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

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Abstract

Background: Adverse event studies of favipiravir use in treating 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 in developing and assessing the recognition of effective treatments for COVID-19.

Method: This was a systematic review based on studies and case reports on favipiravir monotherapy in COVID-19. Access to the included studies was gained via PubMed, SCOPUS, Science Direct, SpringerLink, and MedRxiv.

Results: Twelve studies consisting of eight 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 were reported in case reports such as drug fever, acute generalized exanthematous pustulosis (AGEP), and transient increase in viral load. The side effects would mostly be subsided after the treatment was discontinued.

Conclusion: The use of favipiravir to treat COVID-19 cause dose-related side effects such as diarrhea, changes in liver enzymes, and increased level of uric acid. There were no serious side effects 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 patients with organ dysfunction.

Keyword: Favipiravir, SARS CoV-2, COVID-19, adverse event, side effects.

Keamanan Favipiravir untuk Terapi COVID-19: Tinjauan Sistematis Terbaru

Abstrak


Hasil: Dua belas penelitian, terdiri dari delapan uji klinis dan empat laporan kasus, dilakukan dalam studi ini. Efek samping yang paling umum adalah diare, peningkatan kadar enzim hati, dan hiperurisemia. Tidak terdapat perbedaan bermakna dari perbandingan yang ada. Saat ini, berbagai kejadian merugikan dilihatkan dalam laporan kasus seperti demam obat, pustulosis eksantematosa akut menyeluruh (AGEP), serta peningkatan kadar virus sementara. Efek samping sebagian besar akan pulih setelah pengobatan dihentikan.


Kata kunci: Favipiravir, SARS CoV-2, COVID-19, kejadian merugikan, efek samping.

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INTRODUCTION

Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) emerged in Hubei, China in 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 artery disease, hypertension, and diabetes mellitus had been recognized as dangerous elements for exacerbation of infection.\(^2\)

SARS-CoV-2 belongs to the elegance of enveloped coronavirus and has a genetic collection such as the SARS-CoV-1 (80%) and RaTG-13 coronaviruses (96.2%) discovered in bats.\(^3\) Drug substitute consisting of the usage of off-label medicines is executed presently as an emergency alternative within the remedy of SARS-CoV-2 infection. Several medications were used for the remedy of COVID-19 consisting of ribavirin, interferon, favipiravir, lopinavir/ritonavir which had been utilized in SARS or MERS patients.\(^4\)

Favipiravir was an anti-influenza drug authorized in Japan and revealed a diverse antiviral activity against one type of RNA virus. Favipiravir was well tolerated in medical trials, although it was associated with a dose-dependent increase in serum uric acid levels.\(^5\)

Studies on aspects of the consequences of favipiravir on its use within the remedy of COVID-19 have advanced in view that this drug is installed as one of the therapy options. A higher expertise of the increasing antivirus aspects of the consequences of favipiravir in COVID-19 patients from latest research is essential in growing and comparing the adoption of powerful remedies for COVID-19. The purpose of this article was to review the safety of using favipiravir for the treatment of the SARS-CoV-2 virus based on the incidence of adverse events in hospitalized COVID-19 patients.

METHOD

This systematic review included the original full article from PubMed, SCOPUS, Science Direct, SpringerLink, and MedRxiv. We looked for appropriate original articles using certain specific keywords such as favipiravir, SARS-Cov-2, COVID-19, adverse events, side effects, etc. Studies reviewed were limited to and included people who used English and were published in the last two years.

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

The conclusions analyzed were 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, publication year, study design, and qualified interventions.

RESULTS

Based on searches on PubMed, SCOPUS, Science Direct, SpringerLink, and MedRxiv, the author found 487 articles. About 289 articles were excluded due to inappropriate title, type of article, and summaries. The rest of the articles were 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 satisfied, based on the title, type of article, method, and results determined by the author. The study selection flowchart is shown in Figure 1.
A total of 434 patients participated in eight studies that examined the efficacy and observed the side effects of favipiravir in the treatment of COVID-19. The study period varied 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 showed similarities: 1600 mg twice daily on the first day of treatment and 600 mg 2-3 times daily for up to 10-14 days of treatment, but the controls in each study were different and still acceptable.

