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RETHINKING: IS FAVIPIRAVIR EFFECTIVE FOR ACHIEVING FASTER TIME TO VIRAL CLEARANCE IN MODERATE HOSPITALIZED COVID-19 PATIENTS?

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Abstract

Background and Aim: Despite favipiravir being a recommended antiviral for patients with mild symptoms of COVID19, there is still debate about whether it can be used for patients with moderate severity. Therefore, the current review was aimed to determine the efficacy of favipiravir in achieving viral clearance compared to standard care in hospitalized moderate COVID-19 patients.

Methods: We conducted literature search in studies investigating the efficacy of favipiravir vs standard care in hospitalized patients with moderate to severe COVID-19 in the time to achieve viral clearance. Eligible studies were included and appraised in terms of their validity, importance, and applicability. Furthermore, included studies were ranked according to their level of evidence (LOE)

Results: Five studies were included and assessed further. All studies showed the superiority of favipiravir administration which has successfully lowered the time to viral clearance up to 95% compared to standard care and achieved a higher viral clearance rate at a certain period (day 5 and day 10). However, some studies have shown insignificant results. Despite that, further studies are still needed to confirm these findings.

Conclusion: In moderate hospitalized COVID-19 patients, favipiravir can potentially accelerate viral clearance rate or time to viral clearance by up to 95% compared to standard of care. Favipiravir, can be an option with fewer side effects than other available antivirals, can be suggested for COVID-19 patients with moderate symptoms.

Keywords: Antiviral, favipiravir, SARS-CoV2, therapy, viral clearance

INTRODUCTION

Since it is declared a pandemic, COVID-19 has caused many deaths and is highly infectious due to its high transmission.[1] Based on the severity of cases, WHO has divided them into asymptomatic, mild, moderate, severe, and critical. Moderate symptoms in adult patients are clinical signs of pneumonia (fever, cough, shortness of breath, rapid breathing) but no signs of severe pneumonia.[2] According to the experiences in several countries such as India, Saudi Arabia and Japan, patients with

mild or moderate symptoms can be given favipiravir as an antiviral treatment plus supportive therapy.[3-5]

Favipiravir is an RNA-dependent RNA polymerase (RdRp) inhibitor that has the effect of inhibiting viral replication and is currently being used for patients with mild symptoms according to the Covid-19 management guidelines. Favipiravir also has a relatively safe safety profile but high therapeutic efficacy.[6,7] However, the results are still unclear, and the differences in recommendations between countries explain the debate about whether favipiravir can still be used for patients with COVID-19 to provide effective therapy.[3-5]

Currently, the recovery parameter used for COVID-19 patients is symptom improvement. However, recent evidence has shown that a patient with symptomatic improvement and a complete isolation period can still infect other patients and does not necessarily indicate that the patient is completely cured. Therefore, viral clearance is the result suggested by various studies as the primary indicator of recovery in patients as it lowers the possibility of transmission, which endangers patients' surroundings.[8-10]

Given the debate about whether favipiravir can still be used for patients with moderate COVID-19 and the recommendation of viral clearance as a recovery parameter, this literature review was aimed to determine whether favipiravir is effective in achieving viral clearance or shortening the time to viral clearance compared to standard of care in hospitalized moderate COVID-19 patients.

METHODS

Search strategy

A comprehensive search through PubMed, CENTRAL, Wiley Library, EBSCOhost, Embase, and gray literature databases (Google Scholar, Scopus, and ProQuest) search was done for studies assessing the efficacy of favipiravir in achieving faster time to viral clearance in hospitalized moderate COVID-19 patients compared to standard care using the keyword listed in Table 1. Hand searching through systematic reviews included studies or references was also done to include more relevant studies.

