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Original Article

Safety of Favipiravir for Treatment of COVID-19: Latest Systematic Review

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Abstract

***Background**: Adverse event studies of favipiravir used to treat COVID-19 have been ongoing since it was established as a treatment option. A better understanding of the side effects of favipiravir from recent studies is important for developing and assessing the introduction of effective treatments for COVID-19.*
***Method:** The author conducted a systematic review based on research studies and case reports on favipiravir monotherapy in COVID-19. Access to the included studies is via PubMed, SCOPUS, Science Direct, SpringerLink, and MedRxiv.*
***Results:** Twelve studies consisting of eight research studies and four case reports were reviewed. The most common side effects were diarrhea, elevated liver enzyme levels, and hyperuricemia. None of which were significantly different from the comparison. Currently, various adverse event was reported in case reports such as drug fever, acute generalized exanthematous pustulosis (AGEP), and transient increase in viral load. The side effects mostly will recover after the treatment is discontinued.*
Conclusion:** The use of favipiravir to treat COVID-19 causes dose-related side effects such as diarrhea, changes in liver enzymes, and increased uric acid. Nothing is important when compared to other antiviral drugs. To improve the efficacy and safety of COVID-19 therapy, it is important to prepare an incidence report of antiviral adverse events in special populations such as children, pregnant women, and organ dysfunction. **(J Respirol Indones 2022; 42(1): 67-75)
***Keyword**: Favipiravir, SARS-Cov-2, COVID-19, adverse event, side effects.*

Keamanan Favipiravir untuk Terapi COVID-19: Tinjauan Sistematis Terbaru

Abstrak

***Latar belakang**: Pemahaman yang lebih baik tentang efek samping antivirus favipiravir dari penelitian saat ini penting untuk mengembangkan dan menilai pengenalan pengobatan yang efektif untuk COVID-19.*
***Metode:** Penulis melakukan tinjauan sistematis terhadap uji klinis dan laporan kasus monoterapi favipiravir dalam pengobatan COVID-19. Akses ke studi yang disertakan adalah melalui PubMed, SCOPUS, Science Direct, SpringerLink, dan MedRxiv.*
***Hasil:** Dua belas studi, terdiri dari delapan studi efikasi dan empat laporan kasus, memenuhi kriteria penulis. Efek samping yang paling umum adalah diare, peningkatan kadar enzim hati, dan hiperurisemia. Tidak terdapat perbedaan yang signifikan dari perbandingan. Saat ini, berbagai efek samping dilaporkan dalam laporan kasus seperti demam obat, pustulosis eksantematosa umum akut (AGEP), serta peningkatan viral load sementara. Efek samping sebagian besar akan pulih setelah pengobatan dihentikan.*
Kesimpulan:** Penggunaan favipiravir untuk mengobati COVID 19 memiliki efek samping seperti diare, perubahan enzim di siang hari, dan peningkatan asam urat yang reversibel. Efek samping yang terjadi juga kurang penting dibandingkan obat antivirus lainnya. Membuat laporan tentang terjadinya efek samping antivirus pada populasi khusus seperti anak-anak, wanita hamil, dan disfungsi organ penting untuk meningkatkan terapi COVID-19 yang efektif dan aman. **(J Respirol Indones 2022; 42(1): 67-75)
***Kata kunci:** Favipiravir, SARS-Cov-2, COVID-19, adverse event, side effects.*

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INTRODUCTION

SARS-coronavirus-2 (SARS-CoV-2) emerged in Hubei, China in past due 2019 as a reason of acute respiration misery syndrome and respiration contamination which could cause death (COVID-19).[1,2] Older age, male sex, smoking, and the presence of comorbidities consisting of coronary heart disease, hypertension, and diabetes had been recognized as danger elements for exacerbation of infection.[2]

SARS-CoV-2 belongs to the elegance of enveloped coronavirus and has a genetic collection just like the SARS-CoV-1 (80%) and RaTG-13 coronaviruses (96.2%) discovered in bats.[3] Drug substitute consisting of the usage of off-label capsules is executed presently as an emergency alternative withinside the remedy of SARS-CoV-2 infection. Several capsules used for the remedy of COVID-19 consisting of ribavirin, interferon, favipiravir, lopinavir/ritonavir which have been utilized in SARS or MERS sufferers.[4]

