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OVERVIEW OF FAVIPIRAVIR AND REMDESIVIR TREATMENT FOR COVID-19

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ABSTRACT: The current coronavirus disease 2019 (COVID-19) outbreak caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in the wholesale market in Wuhan, China in the last months of 2019 and spread to almost all countries of the world. Although several vaccines have already been developed in different countries of the world, there is currently no specific treatment for COVID-19. Some agents are used all over the world based on *in-vitro*, *in-vivo* studies, and randomized controlled studies. The number of studies on antiviral therapy has been increasing day by day. However, the efficacy of antiviral drugs for COVID-19 remains controversial. In this review, brief information about antiviral drugs favipiravir and remdesivir used for the treatment of COVID-19, the results of the conducted studies, and the possible adverse effects of these drugs are summarized. We hope that this review will provide an impression of favipiravir and remdesivir used to treat and control COVID-19 patients until the approval of specific drugs that target SARS-CoV-2.

INTRODUCTION: Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the main factor of coronavirus disease 2019 (COVID-19) announced a global epidemic by the World Health Organization (WHO) on March 11, 2020 [1]. SARS-CoV-2 first appeared in Wuhan, China in December 2019. The source of the virus was initially unknown, but it was later discovered that newly diagnosed cases were linked to the Huanan Seafood Wholesale Market, where people could buy wild animals such as bats [2]. After the first cases emerged in China, the virus is known to spread rapidly throughout the world [3].

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SARS-CoV-2 has been reported to have phylogenetic similarity with the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV) [4]. SARS-CoV-2 is associated with human SARS-CoV showing 82% nucleotide similarity [5]. Early studies on COVID-19 have reported that SARS-CoV-2 may be transmitted from animal to human by droplets or from person to person by direct contact [6].

In addition, SARS-CoV-2 has been reported to be transmitted from human angiotensin. Studies have also shown that it encodes the spike S protein, which allows binding to transforming enzyme 2 (ACE2), and by supporting the membrane fusion of this protein, it enables the virus to enter human cells such as the lung by endocytosis. After entering human cells, SARS-CoV-2 uses the protein synthesis mechanism of human cells to

synthesize viral proteins and subsequently provide viral replication [7]. Once in the human body, viruses generally trigger a range of responses, such as autophagy, apoptosis, and stress response [8]. Approximately 20% of individuals infected with SARS-CoV-2 who suffer from health problems such as lung disease have serious respiratory symptoms causing to acute respiratory distress syndrome (ARDS) and even death. A key point to note is that the disease the onset of ARDS in the early stages and preceding acute lung injury [9]. Currently, there is no specific antiviral drug used for the treatment of COVID-19. Therefore, deciding which treatment regimen to apply to prevent and treat severe COVID-19 cases remains a major challenge [10]. As of now, many studies are being carried out to develop vaccines that can be effective against COVID-19 worldwide. Until the discovery of specific vaccines or therapeutic drugs targeting SARS-CoV-2, medications approved by the FDA for other indications are used to treat COVID-19 patients [11]. In this review, we synthesized the available information regarding two of the most important antiviral drugs favipiravir and remdesivir for SARS-CoV-2 therapy.

1. Favipiravir: Favipiravir, also known as T-705, is a pyrazine analog **Fig. 1** and potent inhibitor of influenza viral RNA polymerase [12]. Favipiravir is converted intracellularly into its ribofuranosyl 5′-triphosphate (favipiravir-RTP) metabolite, and the antiviral activity of this drug is decreased in the existence of the purine nucleotides ATP and GTP, implying that favipiravir-RTP can be recognized as a pseudo-purine by the viral RNA-dependent RNA polymerase (RdRp) [13]. For influenza a virus polymerase it was demonstrated that favipiravir-RTP was known as an effective substrate for incorporation in the RNA [14]. Incorporation of favipiravir-RTP in the viral RNA could eventuate in lethal mutagenesis [15].

The results of several studies have suggested that one of favipiravir's mechanisms of action for different viruses is lethal mutagenesis [16, 17]. Otherwise, there are some studies that have indicated that incorporation of favipiravir-RTP into the viral RNA strand prevented further, RNA strand extension is the mechanism of action of this antiviral drug [18, 19].