Table 1. Keywords for literature search used in the study

Database	Search strategy	Hits
PubMed	((favipiravir) AND (covid*)) AND (moderate) AND (severe)	47
Scopus	((favipiravir) AND (standard care) AND (covid*) AND (severe))	48
Cochrane	((favipiravir):ti,ab,kw) AND (((covid*):ti,ab,kw) OR (sars-cov-2): ti,ab,kw)) AND (((moderate):ti,ab,kw) AND (severe):ti,ab,kw))	28
Proquest	((favipiravir) AND (covid*)) AND (moderate) AND (severe)	220
Wiley library	"covid*" anywhere and "favipiravir" anywhere and "severe" anywhere and "moderate" anywhere	276
Google Scholar	Favipiravir AND COVID [MeSH] AND Moderate AND Severe	1110
Embase	('favipiravir'/exp OR favipiravir) AND covid* AND moderate AND severe AND ([systematic review]/lim OR [meta-analysis]/lim OR [randomized controlled trial]/lim)	32
EBSCO	(favipiravir) AND ((covid*[MeSH Terms]) OR (sars-cov-2[MeSH Terms])) AND (moderate) AND (severe)	17
	TOTAL	**1778**

Eligibility criteria

Studies were then screened using the predetermined eligibility criteria, which includes randomized controlled trial (RCT) or systematic review/meta-analysis of RCTs that utilized male or female adult patients with moderate symptoms as defined by WHO guidelines as their population, favipiravir given 7 to 14 days with its respective dosage, in addition to standard care as their intervention, standard care defined as standard supportive care, symptomatic care, with or without oxygen therapy, or other antivirals which all based on each country guidelines, and viral clearance or time to viral clearance as their outcome. Studies including pediatric or pregnant patients were further excluded to increase the comparability of included studies.

Critical appraisal

The included studies were then appraised in terms of their validity, importance, and applicability according to standardized tool.[11] The process of critical appraisal and literature searching was done by five independent adjudicators (AGIK, BS, DAN, EFM, and LBL), who were then consulted to reach a consensus between the authors. Studies were finally ranked based on their level of evidence (LoE)

RESULTS

A literature search yielded a total of 1778 articles. Based on the title and abstract, there were 20 articles retrieved for the present review. Among the articles, 11 were excluded due to irrelevant outcomes which did not assess viral clearance, two were excluded due to study types of narrative review, and another two were excluded due to only assessing pediatric patients. Thus, we obtained five randomized controlled trials that were suitable and qualified for inclusion. The detailed planned procedure is illustrated in Figure 1. The study outcome is summarized in Table 2, while the critical appraisal results are shown in Table 3.

