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Safety Evaluation and Tolerability Overview of Favipiravir in the Management of COVID-19: A Real-Life Experience from Turkey

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ABSTRACT

Introduction: Coronavirus diseases-2019 (COVID-19) have been ongoing for more than two years. Despite the scientific research conducted in this process, there is still no widely accepted definitive treatment for the disease. For treating COVID-19, using antiviral agents previously used for the treatment of other RNA-virus infections has been seen as a fast way to a solution, and favipiravir is one of the leading agents. This prospective, multicenter, observational study was designed to investigate the safety of favipiravir in 500 patients treated with favipravir for favipravir.

Methods: This study was conducted as a multicenter prospective study. Eight different sites from four cities participated, and 500 patients were included in the study. Follow-up of laboratory parameters, adverse events (AEs), and amelioration of fever, dyspnea, and cough symptoms of the patients was recorded in a case report form.

Results: A total of 475 patients from eight centers completed the study. A total of 401 AEs were reported in 206 (51.4%) patients, which were mild-to-moderate in the majority of cases. Serious AEs occurred in 5 patients and death occurred in 4 patients. From the first to the last measurement, serum alanine aminotransferase levels (31.9±27.7 vs. 47.2±49.7 U/L, $p<0.001$) increased, whereas C-reactive protein (39.9±66.4 vs. 15.2±30.5 mg/L, $p<0.001$) and creatine kinase (101.7±187.7 vs. 71.9±43.5 U/L, $p=0.018$) levels decreased. In follow-up parameters, oxygen saturation (SpO_2; 96.2±2.7 vs. 97.5±2.1%, $p<0.001$) and amelioration of fever (>37.8 for 6.6% on day 3, 3.2% on day 5, and 0.6% on day 10), dyspnea (for 56.4% on day 5, 62.4% on day 7, and 81.2% on day 10), and cough (46.0% on day 5, 73.0% on day 7, and 87.3% on day 10) were noted in an increasingly higher percentage of patients with continued therapy.

Conclusion: The current study provides real-life data of favipiravir, which is a unique option in Turkey for treating COVID-19 patients. The results revealed that favipiravir is a well-tolerated agent with a low side-effect profile. However, it needs to be evaluated with well-designed, dose-compared, randomized controlled studies for the evaluation of efficacy.

Keywords: COVID-19, favipiravir, adverse event, safety, real-life, Turkey

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Introduction

The coronavirus disease-2019 (COVID-19), an infectious disease caused by a novel severe coronavirus designated as severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), has spread rapidly worldwide and has placed an enormous burden on the healthcare system since its onset in Wuhan, China, at the end of 2019 (1-6).

Although there is currently no worldwide accepted specific antiviral therapy with proven efficacy for COVID-19, the use of potent antiviral agents approved for other viral infections as repurposed drugs against SARS-CoV-2 is considered one of the quickest strategies for the response to the COVID-19 outbreak and a pragmatic way to accelerate the drug approval process (6-9).

Favipiravir is an oral broad-spectrum RNA-dependent RNA polymerase (RdRp) inhibitor that acts as a nucleotide analog that selectively inhibits viral RNA-dependent RNA polymerase or causes lethal mutagenesis after incorporation into viral RNA (5,6,10-12). It is considered to be effective against infections caused by not only influenza virus but also by a wide range of RNA viruses (5,8). Given that SARS-CoV-2 has a genome sequence that is 75-80% identical to that of SARS-CoV, the existing treatment for SARS and middle east respiratory syndrome is suggested to be helpful for developing COVID-19 therapeutics (13,14). Early clinical studies in favipiravir-treated COVID-19 patients have shown promising results in terms of rapid viral clearance as well as improvement in clinical and radiological outcomes compared with other repurposed antiviral drugs (7,8). In the treatment guidelines of many countries, favipiravir has been used for a period of time for the treatment of both outpatients and inpatients, but it has never been used in many other countries (15). However, in some studies published later, the effectiveness was found to be insufficient. It has been used from March 2020 to February 2022 in Turkey, and this study examines the side effects and safety profile in patients who started favipiravir from the first period of use (7,8,15-18). This prospective, multicenter, observational study was designed to investigate the safety of favipiravir in 500 patients under treatment of COVID-19 with favipravir.