Favipiravir is an anti-influenza drug authorized in Japan and reveals diverse antiviral sports towards RNA viruses. Favipiravir is nicely tolerated in medical trials, even though it is related to a dose-based boom in serum uric acid levels.[5]

Studies at the aspect consequences of favipiravir on its use withinside the remedy of COVID-19 have advanced in view that this drug became installed as one of the healing options. A higher expertise of the rising antiviral aspect consequences of favipiravir in COVID-19 sufferers from latest research is essential in growing and comparing the adoption of powerful remedies for COVID-19. The purpose of this article is to review the safety of using favipiravir for the treatment of the SARS-CoV-2 virus based on the incidence of adverse events in patients diagnosed with COVID-19 and hospitalized.

METHOD

This systematic review includes the original complete article from PubMed, SCOPUS, Science Direct, SpringerLink, and MedRxiv. We searched for suitable native articles using some specific keywords such as favipiravir, SARS-Cov-2, COVID-19, adverse events, side effects, etc. The studies reviewed were limited to and included people who used English and were published in the last two years.

The selection criteria for research article topics included in this systematic review were adult patients (>18 years) diagnosed with COVID-19 with mild to severe symptoms. This study included patients who were first treated for the diagnosis of COVID-19. This study was conducted from the time the patient was hospitalized until remission or death. Clinical study that included in this review describes studies using favipiravir monotherapy and compares it to other antivirals, placebo, or different times when favipiravir was given. The outcome included is the frequency of side effects in the subjects tested. For case report, we included reports of adverse events that happened during and after treatment of favipiravir.

The conclusions analyzed are the major side effects that occurred in patients based on the studies included and the rare side effects based on case reports of favipiravir use.

Data were extracted using Microsoft Excel which included the author's name, year of publication, research design, and intervention that eligible.

RESULTS

Based on research at PubMed, SCOPUS, Science Direct, SpringerLink, and MedRxiv, the author found 487 articles. 289 articles were excluded due to inappropriate titles, article types, and summaries. The rest of the article was then analyzed based on the intervention criteria and the suitability of the method and results section for the intended outcome. A total of 12 articles were considered to be satisfied, based on the title, article type, method, and results specified by the author. The study selection flowchart is shown in Figure 1.

A total of 434 patients participated in eight studies, examining the efficacy and observed side effects of favipiravir in the treatment of COVID-19. The study period varies from a minimum of 11 days to a maximum of 8 months. Various study methods were conducted, consisting of randomized and non-

randomized clinical studies, as well as prospective and retrospective cohort studies. The doses of favipiravir in 7 studies show similarities. That is, use 1600 mg each on the first day of treatment and take an additional 600 mg 2–3 times daily until 10–14 days of treatment, but the controls in each study are of different types and cans received.

In case reports, we found four reports of adverse events in 5 patients. Patient side effects were determined both after treatment and during favipiravir treatment according to international guidelines. In three reports, patients were given a starting dose of 3600 mg favipiravir followed by a maintenance dose of 1600 mg, while a report from Atak showed 20 years old patient received an initial dose of 1600 mg followed by 600 mg.[6] Tables 1 and 2 summarize the characteristics of the studies included in this systematic review.

Table 3 shows the side effects reported during administration of favipiravir in each observational study. Three studies reported the incidence of hyperuricemia, four studies reported the incidence of gastrointestinal disorders, the main case of diarrhea, and five studies reported changes in liver enzyme levels. However, in these studies, there was no statistically significant difference in the side effects experienced from favipiravir compared to other antivirals or standard hospital treatments. Chen mentioned in his study the potential for significant hyperuricemia due to favipiravir compared to antiviral arbidol, but overall side effects were not significantly different during the observation period.[4]