Favipiravir was priorily presented to be an effective antiviral against influenza virus infections; it has also been shown to be efficient against a large number of RNA viruses [20].

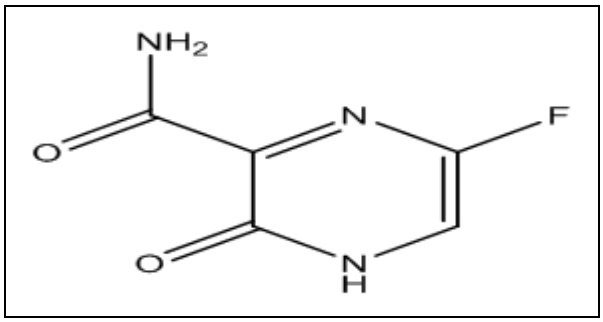

FIG 1: CHEMICAL STRUCTURE OF FAVIPIRAVIR

An *in-vitro* study investigating seven potential anti-SARS-CoV-2 drugs has shown that favipiravir has exhibited efficacy in Vero E6 cells infected with SARS-CoV-2 with half-maximal effective concentration (EC_{50}) of 61.88 μM and half-cytotoxic concentration (CC_{50}) at over 400 μM, indicating the high concentration is required for effective and safe treatment [21]. Favipiravir is also an antiviral agent that has been demonstrated to be effective for Ebola virus disease. In a retrospective analysis of patients with Ebola virus disease treated with favipiravir had a remarkably higher survival rate compared to receiving supportive therapy (56.4% *vs.* 35.3%; P=0.027) [22]. Favipiravir is currently being investigated for the novel coronavirus disease COVID-19. In an open-label non-randomized study of 80 patients with COVID-19 in China, a significant decrease in SARS-CoV-2 viral clearance was observed in patients treated with favipiravir compared to those treated with lopinavir/ritonavir [23]. In another multicentered randomized clinical trial in China, favipiravir treatment has been demonstrated to increase the 7-day clinical recovery rate (from 55.86% to 71.43%) and significantly reduce fever and cough relief time in COVID-19 patients [24]. Clinical trials testing favipiravir for COVID-19 have been conducted in different countries worldwide **Table 1** and **2.**

Several studies have indicated that the maximum plasma concentration of favipiravir occurred at two hours after oral administration and then reduced quickly with a short half-life time of 2–5.5 h, and the fraction of its metabolites excreted in the urine increases overtime to reach 80–100% after seven days [25].

Favipiravir exhibits dose and time-dependent pharmacokinetics. It is not metabolized by the cytochrome P450 system, however, it inhibits one of its components (CYP2C8). Therefore, it needs to be used with caution when co-administered with drugs metabolized by the CYP2C8 system [26]. The most common side effects of favipiravir are gastrointestinal discomfort, abnormal trans-aminases, elevated serum uric acid, and psychiatric symptoms.