Methods

Study Population

The study was conducted between 24 December 2020 and 19 February 2021. A total of 500 patients diagnosed with COVID-19 who were prescribed favipiravir (2x800 mg; 1 day, then 2x600 mg; 4 days) treatment were included in this prospective observational study conducted at eight centers across Turkey: XX[1], XX[2], XX[3], XX[4], XX[5], XX[6], XX[7], XX[8] (Table 1). Adult (≥18 years of age) patients with lung computed tomography imaging or reverse transcription polymerase chain reaction analysis-based diagnosis of COVID-19 who were planned to receive favipiravir treatment but not yet received the first dose were included in this study. Patients who had become unable to take oral medication due to disease progression, patients on another trial, and patients with allergy or hypersensitivity to any of the treatment agents and/or any of the excipients of the products as well as those with severe liver disease [Child-Pugh score ≥C, aspartate aminotransferase (AST) >15 times the upper normal limit], severe renal impairment (glomerular filtration rate ≤30 mL/min/1.73 m^2) or need for dialysis or renal replacement therapy, and pregnant or breastfeeding patients were excluded from the study. Ethical approval was taken from Gaziantep University Clinical Research Ethics Committee (approval number: 2020/18, date: 24.07.2020). Written informed consent was obtained.

Study Design

All patients diagnosed with COVID-19 were treated in accordance with the official COVID-19 Adult Treatment Algorithm guidance established by the Republic of Turkey MoH (18). Favipiravir treatment (1600 mg of loading dose BID on day 1 followed by 600 mg BID from day 2 to day 5-rarely up to day 10) was applied in accordance with the prescribing recommendations according to the treatment algorithm established against COVID-19. In line with the observational study design, the decision to initiate treatment with favipiravir, the time of hospital discharge, and the frequency and timing of visits were at the treating physician's discretion (Figure 1). The time frame of this study was defined as 14 days, and at the end of favipiravir treatment, all patients (outpatients, discharged and hospitalized) were followed up for up to fourteen days from the first medication day of the treatment. Outpatients were asked to bring their patient's diary on the day of the end of the study visit. Site investigators examined the patients, and biochemical and hematological analyses were performed if deemed necessary.

Assessments

In the clinical study, data on patient demographics (age, gender), complete physical examination, vital signs, body temperature (ºC),

Table 1. Sites and numbers of patients included in the study

Patients / Site	Screened	Included	Completed the study	Discontinued
Gaziantep University Hospital	207	200	198	2
Antalya Training and Research Hospital	131	131	123	8
Dokuz Eylül University Hospital	55	55	54	1
Dr. Suat Seren Chest Disease and Surgery Training and Research Hospital	35	29	25	4
Akdeniz University Hospital	33	33	27	6
Gaziosmanpaşa Training and Research Hospital	24	24	23	1
İzmir Katip Çelebi Training and Research Hospital	22	22	22	0
İzmir Tepecik Training and Research Hospital	6	6	3	3

Study	Medication Days		End of Study	Early withdrawal
	Day 1- Screening and Medication Day	Other Medication Days after Day 1	Discharge day** or 14th day of the initiation of the medication	
Informed consent	•			
Inclusion/ exclusion criteria	•			
Demography (Birth date, ethnic group, gender)	•			
Medical/Surgical history	•			
Comorbid Condition	•			
12-lead ECG	•		•	
Clinical/Physical examination*	•	•*	•	
Confusion or Tachicardia*	•		•	
Tachipnoea*,γ	•		•	
SPO_2	•		•	
Difficulty of Breath		• γ		
Severity of Cough		• γ		
Biochemistry and haematology*	•	• *	•	
Blood pressure, pulse rate*,γ	•	• *,γ	•	
Body temperatureγ	•	• γ	•	
Chest imaging (CT) or Posteroanterior Lung Graphy	•			
Enrolment	•			
Drug administration	•	• γ		
Recovery		•	•	
Phone visit (teleconsultation)β		•		•
Adverse event questioningγ	•	• γ	•	•

* For the inpatients, if deemed necessary by the investigator during medication

** If the patient is discharged earlier than 14th day of the study.

γ Patients will be asked to record data into their diaries.

β For the outpatients, if deemed necessary

Figure 1. Flowchart of the study

severity of dyspnea and cough, oxygen saturation (SpO_2,%), and laboratory findings for hematological and biochemical parameters including platelet counts (x10^9/L), D-dimer (µg/mL), prothrombin time [(PT), sec.] and activated partial thromboplastin time [(aPTT), sec.], activated clotting time (sec), alanine aminotransferase [(ALT), IU/L], AST (IU/L), C-reactive protein (CRP, mg/L), creatinine (mg/dL) and creatine kinase [(CK), IU/L] were recorded for the assessment of safety and efficacy of favipiravir. Adverse events (AEs) and serious adverse events (SAEs); symptoms that reduce quality of life and life-threating events were recorded at each visit to assess the safety and tolerability of favipiravir treatment.