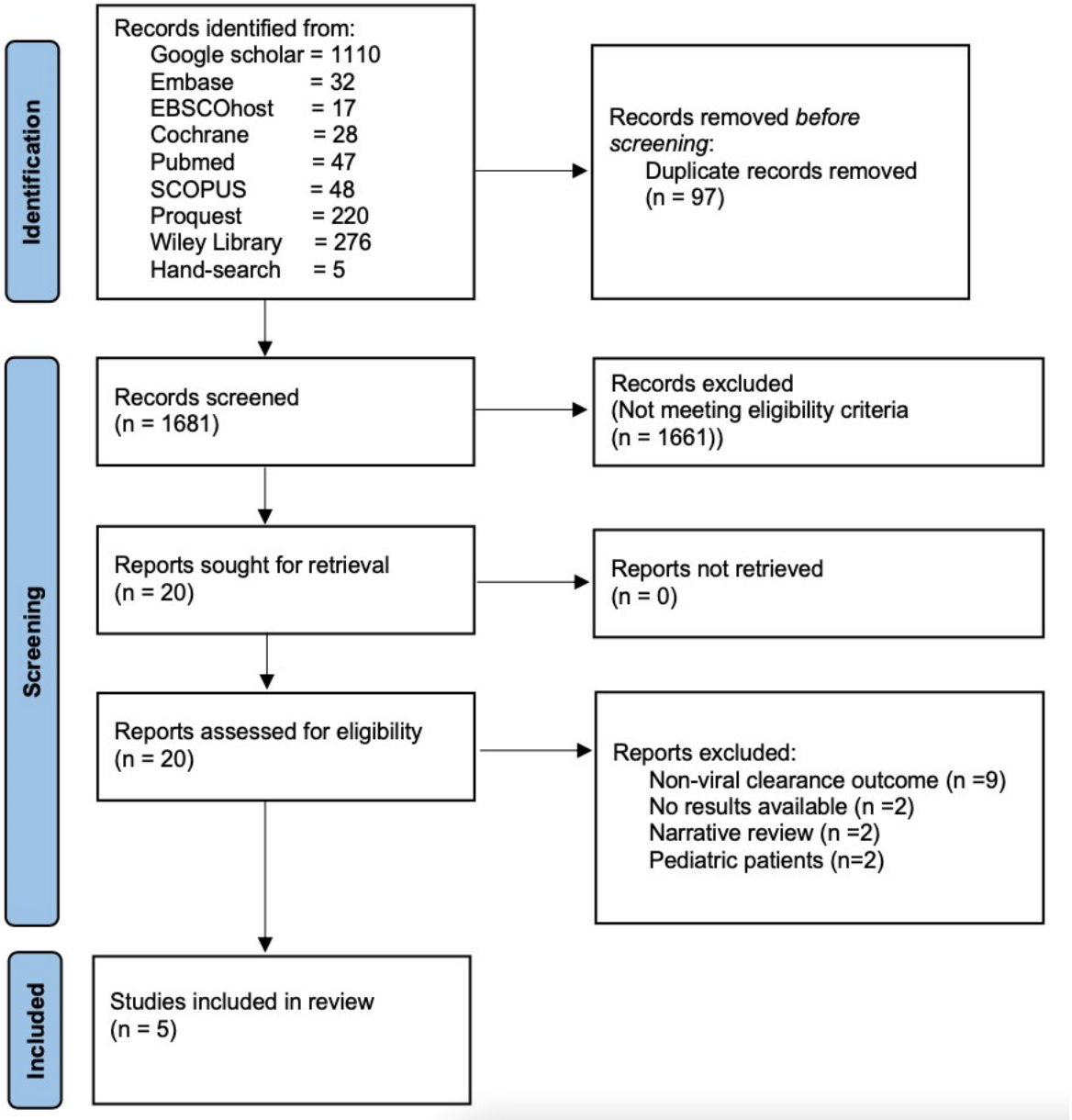

Figure 1. The flow of article selection throughout the study

Table 2. Outcomes of the included studies

Author and Year	Study Design	Study Location	Sample Size	Mean/ Range Age	Intervention	Control	Viral Clearance Outcome
Outcome: Viral Clearance							
Ivashchenko et al. 202012	Phase II/III. A randomized, openlabel, multicenter trial	Russia	Total: 60 Favipiravir 1600/600 mg (n=20), Favipiravir 1800/800 mg (n=20) SOC (n= 20)	>18 years old, unclear	Favipiravir I: 1600mg on day 1, followed by 600mg BID Favipiravir I: 1800mg on day 1, followed by 800mg BID	SOC alone	The mean period of Favipiravir duration: 10.9 ± 2.8 days. Favipiravir : 37 /40 (92.5%) SOC: 16/20: (80%) p-value = 0.1
Finberg RW, et al. 202113	Phase 2, randomized, openlabel, multicenter trial	US	Total: 50 Favipiravir + SOC: 25 SOC alone: 25	Favipiravir + SOC Group: 55.4 years old SOC alone Group: 58.9 years old	1800 mg of favipiravir orally b.i.d. on day 1, followed by 1000 mg b.i.d. in addition to SOC	SOC alone	Interventio n group: 16.0 days(90% CI, 12.0-9.0) Control group: 30.0 days (90% CI, 12.031.0) p-value = 0.0415
Outcome: Time to Viral Clearance							
Udwadia ZF, et al. 2021[14]	Random-ized, openlabel, parallelarm, multicenter , phase 3 trial	India	Mild symptom samples: Favipiravir : 44SOC45 Moderate symptom samples: Favipiravir : 28 SOC: 30	Favipiravir group: 43.6 years old SOC group: 43 years old	Oral favipiravir: 1800 mg BID loading dose on day 1; 800 mg BID maintenance dose after that, plusSOC for upto a maximum of 14 days	SOC alone (the control arm) included antipyretics, cough suppress ants, antibiotic s, and vitamins. SARSCoV-2	Interventio n group: 4.5 days (95% 3.0-7.0); Control group: 6.5 days (95% CI, 3.014.0) p = 0.0672
						antiviral drugs (such as hydroxychloroqu ine) were banned because of their possible effective ness against the virus.	
Promomed LLC, et al 2021.[15]	Randomize d, openlabel, multicenter phase 3 trial	Russia	200 patients with moderate Covid-19	18-80 years old	Oral favipiravir: On day 1 of therapy, use 1600 mg twice daily; on days 2-14 of treatment - 600 mg twice daily until 14 days.	Standard of care used in Russia: hydroxychloroqu ine (with or without azithrom ycin), chloroqu ine, lopinavir /ritonavir , or other recommended schemes	Favipiravir group: 98%. SoC Group: 79%.
Ruzhentso va et al., 2021[16]	Randomize d, openlabel, phase 3 activecontrolled trial	Russia	Favipiravir : 112 SOC: 56	Favipiravir : 41.7± 10.6 years SOC group: 42.0 ± 10.4 years	Oral favipiravir (1800 mg BID on day 1, followed by 800 mg BID for up to 9 days)	Standard of care (umifeno vir+intra nasal interfero n alpha2b, or Hydroxy chloroqu ine) for up to 10 days	Interventio n group: 3 days SOC: 5 days p-value = 0.038