TABLE 1: THE ONGOING AND UPCOMING CLINICAL TRIALS WITH FAVIPIRAVIR FOR THE TREATMENT OF COVID-19

Study	Clinical Trials.gov Identifier	Interventions	Primary Outcome
Study on Safety and Efficacy of Favipiravir (Favipira) for COVID-19 Patient in Selected Hospitals of Bangladesh	NCT04402203	*Favipiravir 200 mg (Favipira) tablet will be given orally. Day 1: Tablet Favipiravir 1600 mg twice daily Days 2−Days 10: Tablet Favipiravir 600 mg twice daily.	Number of participants negative by RT-PCR for the virus at 4-10 days after initiation of therapy.
Favipiravir Therapy in Adults With Mild COVID-19 (Avi-Mild)	NCT04464408	*Favipiravir: 1800 mg (9 tablets) by mouth twice daily for one day, followed by 800mg (4 tablets) twice daily *Placebo: 9 tablets by mouth twice daily for one day, followed by 4 tablets twice daily	PCR negative.
Favipiravir in Hospitalized COVID-19 Patients (FIC)	NCT04359615	*Favipiravir: This will be drug only used in the intervention *Hydroxychloroquine: This drug will be used in all arms as mandated by their governmental guidelines	Time to clinical improvement
Favipiravir vs Hydroxychloroquine in COVID -19	NCT04387760	*Hydroxychloroquine: 400mg BID PO day 1 then 200mg BID PO from day 2-day 10. *Favipiravir: 1600mg BID PO day 1, 600mg BID PO day 2 to 10.	Primary outcome measure will be time to viral clearance
Oral Favipiravir Compared to Placebo in Subjects With Mild COVID-19	NCT04346628	*Favipiravir: for 10 days, and be evaluated for health outcomes through day 28. *Placebo: for 10 days, and be evaluated for health outcomes through day 28.	Time until the cessation of oral shedding of SARS-CoV-2 virus
A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 3 Study Evaluating Favipiravir in Treatment of COVID19	NCT04425460	*Favipiravir: Day 1: 1800 mg x2; Day 2 up to a maximum of 14 days 600 mg x 3 *Placebo: Day 1: 1800 mg x2; Day 2 up to a maximum of 14 days 600 mg x 3	Time from randomization to clinical recovery.
Efficacy and Safety of Favipiravir in Management of COVID-19	NCT04349241	*Favipiravir in a regimen of 3200 mg (1600 mg 12 hourly) loading dose on day-1 followed by 1200 mg maintenance dose (600 mg 12 hourly daily) on day-2 to day-10	1. Viral clearance 2. Clinical improvement
Early Intervention in COVID-19: Favipiravir Verses Standard Care (PIONEER)	NCT04373733	*Favipiravir: Day 1 1800mg twice per day, Days 2-10 800mg twice per day	Time to improvement by two points on a seven-category ordinal scale
Efficacy of Faviprevir in COVID-19 Treatment	NCT04351295	*Favipiravir *Placebos	Number of patients with viral cure

*A registry and results database of privately and publicly supported clinical studies of human participants conducted around the world. Available online: www.ClinicalTrials.gov

In addition, other existing safety concerns, such as the potential for QTc prolongation, are still unresolved [27]. Furthermore, there is proof that favipiravir has teratogenic potential. When the doses equivalent to the recommended human regimens were tested in animal models, retarded development of embryonic death was observed in four different animal species in the first trimester [28]. There is no information about the use of favipiravir during breastfeeding or its excretion into

breast milk. However, since favipiravir is a small molecule that is approximately 60% protein-bound in plasma, it may be expected to appear in breast milk and be absorbed by the infant slightly. Therefore, the breastfed infant should be monitored in terms of some parameters such as gastro-intestinal symptoms, liver enzyme abnormalities, and serum uric acid elevations [29]. Favipiravir seems to be safe and tolerable in short-term use, but more evidence is needed to evaluate the longer-term effects of COVID-19 treatment. The clinical application of favipiravir is being researched for clear information about its effectiveness and safety.

2. Remdesivir: Remdesivir (GS-5734) is a monophosphoramidate prodrug, a C-adenosine nucleoside analog **Fig. 2** and a new antiviral drug with broad antiviral action against zoonotic and human pathogens from multiple virus families. It was developed by Gilead Sciences as a treatment for Ebola virus disease and Marburg virus infections [30]. Remdesivir terminates viral RNA synthesis by inhibiting viral RNA-dependent RNA polymerase (RdRp) [31]. The active form, remdesivir triphosphate, compete for the inclusion of the native adenosine triphosphate chain, resulting in chain termination [32]. Remdesivir is a broad-spectrum antiviral drug with effects on ribonucleic acid (RNA) viruses, including Coronaviridae (such as SARS-CoV, MERS-CoV, and bat coronavirus strains), Filoviridae (such as EBOV), and Paramyxoviridae (Nipah virus, Hendra virus) [33]. Laboratory tests show that remdesivir is effective against a wide variety of viruses such as SARS-CoV and MERS-CoV.