During follow-up, improvement in high fever (return of fever within normal limits), dyspnea, and cough severity was evaluated based on the 10-day treatment, while laboratory parameters were compared between the first measurement (examination; on day 1) and the last measurement (final examination; for outpatients: end of their quarantine, for hospitalized patients: day 14 or on the day of hospital discharge in those discharged from hospital sooner than 14 days).

Mild cough: Cough that does not affect the quality of life.

Moderate cough: Cough affecting quality of life.

Severe cough: Cough causing dyspnea.

Mild dyspnea: Difficulty breathing but no change in partial oxygen saturation.

Moderate dyspnea: Difficulty in breathing, change in partial oxygen saturation, but no need for oxygen support.

Severe dyspnea: Difficulty in breathing with need for oxygen support.

Study Endpoints

The time frame of this study was defined as 14 days. The primary endpoints were safety and tolerability of favipiravir treatment within a time frame of up to 14 days. Safety was evaluated mainly on the basis of the frequency of AEs and SAEs as well as on the abnormal laboratory values (lymphopenia, thrombocytopenia, alterations in ALT, AST, CRP and D-dimer levels and in PT and aPTT from baseline). The secondary endpoint was to follow-up patients based on time to achieve amelioration in fever, dyspnea, and cough as well as time to recovery (discharge or symptoms recovery time) in COVID-19 patients for up to 14 days. Considering tolerance, the administration of the study medication was performed by the investigator(s) and nurse(s) and supervised by a second medical professional to ensure the correctness of drug administration. The administration of the study medication was documented in the Case Report Form (CRF) and/or the patient's diary. Outpatients were responsible for administering their own medication. They were responsible for recording their medications and clinical condition in the diary designed for this study. The diaries were collected and attached to their CRFs after completion of the study.

Statistical Analysis

The primary analysis was based on a per-protocol dataset that included all study patients who were treated with favipiravir. The chi-square (χ^2) test and Fisher's exact test were used for the comparison of categorical data, while the two-sample dependent t-test and Mann-Whitney U test were used for the analysis of the parametric variables. Data are expressed as mean ± standard deviation (SD), median (minimum-maximum), and percentage (%) where appropriate. $P<0.05$ was considered statistically significant.

Results

Baseline Characteristics

Overall, 25 enrolled patients were dropped out during the study because of arousal of conditions consistent with exclusion criteria in patients, withdrawal of consent, or discontinuation of treatment medication. The study population subjected to final analysis comprised a total of 475 favipiravir-treated COVID-19 patients. The mean patient age was 49.5 years (SD: 18.0, range: 18 to 97 years), while the study population was composed of 243 (51.2%) males and 232 (48.8%) females.

Safety and Tolerance Data

Based on the laboratory findings, from the first (day 1) to the last measurement, a significant increase was noted in platelet count (231.6±76.9 vs. 306.9±100.8 x10^9/L, $p<0.001$), serum ALT levels (31.9±27.7 vs. 47.2±49.7 U/L, $p<0.001$).

Due to the clinical records of the study patients, 401 AEs were reported in 206 (51.4%) patients. The majority of the recorded AEs were submitted as "mild" (270; 67.3%) or "moderate" (128; 31.9%) cases (Table 2). Three of the most commonly reported cases were as follows: muscle pain (63; 15.7%), headache (39; 9.7%), and weakness (33; 8.2%) (Table 3). According to the AE form of the patients, clinicians considered

the relation of the event and the study medication to be "certain" for 9 (2.2%) AEs, "probable/likely" for 8 (2.0%) AEs, and "possible" for 298 (74.3%) AEs (Table 2).

Fifteen SAEs occurred during the study and were reported. None of them were considered to be related to the treatment, but to disease progression. Four deaths occurred during this observational study because of complications of the disease (Table 4).

Follow-Up Data: Improvement in Fever, Dyspnea, and Cough

The fever (body temperature; >37.8) was reported in 8.9% of patients on day 1, ranged from 6.4% to 3.2% from day 2 to day 5, and then decreased remarkably within the next 5 days of therapy (0.6% on day 10) (Figure 2).