In case reports, we obtained four reports of adverse events in 5 patients. The side effects were determined both after and during favipiravir treatment according to international guidelines. In three reports, patients were given an initial dose of 3600 mg favipiravir followed by a maintenance dose of 1600 mg, while a report from Atak stated that a 20-year-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 favipiravir administration in each observational study. Three studies reported the incidence of hyperuricemia, four studies reported the incidence of gastrointestinal disturbances, major cases of diarrhea, and five studies reported changes in liver enzyme levels. However, in these studies, there were no statistically significant differences 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 albidol, but the overall side effects were not significantly different during the observation period.4
Table 1. Summary of the characteristics of included studies. RCT: randomized control trial, SOC: standard of care

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

<table>
<thead>
<tr>
<th>No.</th>
<th>Author, year</th>
<th>Patient criteria</th>
<th>Favipiravir dose</th>
<th>Occurrence of adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Murai, 2021 14</td>
<td>A 64-year-old woman tested positive for COVID-19 and was admitted to the hospital. For about a week, the patient complained of persistent fever.</td>
<td>Dose of 3600 mg per day on the first day and 1600 mg per day thereafter</td>
<td>Patient developed a fever (38°C) on day 12, suspected to be caused by bacterial pneumonia or drug fever. On day 13, favipiravir was discontinued. The patient’s body temperature gradually decreased thereafter, there were no worsening of symptoms, and the fever was relieved without the use of antimicrobials.</td>
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<tr>
<td>2.</td>
<td>Koshi, 2021 15</td>
<td>A 52-year-old woman who tested positive for SARS-CoV-2 had undergone maintenance hemodialysis three times a week for three years due to diabetic nephropathy. The patient had a history of severe diarrhea for 6-month and had undergone coronary artery stent placement, right lower extremity amputation, and therapy for latent pulmonary TB.</td>
<td>Initial dose of 3600 mg followed by 1600 mg orally per day in two divided doses</td>
<td>Mild and reversible increase of alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase (γ-GTP).</td>
</tr>
<tr>
<td>3.</td>
<td>Atak, 2021 6</td>
<td>A 20-year-old man was hospitalized for COVID-19 infection 16 days ago and was receiving favipiravir</td>
<td>Initial dose of 1600 mg twice daily, followed by 600 mg twice daily for 7 days</td>
<td>The patient was re-admitted after complaining for two days of a mild itchy eruption of rapid onset. Histology revealed epidermal acanthosis with numerous neutrophilic subcorneal/intracorneal spongiform 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 (Acute Generalized Exanthematous Pustulosis) caused by favipiravir.</td>
</tr>
<tr>
<td>4.</td>
<td>Tsuboi, 2021 16</td>
<td>FIRST PATIENT: A 70-year-old woman, was an ex-smoker with co-morbidities such as: emphysema, dyslipidemia, and an overactive bladder. SECOND PATIENT: A 61-year-old woman, had never smoked but suffered from hypertension and dyslipidemia.</td>
<td>Initial dose of 3600 mg on the first day and 1600 mg on second day and thereafter.</td>
<td>FIRST PATIENT: decreased of viral load as measured by real-time RT-PCR after treatment, but increased back on day 12. 2 days after treatment ended. The patient showed transient fever, dyspnea on exertion, decreased 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 as well as a transient increase in viral load were observed the day after treatment ended.</td>
</tr>
</tbody>
</table>
DISCUSSION

This systematic review included 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 on 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 was indicated by the percentage that occurred in the observed studies compared to other side effects. Favipiravir is mainly metabolized by aldehyde oxidase, partially metabolized by xanthine oxidase in the liver, and produces favipiravir M1 as an inactive metabolite which is excreted by the kidneys. The increase in serum uric acid 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 organic anion transporters 1 and 3 (OAT1 and OAT3) that transport uric acid for luminal excretion in the basolateral region. Decreased uric acid secretion and increased uric acid reuptake via uric acid transporter 1 due to inhibition of OAT1 and OAT3 lead to a mechanism of increasing serum uric acid.17

The dose-dependent effect of favipiravir has been observed in Phase III safety studies. Serum uric acid levels were found to have returned to baseline after discontinuation of treatment. Serum 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 elevated serum uric acid level (including hyperuricemia) occurred in 9.9% (24/242) of healthy adults in Japan, but it was 5.8% (23 of 394) in those treated with the recommended dose of favipiravir.18 This might also support the results of several observational studies which found that there were no significant differences in serum uric acid levels between patients receiving favipiravir and other antivirals.