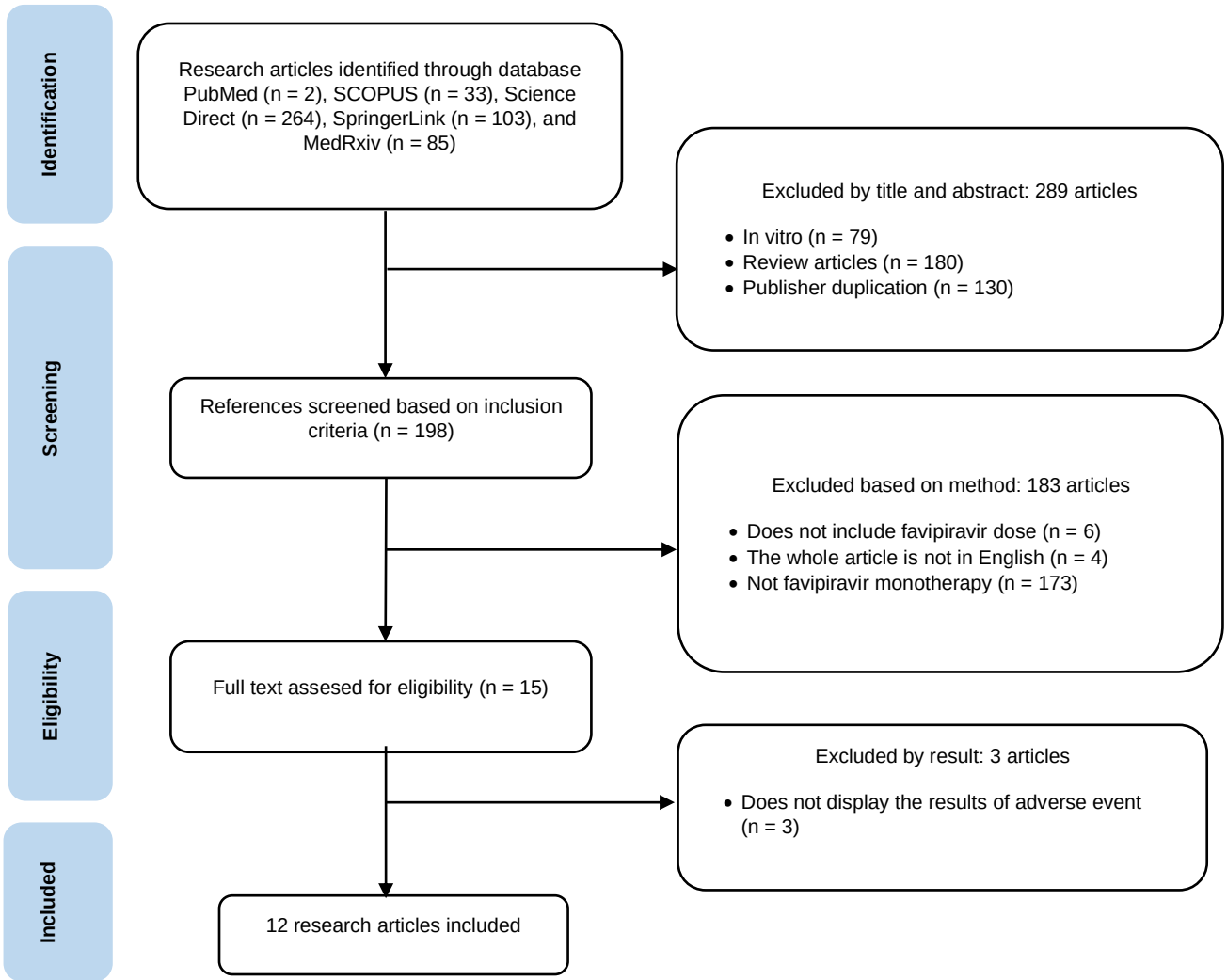

Figure 1. PRISMA flowchart of article selection

Table 1. Summary characteristics of included studies. RCT: randomized control trial, SOC: standard of care

