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The Efficacy of Favipiravir Therapy in COVID-19 Patients: A Review Article

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ABSTRACT

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), has resulted in a major global public health crisis. In the absence of a universally approved specific antiviral therapy, several existing antiviral agents have been repurposed, including favipiravir. Favipiravir is a purine nucleoside analog that inhibits RNA-dependent RNA polymerase (RdRp), an essential enzyme for viral RNA replication. This review aims to evaluate the clinical efficacy of favipiravir therapy in patients with COVID-19. A narrative literature review was conducted using databases such as PubMed and Google Scholar, including national and international peer-reviewed journals published between 2019 and 2021. Clinical trials, randomized controlled trials, and observational studies assessing favipiravir in COVID-19 patients were included, while articles lacking accessible full texts or reliable data were excluded. The reviewed studies indicate that favipiravir therapy is associated with improved clinical outcomes, including reduced duration of fever and cough and accelerated viral clearance within 7–14 days of hospitalization, particularly in patients with mild to moderate COVID-19. However, considerable variability in outcomes was observed due to differences in study design, sample size, dosing regimens, comparator therapies, and treatment duration. Overall, favipiravir demonstrates potential as an antiviral therapy for COVID-19; nevertheless, large-scale, well-designed randomized controlled trials are required to definitively confirm its efficacy and safety across different patient populations.

Keywords: COVID-19; SARS-CoV-2; favipiravir; clinical efficacy; antiviral therapy.

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1. Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a single-stranded RNA virus belonging to the Betacoronavirus genus. The disease was first identified in Wuhan, China, in December 2019, and was subsequently declared a global pandemic by the World Health Organization (WHO) in March 2020 [1]. COVID-19 primarily affects the respiratory system and is transmitted through respiratory droplets; however, it is also associated with a wide range of clinical manifestations, from asymptomatic infection to severe pneumonia, acute respiratory distress syndrome, and multi-organ failure [2,3].

The rapid spread and high morbidity of COVID-19 have posed significant challenges to healthcare systems worldwide, leading to an urgent need for effective therapeutic strategies. In the absence of specific antiviral agents, several existing antivirals previously used against other RNA viruses have been investigated for repurposing [4]. Favipiravir is one such antiviral drug that has demonstrated broad-spectrum activity against RNA viruses [5].

Favipiravir (T-705) is a purine nucleoside analog that is intracellularly converted into its active form, favipiravir ribofuranosyl-5′-triphosphate, which selectively inhibits viral RNA-dependent RNA polymerase (RdRp), thereby disrupting viral RNA replication. Originally approved in Japan for the treatment of influenza, favipiravir has demonstrated broad-spectrum antiviral activity against various RNA viruses and has subsequently been investigated for use in COVID-19. In several countries, including Indonesia, favipiravir has been incorporated into national COVID-19 treatment guidelines for patients with mild to severe disease. [6,7]. However, despite its widespread clinical use, the evidence regarding the effectiveness of favipiravir in COVID-19 patients remains inconsistent. While some clinical trials and observational studies report favorable outcomes such as faster symptom resolution, reduced duration of fever and cough, and earlier viral clearance, other studies have failed to demonstrate significant benefits in terms of viral eradication or overall clinical recovery. These conflicting findings may be attributed to heterogeneity in study design, patient populations, disease severity, dosing regimens, timing of initiation, and comparator therapies. As a result, the true clinical efficacy of favipiravir in COVID-19 remains unclear. In Indonesia, favipiravir has been included in national COVID-19 treatment guidelines for mild to severe cases. Nevertheless, clinical evidence regarding its efficacy remains inconsistent [8,9]. This inconsistency in the existing literature represents an important knowledge gap and underscores the need for a comprehensive review of available clinical trial data. A narrative evaluation of clinical and observational studies is necessary to systematically examine reported outcomes, identify sources of variability, and clarify the potential role of favipiravir in the management of COVID-19. Therefore, this review aims to critically assess the evidence from clinical trials and observational studies regarding the efficacy of favipiravir therapy in COVID-19 patients, with particular attention to clinical improvement and viral clearance outcomes.

2. Method

This study employed a narrative review design to evaluate the clinical

efficacy of favipiravir therapy in patients with COVID-19. A comprehensive literature search was conducted using electronic databases, including PubMed and Google Scholar, to identify relevant national and international peer-reviewed articles published between 2019 and 2021. The search strategy used combinations of keywords such as “favipiravir,” “COVID-19,” “SARS-CoV-2,” “antiviral therapy,” and “clinical efficacy.”