The incidence of diarrhea was also mentioned in several studies, but there were no significant

<table>
<thead>
<tr>
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<th>Adverse events</th>
<th>Signification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Lou, 2021</td>
<td>Respiratory failure or ARDS (44%); Lymphopenia (77%); leukopenia (11%); decreased hemoglobin (77%); increased aspartate aminotransferase (11%); increased alanine aminotransferase (44%); elevated total bilirubin (11%); decreased albumin (88%); elevated creatine phosphohokinase (11%); increased lactate dehydrogenase (55%); increased triglycerides (66%); improved D-dimer (55%); diarrhea (22%); rash (11%); nausea (11%)</td>
<td>NR</td>
</tr>
<tr>
<td>2.</td>
<td>Fuji, 2021</td>
<td>Hyperuricemia (55.5%); impaired liver function (31.4%); drug eruption (7.4%); drug fever (5.5%); and increased eosinophil count (1.8%)</td>
<td>NR</td>
</tr>
<tr>
<td>3.</td>
<td>Ivashchenko, 2021</td>
<td>About 17.5% of patients experienced diarrhea, nausea, vomiting, chest pain, and increased levels of liver transaminases.</td>
<td>NR</td>
</tr>
<tr>
<td>4.</td>
<td>Udwadia, 2021</td>
<td>Hyperuricemia (16.4%); abnormal liver function tests (6.8); viral pneumonia (2.7%); gastrointestinal disturbances (1.4%)</td>
<td>NR</td>
</tr>
<tr>
<td>5.</td>
<td>Cai, 2020</td>
<td>Diarrhea (5.71%); liver and kidney injury (2.86%) and others (2.86%)</td>
<td>P-value&lt; 0.001</td>
</tr>
<tr>
<td>6.</td>
<td>Dabbous, 2021</td>
<td>Diarrhea (6.8%); elevated liver enzymes (6.8%); nausea (2.3%); headache (2.3%); anemia (4.5%); hyperuricemia (4.5%); decreased neutrophils (4.5%)</td>
<td>P-value&gt; 0.05</td>
</tr>
<tr>
<td>7.</td>
<td>Chen, 2020</td>
<td>Abnormal LFT (8.62%); increased serum uric acid (13.79%); reaction to psychiatric symptoms (4.31%); gastrointestinal tract reactions (13.79%)</td>
<td>P-value&lt; 0.05 in the incidence of hyperuricemia</td>
</tr>
<tr>
<td>8.</td>
<td>Rattanaumpawan, 2020</td>
<td>Diarrhea (54.0%), nausea/vomiting (7.9%), hepatitis (6.4%), and QT interval prolongation on the ECG (6.4%). None of these side effects were life-threatening.</td>
<td>NR</td>
</tr>
</tbody>
</table>
differences between favipiravir and comparative antivirals or standard treatments. This is believed to be 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 levels of gastrointestinal ACE2 expression were found in ileal epithelial cells, especially resorbable enterocytes. The direct and indirect effects of cytokines could combine to cause an enterocyte ion imbalance, which contribute to the development of diarrhea. Viral E-proteins, ion imbalance, impaired barrier integrity, and dysregulation of the renin-angiotensin-aldosterone system, which causes inflammation, play an important role in secretory diarrhea and intestinal leakage in COVID-19 patients.19

We included 2 cases which reported adverse events during therapy with favipiravir such as drug fever, as well as mild and reversible elevations of liver enzymes. Drug fever is a type of reaction associated with transient fever induced by drug therapy and disappears when the cause is discontinued. The main feature that distinguishes drug fever from other causes is a fever that disappears after the drug is stopped. Five mechanisms of drug fever have been identified. Fever can be produced 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 case reports showed adverse events following favipiravir treatment, with 2 cases occurring during hospital admission and 1 case after remission. In the two cases reported by Tsuibo, 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 transient increase in viral load called “blip” were also reported during treatment. From this perspective, these two cases might represent an outbreak-like phenomenon in antiviral treatment. In the case of COVID-19, delays in hospitalization after the onset of the disease were also reported to prolong SARS-CoV-2 infection.20 In both cases reported, antiviral therapy was started relatively late, 10 days after the onset of the disease. This might lead to a “blip”-like phenomenon. Koshi, et al. notified the first report on the efficacy of favipiravir in end-stage renal disease (ESRD) patients undergoing hemodialysis.15 This suggested that favipiravir might be an effective option for treating patients with ESRD who were infected with COVID-19 based on improvement in vital signs and laboratory data, with mild and reversible elevation of alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase (γ-GTP). Despite these findings, 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 consequence, 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 involving 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 serious than other antiviruses and are reversible. In case reports, there are rare adverse events such as AGEP, we also included a transient increase in viral load the day after treatment with favipiravir ended.

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

REFERENCES


