who died were female and 30 were male). It was found that those with one or more comorbidities had higher mortality rates. We observed that as the number of comorbidities increased, the mortality rate increased. The comorbidities of patients were listed as hypertension (79 patients have a diagnosis of hypertension, 29 patients use ACEIs, and 36 patients use ARB), hyperlipidemia (57 patients diagnosed with hyperlipidemia), diabetes mellitus (52 patients with diabetes mellitus diagnosis), and CAH (33 patients with a diagnosis of CAH). Of the 47 patients who died, 42 had at least one comorbid disease (89%). 63% of 180 patients had at least one comorbid disease. When the symptoms at admission are evaluated, cough (52%, 94 patients), dyspnea (47%, 86 patients), and fever (45%, 82 patients) are the first three clinical findings. When the blood types of the ex-patients were examined, the majority were blood type A. When we examined the blood types, the A blood type mortality was found to be the highest. While the A blood type was 55% in all patients, the A blood group was 68% in the ex-patients. The rate of A blood group was higher than the non A-blood groups, among ex patients. (p:0.03).

Anemia, leukocytosis, neutrophilia, lymphopenia, and thrombocytosis were found in the hemogram of the patients at the time of the first application, who later died. We found that ex-patients had significantly higher levels of CRP, D-dimer, LDH, and Ferritin. When we evaluated the Favipiravir initiation time after hospitalization, we found that the mortality rate was significantly lower in those who received Favipiravir treatment within the first 72 hours of hospitalization (p:0.002). Regarding patient characteristics, there was no difference between the characteristics of patients who were started Favipiravir in the first 3 days and after 3 days ($p>0.05$).

Discussion

Based on the experience of other viral infections, the opinion prevails that early antiviral therapy will be more useful in the treatment of COVID-19. The most important benefit of early antiviral therapy is that it reduces the rate of viral replication. The greatest experience of the benefits of early antiviral therapy has been observed during Influenza treatment. SARS, MERS, and COVID-19 are viruses with similar genetic structures [9]. Fiore AE et al. found that antiviral treatment initiated with the correct indication in the first 48 hours of influenza significantly shortened the disease duration, provided a milder course, and prevented the development of complications, especially secondary infections [10]. In severe influenza infection, late-onset antiviral treatment was identified as an independent risk factor for longer- term viral transmission, long-term viral detection, and disease progression [11]. Uyeki TM et al. claimed that early antiviral treatment in seasonal influenza reduces the duration of symptoms, reduces hospitalization, reduces the risk of complications (reduces secondary cases such as pneumonia, bronchitis, and otitis media), and can reduce mortality in the high-risk population [12]. Hsu J et al. observed that when oral oseltamivir is taken within the first 48 hours of infection in influenza, it reduced mortality, hospitalization, ICU admission, and respiratory failure compared to subsequent treatment [13]. Studies analyzing data from the 2009 influenza A/H1N1 pandemic have consistently shown that delays in initiating antiviral treatment following symptom onset are significantly associated with disease severity and death. Optimal survival and minimal disease severity occur when antivirals are initiated as soon as possible after symptom onset [14]. Delays in starting treatment with oseltamivir for influenza A/H1N1 infections in 2009 were associated with more severe disease [15]. It is known that antiviral treatment is most likely to be beneficial when initiated earlier in the course of the disease in both influenza and SARS. Similarly, since it is not known precisely which patients will have a more severe course of viral infection, antiviral treatment should be initiated without delay, especially in the elderly, patients with multiple chronic diseases, and COVID- 19 patients who meet the clinical and laboratory criteria for the severe disease at the time of onset. Against MERS-CoV, Sheahan et al. [16] evaluated the therapeutic efficacy of Remdesivir among infected mice and found that the treatment significantly reduced virus lung titers, weight loss, lung bleeding, and lung injury rates. The researchers suggested the importance of initiating early treatment to reduce virus replication and promote pulmonary repair because Remdesivir showed less clinical benefit with high-titer virus vaccination. Most importantly, the researchers also noted that prophylactic Remdesivir reduced MERS-CoV replication and disease and was similar to findings in the mouse model with SARS-CoV-1.

Early antiviral therapy can effectively shorten the virus clearance time and prevent the rapid progression of COVID-19. Therefore, COVID-19 patients should receive combination treatments with antiviral treatment at an early stage. In a study with Remdesivir, another nucleoside analog, Wang Y et al. found that patients taking Remdesivir had a numerically faster clinical recovery time among patients with symptom duration of 10 days or less than those receiving placebo. Similarly, studies have shown that early antiviral treatment is successful in COVID-19, which has not yet had a definitive treatment or vaccine. In their study, Wu J et al. found that older adults and patients with underlying diseases are more likely to experience severe COVID-19 progression. It is recommended to start antiviral treatment in time to slow the progression of the disease and improve the prognosis. Ting Yu et al. divided 129 confirmed mild to moderate COVID-19 patients who were treated with antiviral drugs at the time of their hospitalization at Wuhan Union Hospital, China, into the early antiviral treatment group and the late antiviral therapy group they included. Demographic data, laboratory tests, virus recovery time, and chest CT scans were collected, calculated, and compared between the two groups. The resulting data showed that the median time from the onset of the disease to the onset of antiviral treatment in all patients was 6 days. The group receiving early antiviral treatment showed 7 days shorter virus recovery time compared to the group receiving late antiviral treatment. After the virus was cleared, the group receiving early antiviral treatment showed milder disease than the group receiving late antiviral treatment. Early antiviral treatment can effectively shorten the virus recovery time and prevent the rapid progression of COVID-19. Therefore, COVID-19 patients should receive treatments combined with antiviral treatment at an early stage [17].

Conclusion

The primary defense mechanism against viral infections is the response formed by the humoral immune system. However, in some infectious diseases, such as COVID-19, the immune system may not be able to neutralize the virus. In these cases, it is necessary to use treatments that will reduce the rate of replication of the virus. Early antiviral drugs will reduce the rate of viral replication and save time for the humoral defense mechanism to neutralize the virus. In our study, we found that the initiation of Favipiravir, an RdNP inhibitor antiviral, within the first 72 hours after the onset of disease symptoms significantly reduced mortality. Nevertheless, the research has limitations, such as the fact that the study was conducted with the participation of a small group of patients.

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