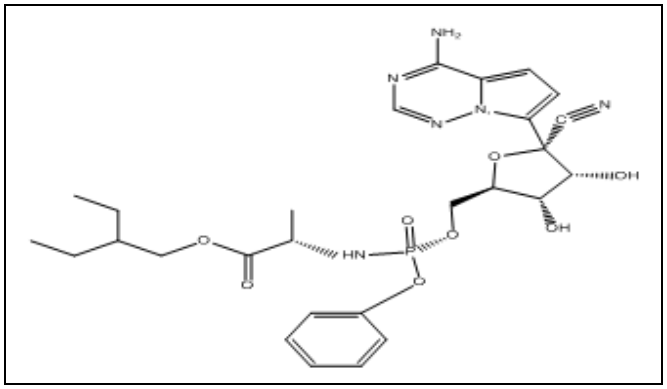

FIG. 2: CHEMICAL STRUCTURE OF REMDESIVIR

In previous studies, it has been tested on RNA viruses such as MERS coronavirus and SARS coronavirus but has not been fully approved as a treatment drug. Remdesivir was originally developed for Hepatitis C, then it was tried in Ebola and Marburg virus, but its effectiveness was not proven in all these infections. Although the drug has proven to be safe, its effect against filoviruses such as the Ebola virus has not been observed [33]. After the COVID-19 pandemic, treatment protocols have begun to be tried on patients, and finally. Remdesivir has been approved for emergency use in the USA and for the treatment of patients with severe symptoms in Japan [33]. A number of factors have led to increased public and medical interest in remdesivir for SARS-CoV-2 treatment recently.

First, its *in-vitro* activity against SARS-CoV-2 was confirmed. Researchers studied the effect of seven drugs: ribavirin, penciclovir, nitazoxanide, nafamostat, chloroquine, favipiravir, and rem-desivir against SARS-CoV-2 in non-human Vero E6 cells. The EC50 was the lowest for remdesivir (0.77 µM), followed by chloroquine (1.13 µM).

The simulated molecular insertion experiment also predicted that remdesivir could bind high-affinity SARS-CoV-2 RdRp [21]. The first clinical efficacy data for remdesivir in COVID-19 focused on case reports of patients. All cases described received 200 mg of remdesivir intravenously on day 1 followed by 100 mg for up to 9 days [33]. The first patient, a 35-year-old man with a limited past medical history and recent travel to Wuhan, diagnosed with COVID-19 in the United States, was treated with remdesivir.

Remdesivir was initiated on day 7 due to increased oxygen requirements and ongoing pyrexia, and was generally asymptomatic in the following days [34]. The largest report included 61 patients from centers in Europe, North America, and Japan. All patients were hospitalized with COVID-19. After 8 patients were excluded for a number of reasons, 53 patients were received remdesivir at a median of 12 days following symptom onset, and clinical improve-ment was detected in 36 of these 53 patients (68%) [35]. In the first randomized, placebo-controlled, double-blind study with remdesivir for COVID-19, Wang and colleagues matched patients receiving remdesivir (n=158) and placebo (n=78) in hospitalized patients with severe COVID-19. Remdesivir was given a dose of 200 mg on day 1,

followed by a dose of 100 mg on days 2-10. In most of the patients with medical comorbidities, the basic characteristics were detected to be balanced, and a higher respiratory rate was found after 10 days [36]. In another open observational study of patients having received a 10-day remdesivir therapy, these patients not requiring mechanical ventilation, the trial did not demonstrate a significant difference between a 5-day course and a 10-day course of remdesivir [37]. Clinical trials testing remdesivir for COVID-19 have been carried out in different countries of the world **Table 3** and **4.**

TABLE 2: THE ONGOING AND UPCOMING CLINICAL TRIALS WITH FAVIPIRAVIR FOR THE TREATMENT OF COVID-19 (CONTINUE)