The rates for severe dyspnea were 10.1%, 7.6%, and 6.1% on days 1, 2, and 3, respectively, and then decreased remarkably within the next 7 days of therapy (from 4.2% on day 4 to 1.9% on day 10) (Figure 3).

The rates of severe cough were 6.3%, 9.3%, and 6.9% on days 1, 2, and 3, respectively, and then remarkably decreased within the next 7 days of therapy (from 4.0% on day 4 to 0.8% on day 10) (Figure 4).

Amelioration of fever, dyspnea, and cough symptoms was noted in an increasingly higher percentage of patients who continued therapy (Figure 1-3).

Table 2. Safety data of the study

Adverse events (n=401)	
Patients, n (%)	206 (51.4)
Number of events	401
Relation to study medication, n (%)	
Certain	9 (2.2)
Probable/likely	8 (2.0)
Possible	298 (74.3)
Unlikely	86 (21.4)
Total	401 (100.0)
Severity, n (%)	
Mild	270 (67.3)
Moderate	128 (31.9)
Severe	3 (0.7)
Total	401 (100.0)
Serious adverse events (n=15)	
Patients, n (%)	15 (3.7)
Number of events	15
Relation to study medication, n (%)	
Unlikely	15 (100.0)

"Certain" defines an event that occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. "Probable/likely" defines a condition in which the effect of a drug cannot be attributed to the disease present in the same period of time or to the drugs given along with it."Possible" defines a condition in which the effect of a drug can be explained by the disease present in the same period of time or by the drugs given concomitantly. "Unlikely" defines a situation in which the situation occurring at the time a drug is administered cannot be explained by this drug, but may occur with the disease in the same period or with the drugs given together

Table 3. Details of the adverse events

Adverse events	**n (%)**
Muscle pain	63 (15.7)
Headache	39 (9.7)
Weakness	33 (8.2)
Cough	31 (7.7)
Dyspnea	27 (6.7)
Diarrhea	23 (5.7)
Loss of smell and taste	18 (4.5)
Vomiting	18 (4.5)
Dizziness	13 (3.2)
Lack of appetite	13 (3.2)
Fatigue	12 (3.0)
Constipation	8 (2.0)
Fever	8 (2.0)
Joint pain	8 (2.0)
High ALT value	7 (1.7)
High AST value	7 (1.7)
Sputum	6 (1.5)
Tachycardia	6 (1.5)
Other	47 (11,7)
Total:	401 (100)

Other AEs: Abdominal pain, chills, hyperglycemia, dry mouth, insomnia, stomach, sweating, throat ache, low saturation, chest pain, earache, itching, kidney pain, runny nose, sore throat, thrombocytosis, tremors in the feet, abdominal swelling, acute respiratory failure, allergy, blurred vision, feeling of pressure in the chest, hypertension, loss of balance, loss of smell and taste, low pulse, palpitation, sneeze, stiff neck, throat tickle, WBC count, and lymphocyte decrease. ALT: Alanine aminotransferase, AST: Aspartate aminotransferase

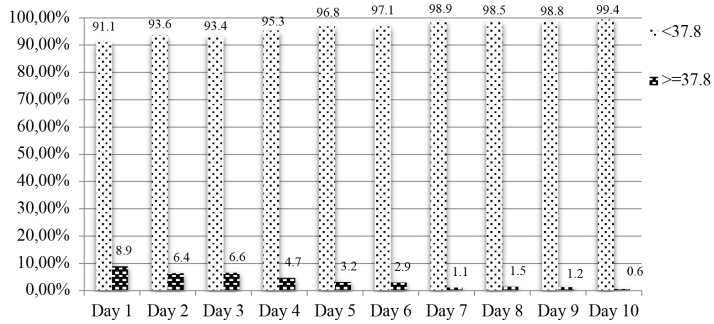

Figure 2. Percentage of patients with body temperature of ≥37.8 ºC vs. <37.8 ºC during 10-day favipiravir treatment

Table 4. Details of the serious adverse events

Serious adverse events	Relation to the study medication	Action taken	Outcome
Fever, nausea, and vomiting	Unlikely	Not necessary	Recovery
Cardiac arrest	Unlikely	Intensive care	Death
Bradycardia	Unlikely	Not necessary	Recovery
Need for hospitalization	Unlikely	Not necessary	Not changed
Increase in oxygen demand	Unlikely	Not necessary	Full recovery
Pneumothorax and low saturation	Unlikely	Not necessary	Death
Sepsis	Unlikely	Not necessary	Death
Sepsis	Unlikely	Not necessary	Death
Respiratory distortion and desaturation	Unlikely	Intensive care	Full recovery
High fever, cough, and low saturation	Unlikely	Hospitalization	Full recovery
Fever and low saturation	Unlikely	Hospitalization	Recovery but still present
Respiratory failure	Unlikely	Intensive care	Full recovery
Respiratory failure	Unlikely	Intensive care	Not recovered within the study period
Respiratory failure	Unlikely	Intensive care	Recovery but still present
Respiratory failure	Unlikely	Intensive care	Not recovered within the study period