No.	Author, year	Study design	Study duration	Patient criteria	Severity	Favipiravir dose	Number of favipiravir group	Comparator
1.	Lou, 2021[7]	RCT; single center	5 months	Participants confirmed COVID-19.	Not stated	The initial dose is 1600 mg or 2200 mg orally, followed by 600 mg three times a day for a total of 14 days of treatment.	9 participants	(1) baloxavir marboxil group; (2) Control group (Continuing existing antiviral treatment including lopinavir/ritonavir or darunavir/cobicistat and arbidol)
2.	Fujii, 2021[8]	single-center, retrospective cohort study	8 months	Patients with fever, shortness of breath, decreased oxygen saturation, pneumonia on imaging, or worsening respiratory failure.	Severe	1800 mg twice daily on the first day, followed by 800 mg orally twice daily for up to 14 days.	54 participants	SOC
3.	Ivashchenko, 2021[9]	RCT; multicenter	4 weeks	Hospitalized patients with moderate COVID-19 pneumonia	Moderate	1600 mg twice daily on Day 1 and 600 mg twice daily on Days 2–14, or 1800 mg twice daily on Day 1 and 800 mg twice daily on Days 2–14 (1800/800 mg).	40 participants	SOC
4.	Udwadia, 2021[10]	RCT; multicenter; open-label	7 weeks	Age 18-75 years, mild to moderate COVID-19 infection (including no symptoms).	Mild to moderate	1600 mg twice daily on Days 1 and 600 mg twice daily on Days 2–14.	73 participants	SOC
5.	Cai, 2020[4]	open-label, non-randomized, before-after controlled study	4-week	aged 16–75 years; had no trouble swallowing the pill	Mild to moderate	1600 mg twice daily on Day 1 and 600 mg twice daily on Days 2–14.	35 participants	Lopinavir/Ritonavir
6.	Dabbous, 2021[11]	multi-center, randomized, interventional study	4 months	SARS-CoV-2 infection with mild or moderate symptoms and hospitalization three days after symptoms start.	Mild to moderate	1600 mg twice daily on day one followed by 600 mg twice daily from day two to ten.	44 participants	Chloroquine
7.	Chen, 2020[12]	prospective, randomized, controlled, open-label multicenter trial	11 days	Positive chest CT scan at the age of 18 years or older; clinical symptoms include fever, cough, shortness of breath, and other signs of lower respiratory tract viral infection.	Moderate, severe, or critical	1600 mg twice daily followed by 600 mg twice daily for 10 days	116 participants	Conventional therapy plus Umifenovir (Arbidol) (200mg three times daily)
8.	Rattanaumpawan, 2020[13]	retrospective observational study	3 months	Patients at least 18 years of age having and receiving at least one dose of favipiravir	Moderate, severe, or critical	1600 mg twice daily on Day 1, followed by 600 mg twice daily on Days 2-10	63 participants	SOC

Table 2. Summary characteristics of the included case report studies.

No.	Author, year	Patient criteria	Favipiravir dose	Occurrence of adverse events
1.	Murai, 2021 [14]	A 64-year-old woman tested positive for COVID-19 and was admitted to the hospital. For about a week, the patient complained of a persistent fever.	3600 mg per day on the first day and 1600 mg per day thereafter	Patient developed a fever (38ºC) on day 12, suspected to be caused by bacterial pneumonia or drug fever. On day 13, favipiravir was stopped. The patient's body temperature gradually decreased after, there was no worsening of symptoms, and her fever was relieved without the use of antimicrobials.
2.	Koshi, 2021 [15]	A 52-year-old lady who tested positive for SARS-CoV-2 had been on maintenance hemodialysis three times a week for three years due to diabetic nephropathy. The patient had a 6-month history of severe diarrhea and had had coronary artery stenting, right lower limb amputation, and latent pulmonary TB therapy.	3600 mg initial dose followed by 1600 mg orally daily in two divided doses	Mild and reversible increase of alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase (γ-GTP).
3.	Atak, 2021 [6]	A 20-year-old man was hospitalized for COVID-19 infection 16 days ago and was receiving favipiravir	Initial dose 1600 mg twice daily, followed by 600 mg twice daily for 7 days	The patient was readmitted after complaining for two days of a minor itching eruption with a rapid onset. Histology revealed epidermal acanthosis with many neutrophilic subcorneal/intracorneal spongiotic pustules and papillary dermal edema. In the dermis, there was a mixed inflammatory infiltration of lymphocytes, neutrophils, and few eosinophils. The patient has been diagnosed with AGEP caused by favipiravir (Acute generalized exanthematous pustulosis).
4.	Tsuboi, 2021 [16]	FIRST PATIENT: A 70-year-old woman, was a past smoker with co-morbidities such as: emphysema, dyslipidemia, and an overactive bladder. SECOND PATIENT: A 61-year-old woman, has never smoked but suffers from hypertension and dyslipidemia.	Initial dose 3600 mg on the first day and 1600 mg on second day and thereafter.	FIRST PATIENT: decreased of viral load that measured by real-time RT-PCR after treatment, but increased back on day 12, 2 days after the end of treatment. Patient showed transient fever, dyspnea on exertion, a decrease in SpO2 at the same time, but did not worsen thereafter. SECOND PATIENT: RT-PCR examination showed a decrease in viral load during treatment, but transient fever, malaise, dyspnea, and tachypnea on activity also a transient increase in viral load were observed the day after treatment ended.