Inclusion criteria consisted of original research articles that evaluated favipiravir therapy in confirmed COVID-19 patients. Eligible studies included randomized controlled trials, non-randomized interventional studies, prospective and retrospective observational studies, and multicenter clinical trials. Studies were required to involve adult patients with mild, moderate, or severe COVID-19 and to report at least one relevant clinical outcome. Primary outcome measures included clinical improvement (e.g., time to recovery, reduction in fever and cough, oxygen saturation improvement), viral clearance (e.g., time to negative RT-PCR results), duration of hospitalization, and disease progression. Secondary outcomes included safety and tolerability when reported.

Exclusion criteria included review articles, meta-analyses, case reports or case series with fewer than 10 patients, in vitro or animal studies, and articles without accessible full texts. Studies lacking clear outcome measures, insufficient methodological detail, or reliable references were also excluded.

Data synthesis was performed descriptively due to heterogeneity among the included studies. The selected articles were systematically compared based on several key variables, including study design, sample size, patient population and disease severity, dosing regimens and duration of favipiravir therapy, comparator treatments, and reported clinical and virological outcomes. Particular attention was given to differences in timing of treatment initiation and outcome assessment points (e.g., Day 7 or Day 14 viral clearance). Findings were synthesized narratively to identify patterns of clinical efficacy, areas of agreement, and sources of inconsistency across studies.

Potential sources of bias were considered in interpreting the findings. These included publication bias, as studies with positive outcomes may be more likely to be published; language bias, as only articles published in English were included; and selection bias arising from the inclusion of open-label and non-randomized studies. Additionally, variability in study design, dosing strategies, and outcome definitions may have influenced the reported results. These limitations were taken into account when drawing conclusions regarding the overall efficacy of favipiravir in COVID-19 treatment.

3. Result

A total of ten studies met the inclusion criteria and were included in this narrative review. The selected studies comprised randomized controlled trials, open-label interventional studies, and observational studies conducted in adult patients with laboratory-confirmed COVID-19. Most studies enrolled patients with mild to moderate disease, although several included individuals with severe or critical illness. Sample sizes varied substantially, ranging from 26 to 236 participants. Favipiravir was administered using loading doses followed by maintenance regimens, with

treatment durations ranging from 7 to 14 days, and was compared with standard care or other antiviral agents such as umifenovir, lopinavir/ritonavir, hydroxychloroquine, or placebo.

Table 1. Efficacy of Favipiravir in COVID-19 Patients

No.	Study design	Dose regimen	Main outcomes	Reference
1	Prospective, randomized, controlled, open-label multicenter trial in 236 patients with moderate/severe COVID-19; favipiravir (n=116) vs umifenovir (n=120) for 10 days	Favipiravir 600 mg twice daily on Day 1, followed by 600 mg twice daily on Days 2–10	Favipiravir significantly alleviated clinical symptoms compared with umifenovir	[10]
2	Multicenter randomized pilot phase II/III trial (AVIFAVIR) based on Russian COVID-19 standard of care	AVIFAVIR 1600 mg twice daily on Day 1 followed by 600 mg twice daily on Days 2–14 **or** 1800 mg twice daily on Day 1 followed by 800 mg twice daily on Days 2–14	SARS-CoV-2 viral clearance achieved in 62.5% of patients within 4 days; treatment was safe and well tolerated	[11]
3	Non-randomized interventional study in 80 patients; favipiravir vs lopinavir/ritonavir	Favipiravir 1600 mg twice daily on Day 1 followed by 600 mg twice daily on Days 2–14	Higher viral clearance rate at Day 7 and better clinical improvement compared with lopinavir/ritonavir	[12]
4	Prospective, randomized, open-label, multicenter trial; early vs late favipiravir initiation	Favipiravir 1800 mg twice daily on Day 1 followed by 800 mg twice daily for >10 days	Reduced duration of fever; no significant improvement in viral clearance	[13]
5	Multicenter randomized trial in 26 patients; favipiravir alone, tocilizumab alone, or combination therapy	Favipiravir 1600 mg twice daily on Day 1 followed by 600 mg twice daily on Days 2–7	Combination with tocilizumab improved lung inflammation and prevented disease progression	[14]
6	Randomized, open-label, parallel-arm, multicenter phase III trial in 150 patients; favipiravir vs supportive care	Favipiravir 1800 mg twice daily on Day 1 followed by 800 mg twice daily up to Day 14	Time to clinical recovery was significantly shorter in the favipiravir group	[15]
7	Exploratory single-center, open-label, randomized controlled trial comparing favipiravir, baloxavir marboxil, and standard antiviral therapy	Favipiravir 1600–2200 mg on Day 1 followed by 600 mg three times daily for ≤14 days	Negative SARS-CoV-2 conversion at Day 14 occurred in 77% of patients receiving favipiravir	[16]
8	Randomized controlled phase III trial; favipiravir vs hydroxychloroquine plus oseltamivir	Favipiravir 3200 mg on Day 1 followed by 600 mg twice daily on Days 2–10	Viral negativity by Day 7 was observed in 48% of the favipiravir group	[17]