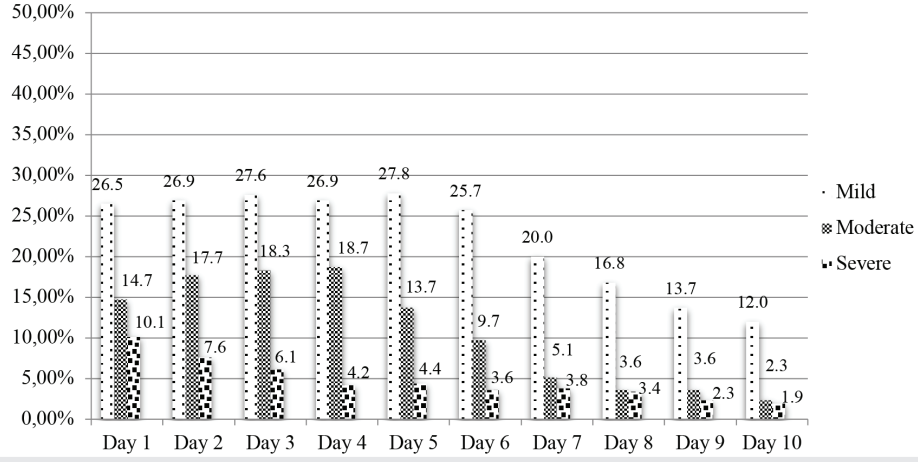

Figure 3. Percentage of patients with dyspnea (mild, moderate, severe) during 10-day favipiravir treatment

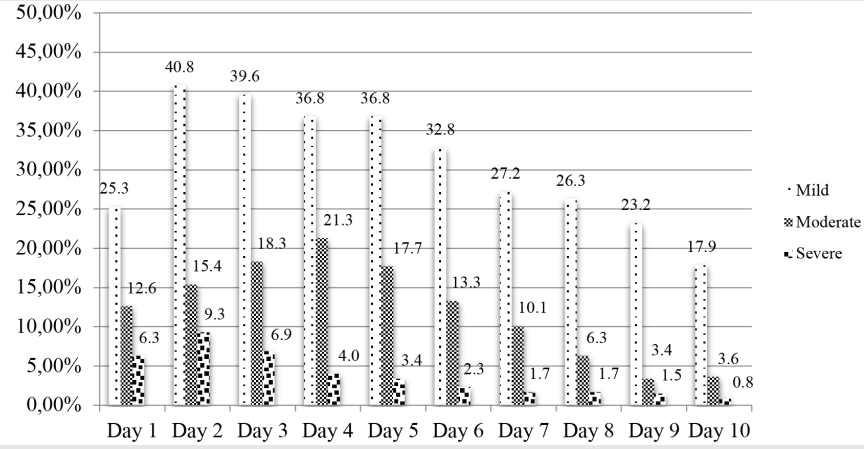

Figure 4. Percentage of patients with cough (mild, moderate, severe) during 10-day favipiravir treatment

Nonetheless, the increase in SpO_2 levels (96.2±2.7 vs. 97.5±2.1%, p<0.001) and significant decrease in serum levels of CRP (39.9±66.4 vs. 15.2±30.5 mg/L, p<0.001) and CK (101.7±187.7 vs. 71.9±43.5 U/L, p=0.018) were quantitatively determined (Table 3). The average day of discharge from the hospital was 11 days (range; 3 to >14 days).

Discussion

According to the MoH Guide for the Management of Adults with COVID-19, favipiravir has been accepted as a standard of care in the management of COVID-19 in Turkey for a significant period of time, almost from the beginning of the epidemic. It was almost the only drug in our country at the time of this study. However, it was removed from the standard treatment recommendations in the final guideline.

Here we present the data of the largest prospective real-life observational study of favipiravir-treated COVID-19 patients in Turkey. Our findings revealed a favorable safety profile for favipiravir.