Table 3. Adverse reactions reported during favipiravir administration in each clinical study. NR: Not reported.

No.	Author, year	Adverse events	Signification
1.	Lou, 2021[7]	Respiratory failure or ARDS (44%); Lymphopenia (77%); Leukopenia (11%); Decreased hemoglobin (77%); Increased aspartate aminotransferase (11%); Increased alanine aminotransferase (44%); Elevated total bilirubin (11%); Albumin decreased (88%); Elevated creatine phosphokinase (11%); Increased lactate dehydrogenase (55%); Increased triglycerides (66%); Improved D-dimmer (55%); Diarrhea (22%); Rash (11%); Nausea (11%)	NR
2.	Fujii, 2021[8]	Hyperuricemia (55.5%), impaired liver function (31.4%), drug eruption (7.4%), drug fever (5.5%), and increased eosinophil count (1.8%)	NR
3.	Ivashchenko, 2021[9]	17.5% of patients experienced side effects in the form of diarrhea, nausea, vomiting, chest pain, and increased levels of liver transaminases.	NR
4.	Udwadia, 2021 [10]	Hyperuricemia (16.4%); Abnormal liver function tests (6.8); Viral pneumonia (2.7%); Gastrointestinal disturbances (1.4%)	NR
5.	Cai, 2020 [4]	Diarrhea (5.71%); liver and kidney injury (2.86%) and others (2.86%)	P<0.001
6.	Dabbous, 2021 [11]	Diarrhea (6.8%); elevated liver enzymes (6.8%); nausea (2.3%); headache (2.3%); anemia (4.5%); hyperuricemia (4.5%); decreased neutrophils (4.5%)	P>0.05
7.	Chen, 2020 [12]	Abnormal LFT (8.62%); Increased serum uric acid (13.79%); Reaction to psychiatric symptoms (4.31%); Gastrointestinal tract reactions (13.79%)	P<0.05 in the incidence of hyperuricemia
8.	Rattanaumpawan, 2020 [13]	Diarrhea (54.0%), followed by nausea/vomiting (7.9%), hepatitis (6.4%) , and QT interval prolongation on the ECG (6.4%). None of these side effects are life-threatening.	NR

DISCUSSION

This systematic review includes publicly available observational studies on the safety of favipiravir use during the COVID-19 pandemic. Favipiravir has dose-dependent side effects and is well tolerated by patients undergoing treatment. The overall safety profile was not significantly different from the comparator products in terms of standard treatment and other antiviral agents.

Favipiravir is associated with the effects of hyperuricemia, such as diarrhea. This is indicated by the percentage that occurred in the observed studies compared to other side effects. Favipiravir is mainly metabolized by aldehyde oxidase, partly metabolized by xanthine oxidase in the liver, and produces favipiravir M1 as an inactive metabolite excreted by the kidneys. The increase in uric acid in the blood caused by favipiravir is due to its action of reducing the amount of uric acid excreted in the urine. Favipiravir and its inactive metabolite M1 are moderate inhibitors of OAT1 and OAT3 (organic anion transporters 1 and 3) that transport uric acid for luminal excretion in the basolateral region. Decreased uric acid uric acid secretion and increased uric acid reuptake via uric acid transporter 1 (uric acid reuptake via uric acid transporter 1) due to inhibition of OAT1 and OAT3 leads to a mechanism of increased blood uric acid.[17]