Note: SOC = standard of care; BID = twice daily

Table 3. The result of critical appraisal of the included studies

Author; year	Study design	Validity					Importance		Applicability			LOE
		R	Ac	Bl	E	Sg	Outcome [adjusted variables]	Estimates [95% CI]	Ss	M I	M II	
Ivashchen ko AA; 2020[12]	RCT	✓	✓	✗	✓	✓	Viral clearance on day 10	10 days; (p = 0.155)	✓	38	38	II
Finberg RW; 202113	RCT	✓	✓	✗	✓	✓	Time to Viral clearance	16 days; 90% [12.029.0]	✓	15.3 8	15.3 8	II
Udwadia ZF; 2021[14]	RCT	✓	✓	✗	✓	✓	Time to Viral clearance	4.5 days; 95% [3.07.0]	✓	19.1 6	29	II
Promomed LLC; 202015	RCT	✓	✓	✗	✗	?	-	-	-	-	-	II
Ruzhentso va TA; 202116	RCT	✓	✓	✗	✓	✓	Time to Viral clearance	3 days (IQR 3.0;3.0)	✓	18.9	31	II
							Clinical improvement	6.0 days (IQR 4.0; 9.3)	✓			

R = Randomization; Ac = Accountability; Bl = Blinding; E = Equal treatment; Sg = Similarity between groups; Ss = Similar to the setting in community; M I = f; M II = 1/(PEERxRRR); LOE = Level of Evidence; IQR = Interquartile range, PEER = Patient expected event rate; RRR = Relative risk reduction

We found that all studies assessing time to viral clearance outcome stated that favipiravir is effectively superior in lowering the time needed to achieve viral clearance in hospitalized moderate COVID-19 patients compared to standard of care, shown by the difference in time to viral clearance, although majorly not significant.[12-16] Only the study by Finberg et al.[13] showed that favipiravir administration significantly shorten the viral clearance time. Three studies assessing time to viral clearance were also heaving great validity, importance, and applicability, showing the study's power. Moreover, two studies assessing viral clearance at a particular time (day 10 or day 5) have also shown that favipiravir increases the viral clearance rate compared to standard care, although insignificant. Although major of the studies included shows no statistical significance; we considered almost all studies were clinically meaningful as it lowers the time to viral clearance and increases the rate of viral clearance in favipiravir groups compared to standard care groups, whereas a study by Promomed LLC[15] was judged inapplicable since it has low validity due to no blinding and equal treatment given for both groups which may potentially cause a high risk of bias.

DISCUSSION

Based on our literature search, we suggested that favipiravir could be administered as moderate COVID-19 patients' treatment if the settings had more favipiravir supply, which was considerable, according to WHO data.[14] However, two out of five studies have low validity. Therefore, the recommendations are given still need to be reconsidered as a standard guideline antivirus using patient settings and the availability of drugs in the local settings.