Side effects of oral favipiravir have been detected in both animal and human studies, particularly in repeated dose use. Effects on hematopoietic tissues, changes in liver function parameters, and vacuolization in hepatocytes are frequently observed adverse effects (19).

In addition, testicular toxicity is a reported side effect (20). Favipiravir has teratogenic effects. Therefore, it should be avoided in pregnant women and those with suspected pregnancy (21).

In a meta-analysis of COVID-19 patients treated with favipiravir, the results are similar to those of our study. Although the frequency of side effects is high, they are generally asymptomatic or mild, and the most common side effect is hyperuricemia. There are no serious side effects that require discontinuation of treatment (22,23).

(In other studies) favipiravir has a well-characterized and a favorable safety profile with respect to total and SAEs including 1.1% rate of treatment discontinuation due to AEs and 0.4% rate of SAEs, and a similar proportion of AEs between low and high doses (7,24). Gastrointestinal symptoms, uric acid elevation, decrease in neutrophil count, increase in liver transaminases, psychiatric symptom reactions, and increase in blood triglycerides were considered to be the most common AEs in favipiravir-treated patients (5,7,24).

Notably, the side-effect profile of the drug also seems acceptable in COVID-19 patients, with asymptomatic hyperuricemia and mild, reversible elevation in transaminases being the most frequently reported adverse effects (18).

In the largest database of favipiravir-treated COVID-19 patients from Japan, the authors noted that a total of 3,324 AEs were reported in association with favipiravir use in 2,841 of 10,986 patients. Including hyperuricemia in 1,960 patients (17.8%), liver disorder or elevated liver enzymes in 834 patients (7.6%), and skin eruption or toxicoderma in 129 patients (1.2%) (23).

In the current study, the majority of reported AEs were mild to moderate, with muscle pain headache and weakness as the most common AEs, and none of the SAEs were related to favipiravir. However, observed AEs might be symptoms related to COVID-19 itself. Platelet counts and ALT levels on the last day of treatment were significantly higher than baseline levels, confirming the overall safety and tolerability profile of favipiravir reported in the literature.

Study Limitations

At the time of the study, there was no approved drug other than favipiravir in our country for this ethical reason; therefore, our study did not include a control group. The efficacy of favipiravir could not be evaluated. In addition, if there is a control group, the relationship of AEs with the drug can be more clearly demonstrated.

Conclusion

Our findings in favipiravir-treated hospitalized COVID-19 patients revealed the association of favipiravir with improved clinical and laboratory parameters, including timely amelioration of fever, dyspnea, and cough, as well as decrease in serum levels of inflammatory markers without causing safety concerns. Accordingly, the current study provides real-world data of a large patient population in Turkey on the utility of favipiravir while it was the unique option for treating COVID-19 patients. Favipiravir, which was repurposed to treat COVID-19 patients, was revealed as a well-tolerated agent with a favorable safety profile in the management of patients diagnosed with COVID-19. Large-scale randomized clinical trials addressing the efficacy and safety of favipiravir for COVID-19 are needed to further elucidate the role of favipiravir clinical benefits in the management of the ongoing coronavirus pandemic.

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Ethics Committee Approval: Ethical approval was taken from Gaziantep University Clinical Research Ethics Committee (approval number: 2020/18, date: 24.07.2020).

Informed Consent: Written informed consent was obtained.

Authorship Contributions: Concept - F.S., V.A.O., G.P., A.N.G., M.O.T., A.N.Z., B.Ö., C.A., Z.A., A.N.Y., Y.T., A.E.; Design - A.Ö.M., T.O.E., V.A.O., G.P., A.N.Z., B.Ö., Y.T., C.A., Z.A., A.N.Y., M.O.T., F.S., A.N.G., A.E.; Data Collection or Processing - A.Ö.M., A.V., T.O.E., K.K., D.D.D., O.P., F.S., F.G., B.Ö., C.A., Z.A., Ü.A.T., G.P., Ö.D., İ.K., Y.T., O.K., D.S., A.N.G., D.İ., B.S., Ş.K.; Analysis or Interpretation - A.V., K.K., D.D.D., O.P., A.N.Z., F.G., V.A.O., Ö.D., D.İ., B.S., O.K., Ş.K., İ.K., D.S., Ü.A.T.; Literature Search - A.Ö.M., K.K., D.D.D., A.N.Y., M.O.T., İ.K., Ö.D., D.S., O.K., F.G., O.P., D.İ., Ü.A.T., B.S., Ş.K., A.E.; Writing - A.Ö.M., A.V., T.O.E.

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