9	Randomized controlled trials, observational studies, and case series in >10 patients with mild–moderate COVID-19	Favipiravir 1600 mg twice daily on Day 1 followed by 600 mg twice daily on Days 2–14	Viral clearance by Day 7 and clinical improvement within 14 days	[18]
10	Multicenter randomized double-blind placebo-controlled trial in adults with mild COVID-19	Favipiravir 1800 mg twice daily on Day 1 followed by 800 mg twice daily on Days 2–7	Faster viral clearance compared with placebo	[19]

3.1. Outcome Measures

The main efficacy outcomes assessed across studies were viral clearance, clinical improvement, and duration of hospitalization. Viral clearance was defined as conversion to a negative SARS-CoV-2 RT-PCR result, commonly evaluated on Days 7 and 14. Clinical improvement was assessed based on resolution of fever and cough, improvement in respiratory symptoms, oxygen saturation, radiological findings, or time to clinical recovery as defined by individual studies. Reduction in hospitalization time was measured as the duration from admission to discharge or clinical stabilization.

3.2. Clinical and Virological Outcomes

Several randomized controlled trials reported that favipiravir therapy was associated with faster clinical improvement compared with comparator treatments. In a multicenter randomized open-label trial involving patients with moderate to severe COVID-19, favipiravir resulted in more rapid resolution of fever and cough than umifenovir, although differences in viral clearance were not consistently significant at later time points.

The AVIFAVIR phase II/III multicenter randomized trial demonstrated that more than half of patients receiving favipiravir achieved viral clearance within four days of treatment initiation, indicating early virological response. Similarly, a non-randomized interventional study comparing favipiravir with lopinavir/ritonavir reported higher viral clearance rates at Day 7 and greater clinical improvement in the favipiravir group.

Studies evaluating the timing of favipiravir initiation found that early administration was associated with shorter duration of fever and reduced length of hospitalization, although viral clearance rates did not differ significantly between early and delayed treatment groups. In a randomized phase III trial involving patients with mild to moderate COVID-19, favipiravir significantly shortened the time to clinical recovery compared with supportive care alone.

Additional randomized trials reported viral negativity rates ranging from 48% to 77% by Day 7 or Day 14 among patients receiving favipiravir. A multicenter double-blind placebo-controlled trial in patients with mild COVID-19 demonstrated faster viral clearance in the favipiravir group, although differences in symptom resolution were modest.

3.3. Summary of Findings

Overall, the reviewed studies suggest that favipiravir therapy is associated with

improved clinical outcomes, including reduced duration of fever and cough, and viral clearance within 7–14 days, particularly in patients with mild to moderate COVID-19. However, the magnitude of benefit varied across studies due to differences in study design, patient characteristics, dosing regimens, timing of treatment initiation, and outcome definitions. These inconsistencies highlight the heterogeneity of the available evidence and underscore the need for standardized outcome measures in future clinical trials.

4. Discussion

The Indonesian COVID-19 Clinical Management Guidelines recommend the use of favipiravir for the treatment of COVID-19 patients with mild to severe or critical disease. Favipiravir acts selectively by inhibiting RNA-dependent RNA polymerase (RdRp) of RNA viruses and inducing RNA transversion mutations that result in nonviable viral phenotypes. Favipiravir is metabolized into its active form, favipiravir ribofuranosyl-5′-triphosphate. The drug is primarily metabolized in the liver and does not produce significant drug–drug interactions. Furthermore, favipiravir does not affect human DNA polymerase subunits α, β, and γ (up to concentrations of 100 μg/mL), thereby minimizing the risk of toxic effects [20].