Study	Clinical Trials. Gov. Identifier	Interventions	Primary Outcome
Efficacy and Safety of Hydroxychloroquine and Favipiravir in the Treatment of Mild to Moderate COVID-19	NCT04411433	*Favipiravir (3200 mg+1200 mg) *Favipiravir (3600 mg+1600 mg) *Favipiravir combined with Hydroxychloroquine *Favipiravir combined with Azithromycin *Hydroxychloroquine *Hydroxychloroquine combined with Azithromycin	1. Time to recovery (discharge) 2. Decrease in viral load
Favipiravir and Hydroxychloroquine Combination Therapy (FACCT)	NCT04392973	*Favipiravir: Administer 1800 mg (9 tablets) by mouth twice daily for one day, followed by 800mg (4 tablets) twice daily (total days of therapy is 10 days or till hospital discharge) *Hydroxychloroquine (400mg) twice daily on day 1; for days 2-5 (200mg) twice daily.	Clinical Improvement..
Corona Virus Disease 2019 Patients Whose Nucleic Acids Changed From Negative to Positive	NCT04333589	*Favipiravir: On the 1st day, 1600mg each time, twice a day; from the 2nd to the 7th day, 600mg each time, twice a day. Oral administration, the maximum number of days taken is not more than 14 days.	Viral nucleic acid test negative conversion rate
Control of COVID-19 Outbreaks in Long Term Care	NCT04448119	*Favipiravir for prophylaxis is 1600 mg (8 x 200 mg tablets) orally twice daily on day 1 followed by 800 mg (4 x 200 mg tablets) orally twice daily on days 2-25 and for treatment is 2000 mg orally twice daily on day 1, the 1000 mg orally twice daily for 13 additional days. *Favipiravir Placebo	Control of Outbreak
Treatments to Decrease the Risk of Hospitalization or Death in Elderly Outpatients With Symptomatic SARS-CoV-2 Infection (COVID-19) (COVERAGE)	NCT04356495	*Favipiravir: 12 tablets twice a day the first day (day 0) then 6 tablets twice a day from day 1 to day 9 *Imatinib: 1 tablet daily from the first day (day 0) to day 9 *Telmisartan: 1 tablet daily from the first day (day 0) to day 9 *Dietary Supplement: Vitamins 2 tablets daily from the first day (day 0) to day 9	1. Proportion of participants with an occurrence of hospitalization 2. Death
Bioequivalence Study of Favipiravir 200 mg Film Tablet (ATABAY, Turkey) Under Fasting Conditions (Favipiravir)	NCT04406194	*Favipiravir 200 mg (FAVICOVIR) *Favipiravir 200 mg (Avigan)	1. Primary PK End Points. AUC_0-t_{last} of favipiravir obtained by plasma concentration 2. Primary PK End Points. C_{max} of favipiravir obtained by plasma concentration

*A registry and results database of privately and publicly supported clinical studies of human participants conducted around the world. Available online: www.ClinicalTrials.gov

Remdesivir is a substrate of several cytochrome P450 enzymes *in-vitro*, but clinical implications are still unclear since the pro-drug is rapidly metabolized by plasma hydrolases [38]. Remdesivir has linear pharmacokinetics and an extended intracellular half-life (>35 h for active parent triphosphate). Remdesivir triphosphate accumulates in peripheral blood mononuclear cells and therefore

recommending a loading dose may accelerate the stable success situation [39]. Detailed information on remdesivir metabolism and elimination is not available. In remdesivir studies, the most common side effects were reported as respiratory failure, organ failure, low albumin, low potassium, reduction in red blood cells and platelet counts leading to clotting and yellowing of the skin.

TABLE 3: THE ONGOING AND UPCOMING CLINICAL TRIALS WITH REMDESIVIR FOR THE TREATMENT OF COVID-19

Study	Clinical Trials. Gov. Identifier	Interventions	Primary Outcome
Multicenter, Retrospective Study of the Effects of Remdesivir in the Treatment of Severe Covid-19 Infections (REMDECO-19)	NCT04365725	*Retrospective cohort trial to assess the efficacy of remdesivir in hospitalized adult patients (158 to remdesivir and 79 to plasebo) diagnosed with COVID-19.	not provide significant clinical or antiviral effects in seriously ill patients with COVID-19.
A Trial of Remdesivir in Adults With Severe COVID-19	NCT04257656	*Remdesivir, 200 mg loading dose on day 1, is given, followed by 100 mg iv once-daily maintenance doses for 9 days.	Time to clinical improvement
Study of Merimepodib in Combination With Remdesivir in Adult Patients With Advanced COVID-19	NCT04410354	Merimepodib 400 mg (total daily dose of 1200 mg) for 10 days Remdesivir 200 mg loading dose on Day 0 followed by 100 mg daily dose for 4 days.	1.Number of subjects not hospitalized or, if hospitalized, free of respiratory failure 2. Adverse Events
Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Remdesivir (GS-5734™) in Participants From Birth to < 18 Years of Age With Coronavirus Disease 2019 (COVID-19) (CARAVAN)	NCT04431453	To evaluate the safety, tolerability, and pharmacokinetics (PK) of remdesivir (RDV) in participants with laboratory-confirmed coronavirus disease 2019 (COVID-19) aged 0 days to < 18 years.	1. Proportion of Participants Experiencing any Treatment-Emergent Adverse Events 2. Proportion of Participants Experiencing any Treatment-Emergent Graded Laboratory Abnormalities 3.Plasma Concentrations of Remdesivir (RDV) and Metabolites
Study in Participants With Early Stage Coronavirus Disease 2019 (COVID-19) to Evaluate the Safety, Efficacy, and Pharmacokinetics of Remdesivir Administered by Inhalation	NCT04539262	Drug: Remdesivir (RDV) Drug: Placebo	Time-weighted Average Change From Baseline in Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Viral Load Through Day 7