Interestingly, a study conducted by Ivashchenko et al.[12] showed that after 10 days of drug administration, favipiravir administration resulted in a viral clearance rate of 92.5% from 40 subjects, compared to standard of care therapy with only 80% viral clearance rate from 20 subjects, with p-value of 0.155. This study has consistent results with other studies, whereas favipiravir has an excellent antiviral response towards SARS-CoV-2, and the adverse effects received by the subjects were only mild to moderate in severity, and there was no increase in toxicity when given high doses. However, this study has several drawbacks, such as not providing the demographic and characteristic table to inform about the homogeneity of the sample population and minimization of bias. Also, there were no detailed criteria explained regarding the subjects. Furthermore, a study done by Promomed

has also shown that the administration of favipiravir increases the viral clearance rate at 10 days compared to the standard of care group (98% vs. 79%).15
A study by Finberg et al. showed the superiority of favipiravir in shortening the length of stay in the Favipiravir group was 16.0 days (90% CI, 12.0-29.0) compared to 30.0 days (90% CI, 12.0-31.0) in the control group significantly.[13] This was supported by the study of Udwadia et al., which that showed in the favipiravir and control groups, each respectively, the median time to the cessation of viral shedding was 5 days (95% CI: 4 days, 7 days) and 7 days (95% CI: 5 days, 8 days), p=0.129 in the control group, whereas the median time to clinical cure was three days (95% CI: 3 days to 4 days) and five days (95% CI: 4 days, 6 days), p=0.030. There was a significant improvement in time to clinical cure. However, the primary endpoint was confounded by interpretation issues with the RT-PCR assay.[14] Despite the limitation, early administration of favipiravir may reduce the duration of clinical signs and symptoms of mild-to-moderate COVID19 patients. In Addition, a study carried out in Russia by Ruzhentsova et al. has also shown that there is a significant difference in the median time to viral clearance in the favipiravir group (3 days; IQR 3.0; 3.0) compared to the control group (5 days; IQR 4.5; 5.5) in hospitalized patients (HR 2.11; 95% CI 1.04-4.31; p=0.038). With both groups reported adverse events mostly mild and similar, this trial suggests that early initiation of a 10-day favipiravir course brings clinical benefits to mild-to-moderate COVID-19 patients.[16]

Additionally, all the five studies found that the adverse effects of favipiravir were considerably mild-to-moderate in severity. Thus, the drug was also considered safe for patients with moderate COVID-19. The most common adverse events stated in the five studies include asymptomatic transient elevation in uric acid that leads to hyperuricemia, gamma-glutamyl transferase, liver enzymes such as ALT and AST. Other drug reactions include chest pain, acute kidney injury, and mild gastrointestinal disturbances such as diarrhea, nausea, and chest pain. However, favipiravir is contraindicated to childbearing or breastfeeding women and patient who has severe renal impairment and severe hepatic impairment.[12-16]

The consideration of using favipiravir to lower the time to viral clearance remains relevant during the COVID-19 pandemic. Our findings suggest that favipiravir administration has successfully lowered the time to viral clearance up to 95% compared to standard care. Moreover, the adverse effects of favipiravir were considerably mild-to-moderate in severity.[12-16] Thus the drug can be considered safe for patients with moderate COVID-19.

All the studies above concluded that favipiravir administration has successfully lowered the time to viral clearance up to 95% compared to standard care, although the results were insignificant. Favipiravir could be continued as a treatment for COVID-19 moderate patients because these results were consistent in all studies. In addition, the Number Needed to Treat (NNT) values in all studies ranged between 5-7, which shows that favipiravir could help patients with COVID-19 achieve faster viral clearance with NNT considerably low. Thus, favipiravir should be given to COVID-19 moderate patients to achieve faster viral clearance. However, further studies are still needed to substantiate these premises to produce strong recommendations.
A systematic review by Manabe et al., 2021[6] shows a similar result where favipiravir induces viral clearance by 7 days and clinical improvement within 14 days. Considering this vital role of favipiravir, we suggested that to shorten the time needed for viral clearance in moderateto-severe COVID-19 patients.

CONCLUSION

Favipiravir can effectively increase viral clearance or time to viral clearance compared to standard of care in moderate hospitalized covid-19 patients by up to 95%. Thus, favipiravir can be recommended to COVID-19 patients with moderate to severe symptoms as a treatment option with fewer side effects than other drugs.

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