In addition, the standard dose of favipiravir for the treatment of influenza is 1600 mg twice daily on the first day, followed by 600 mg twice daily for a total duration of five days [21]. Most eligible studies adopted this standard regimen, with treatment durations generally extending up to 14 days. However, several studies reported dose escalation to 1800 mg twice daily on the first day, followed by 800 mg twice daily.

Various dosing regimens have been proposed depending on the type of viral infection. For the treatment of COVID-19, a loading dose of 2400–3000 mg every 12 hours (two doses) has been considered, followed by a maintenance dose of 1200–1800 mg every 12 hours [22].

Table 1 presents various types of studies conducted as therapeutic approaches for COVID-19, including successful clinical trials and observational studies. Across these studies, several parameters were used to evaluate the efficacy of favipiravir therapy in COVID-19 patients, such as clinical improvement and increased viral clearance, which reflects the elimination of the virus from the patient's body.

Clinical improvement in COVID-19 patients is determined by several variables, including respiratory rate, oxygen saturation, reduction of cough, and improvement in chest computed tomography (CT) scan findings. Clinical signs and symptoms are influenced by pulmonary infection or pneumonia, as well as the involvement of major organs affected by SARS-CoV-2 [23].

Across multiple studies, although other antiviral agents were used as comparators, favipiravir was consistently associated with a significantly higher rate of viral clearance on Day 7, while no significant difference was observed on Day 14. These findings are supported by clinical improvements observed on Days 7 and 14 during hospitalization [24].

According to the study by Chen et al., favipiravir administration was associated with reductions in fever and cough, as well as higher viral clearance rates in COVID-19

patients, although it did not demonstrate a statistically significant improvement in overall clinical outcomes. In contrast, Udwadia et al. reported that the time to clinical recovery was significantly shorter in patients receiving favipiravir compared with those treated with other antiviral agents [10,15].

Furthermore, Doi et al. reported that although favipiravir administration did not significantly improve viral clearance within the first six days, a significant difference was observed in the duration of hospitalization between patients who received favipiravir immediately after confirmed COVID-19 diagnosis and those who received delayed treatment. Favipiravir administration was also associated with a reduction in fever compared with patients who did not receive favipiravir. Early initiation of favipiravir following symptom onset may therefore shorten disease progression and potentially reduce transmission to others [13].

According to the study by Manabe et al., favipiravir shows strong potential for the treatment of COVID-19, particularly in patients with mild to moderate disease, who demonstrated pulmonary recovery within 14 days of favipiravir initiation. Early initiation of favipiravir is recommended for patients with mild COVID-19 before the development of pneumonia or further deterioration of lung function [18].

Overall, the available data indicate that clinical improvement generally occurs on Days 7 and 14 of treatment. In addition, viral clearance within 7–14 days of hospitalization was more frequently observed in patients receiving favipiravir compared with those treated with other antiviral agents. However, further studies are required to evaluate the efficacy, safety, and effectiveness of favipiravir in COVID-19 patients, including assessments of different dosing regimens and treatment durations across varying levels of disease severity.

This review also has implications for guideline development and future research. By synthesizing available clinical trial data, the review helps clarify the contexts in which favipiravir may be most beneficial, particularly early in the disease course and in patients with non-severe illness. At the same time, the findings highlight critical gaps in the evidence base, including the lack of large-scale, double-blind randomized controlled trials with standardized outcome measures. Addressing these gaps is essential to establish clear clinical recommendations regarding optimal dosing, treatment duration, and patient selection.

Variability in study outcomes may be attributed to several limitations, including differences in study design, comparator agents, and the relatively small number of studies and patients. Therefore, further well-designed clinical studies are necessary to establish the definitive role of favipiravir in the management of COVID-19.

5. Conclusion

Favipiravir demonstrates potential clinical benefit in the management of COVID-19, particularly in patients with mild to moderate disease, as evidenced by improved clinical recovery and viral clearance within 7–14 days. These findings support the consideration of favipiravir as an early antiviral treatment option in appropriate patients, especially in healthcare settings where access to newer antiviral agents is limited.

Clinicians should prioritize early initiation of therapy and carefully consider patient selection to optimize treatment outcomes. However, the available evidence remains heterogeneous, and definitive conclusions regarding the efficacy and safety of favipiravir cannot yet be established. Therefore, future research should focus on large-scale, well-designed randomized controlled trials with standardized outcome measures, clear definitions of disease severity, and consistent dosing regimens. Such studies are essential to clarify the optimal role of favipiravir in COVID-19 treatment guidelines and to support evidence-based clinical decision-making.

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