*A registry and results database of privately and publicly supported clinical studies of human participants conducted around the world. Available online: www.ClinicalTrials.gov

Other side effects have been defined as gastrointestinal disorders, increased liver enzymes, and reactions in the treated vessel. During the drug's intravenous administration, patients may experience low blood pressure, nausea, vomiting, sweating, and tremor [33].

Because remdesivir is slightly absorbed orally, infants are unlikely to absorb clinically significant amounts of the drug from the milk. Given the limited information on infants, it does not appear that mothers taking remdesivir should avoid breastfeeding, but until more data are available, remdesivir should be used with careful infant monitoring during breastfeeding [40].

Although the use of remdesivir in COVID-19 seems safe, more studies are needed regarding its efficacy and safety.

TABLE 4: THE ONGOING AND UPCOMING CLINICAL TRIALS WITH REMDESIVIR FOR THE TREATMENT OF COVID-19 (CONTINUE)

Study	Clinical Trials. Gov. identifier	Interventions	Primary Outcome
A Study to Evaluate the Efficacy and Safety of Remdesivir Plus Tocilizumab Compared With Remdesivir Plus Placebo in Hospitalized Participants With Severe COVID-19 Pneumonia (REMDACTA)	NCT04409262	Drug: Remdesivir Drug: TocilizumabDrug: Placebo	Clinical Status as Assessed by the Investigator Using a 7-Category Ordinal Scale of Clinical Status on Day 28
The Efficacy of Different Anti-viral Drugs in COVID 19 Infected Patients	NCT04321616	Remdesivir for 10 days versus hydroxychloroquine for 10 days versus placebo	In-hospital mortality
Trial of Treatments for COVID-19 in Hospitalized Adults (DisCoVeRy)	NCT04315948	Treatment arms include remdesivir for 10 days, lopinavir/ ritonavirc for 14 days, lopinavir/ritonavir for 14 days plus interferon beta-1a 44 mcg subcutaneously on days 1, 3, and 6, hydroxychloroquined for 10 days, or standard care	Percentage of subjects reporting each severity rating on a 7-point ordinal scale
Remdesivir in COVID-19 Lahore General Hospital	NCT04560231	200 mg I/v Remdesivir will be given to moderate disease patients of COVID-19. It will be loading dose then 100 mg I/V dose will be given for 5 days.	Clinical response after administration
Remdesivir *vs* Chloroquine in Covid 19	NCT04345419	Drug: Chloroquine or hydroxychloroquine Drug: Remdesivir	Number of patients with improvement or mortality

*A registry and results database of privately and publicly supported clinical studies of human participants conducted around the world. Available online: www.ClinicalTrials.gov

CONCLUSION: To summarize, favipiravir and remdesivir have been suggested as a promising alternative for COVID-19 therapy based on the findings of in vitro tests, case reports, and clinical trials, but their safety and effects have not yet been fully understood. While vaccine and drug research is still ongoing, various studies on the relationship between antiviral drugs and coronavirus have been conducted at the same time. The use of favipiravir and remdesivir for COVID-19 treatment has not been clarified yet, and more detailed studies are needed on these drugs. The ongoing studies will provide more high-quality evidence on the benefit and harmful effects of favipiravir and remdesivir.

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