The dose-dependent effect of favipiravir has been observed in Phase III safety studies. Blood uric acid levels were found to have returned to baseline after discontinuation of treatment. Blood uric acid levels averaged 4.4 mg/dl above baseline 6 days after favipiravir administration (3,200 mg on day 1, followed by 1,200 mg on day 25) and returned to normal 7 days after discontinuation.[17] The incidence of increased blood uric acid (including hyperuricemia) occurred in 9.9% (24/242) of healthy adults in Japan, but was 5.8 in those treated with the recommended dose of favipiravir. It was 5.8% (23 out of 394).[18] This

may also support the results of several observational studies that found that there was no significant difference in blood uric acid levels between patients receiving favipiravir and other antivirals.

The incidence of diarrhea was also mentioned in several studies, but there was no significant difference between favipiravir and comparative antivirals or standard treatments. It is believed that this is because SARS-CoV-2 can also cause diarrhea. The SARS-CoV-2 ACE2 cell receptor is expressed in various types of cells and tissues, including the esophagus, stomach, small intestine, colon, and rectum. The highest gastrointestinal ACE2 expression levels are found in ileal epithelial cells, especially resorbable enterocytes. The direct and indirect effects of cytokines can combine to cause an enterocyte ion imbalance, which can contribute to the development of diarrhea. Viral E-proteins, ionic imbalances, impaired barrier integrity, and dysregulation of the renin vascular tension aldosterone system, which causes inflammation, play important roles in secretory diarrhea and intestinal leakage in patients with COVID-19.[19]

We include 2 cases reported adverse event during therapy with favipiravir such as drug fever, also mild and reversible elevation of liver enzyme. Drug fever is a type of reaction associated with temporary fever caused by drug therapy and disappears when the pathogen is stopped. The main feature that distinguishes drug fever from other causes is the fever that disappears after the drug is stopped. Five mechanisms of drug fever have been identified. Fever can be caused by the effects of drugs on thermoregulation, drug administration-related reactions, pharmacological effects of drugs, idiosyncratic reactions, and hypersensitivity reactions, the most common mechanism of drug fever.

Another 3 cases report showed adverse event after treatment of favipiravir, with 2 cases happened during hospital admission and 1 case after remission. In the two cases reported by Tsuboi et.al, the viral load increase after completion of favipiravir treatment was transient.[16] The viral load spontaneously decreased and the clinical symptoms improved. A slight temporary increase in viral load called "blip" has also been reported during treatment. From this perspective, these two cases may represent phenomena such as "outbreaks" in antiviral treatment. In the case of COVID-19, delays in hospitalization after the onset of the disease have also been reported to prolong SARS-CoV-2 infection.[20] In both cases of this report, antiviral therapy was started relatively late, 10 days after the onset of the disease. This may have caused a phenomenon like "blip".

Koshi et.al reported the first report on the efficacy of favipiravir in end- stage renal disease (ESRD) patients undergoing hemodialysis.[15] It showed that favipiravir may be an effective option for treating patients with ESRD infected with COVID-19 based on improvement in vital sign and laboratory data, with mild and reversible elevation of alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase (γ-GTP). Despite this finding, the safety of Favipiravir in COVID-19 patients with or without concurrent renal problems requires further data and a more comprehensive analysis.

The studies included in this review are limited. This work was limited to the environment and population contained in the research center with adult participants. As a result, the results are less applicable to younger patients with COVID-19. No conclusions can be drawn from the 12 studies due to the different study designs that involve the discussion of case reports. Case reports are for support purposes only.

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CONCLUSIONS

Based on clinical study, the use of favipiravir to treat COVID-19 causes several adverse events such as diarrhea, changes in liver enzymes, and increased uric acid. Some are less important than other antiviruses and reversible. In case reports, there are rare adverse event such as acute generalized

exanthematous pustulosis (AGEP), we also include transient increase in viral load the day after treatment favipiravir ended.

To improve the efficacy and safety of COVID-19 therapy, it is important to develop incident reports of antiviral side effects in special populations such as children, pregnant women, and organ dysfunction. If favipiravir is considered prophylactic, further studies of the long-term effects of treatment are needed.

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