A Single-Centered Cohort Study on Favipiravir Safety and Efficacy in Pediatric Patients with COVID-19

Sedigheh Rafiei Tabatabaei [1], Omid Moradi [2], Abdollah Karimi [3], Shahnaz Armin [1], Alireza Fahimzad [1], Roxana Mansour Ghanaie [1], Mahnaz Jamee [4], Azam Mousavizadeh [2], Hossein Amini [2] and Bahador Mirrahimi [1, 2, *]

[1]Pediatric Infections Research Center, Research Institute for Children's Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Department of Clinical Pharmacy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3]Research Institute for Children's Health, Mofid Children's Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[4]Pediatric Nephrology Research Center, Research Institute for Children's Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Corresponding author: Department of Clinical Pharmacy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Email: mirrahimi@sbmu.ac.ir

Abstract

Background: Coronavirus disease 2019 (COVID-19) affects the pediatric population.

Objectives: Due to limited data, this study aimed to evaluate the safety and efficacy of favipiravir in the hospitalized pediatric population diagnosed with COVID-19.

Methods: The present retrospective cohort study was conducted on pediatric patients aged 1 - 18 years with a diagnosis of COVID-19 admitted to Mofid Children's Hospital, Tehran, Iran. Favipiravir was administrated at a dose of 60 mg/kg/day (max: 3200 mg/day) on the first day and then 23 mg/kg/day (max: 1200 mg/day) for 7 to 14 days. The patients were evaluated regarding the need for invasive mechanical ventilation, intensive care unit admission, duration of hospital stay, and mortality. Safety was measured by the occurrence of related adverse drug reactions (ADRs).

Results: A total of 95 patients were included in the study. Favipiravir was administered to 25 patients. The need for invasive mechanical ventilation was reported in 4 (16.00%) and 11 (15.71%) patients in the favipiravir and control groups, respectively (P = 1.000). The median duration of hospital stays was significantly higher in patients who received favipiravir than in the controls (P = 0.002). No difference was observed in the mortality rate (P = 0.695). The ADRs, including decreased appetite, hypotension, and chest pain, were more prevalent in patients who received favipiravir than in the controls (P < 0.05).

Conclusions: The administration of favipiravir in the pediatric population is associated with higher ADR occurrence with no positive effect on the need for invasive mechanical ventilation, hospital stay, and mortality. Further randomized controlled trials are necessary for better judgment.

Keywords: COVID-19, Pediatrics, Favipiravir, Adverse Drug Reaction, Safety, Effectiveness

1. Background

Since late 2019, coronavirus disease 2019 (COVID-19) has resulted in more than 200 million confirmed cases and 4.5 million deaths worldwide (1). The data from previous studies showed that the novel coronavirus 2019 causes mainly no symptoms or mild disease in the pediatric population, which needs only supportive care (2). Furthermore, it could cause a more severe course of the disease and multisystem inflammatory syndrome in children (MIS-C) (3-5).

To date, numerous antiviral agents, including favipiravir, remdesivir, and interferons, have been tried to treat COVID-19 (6, 7). Currently, remdesivir is the only antiviral agent approved to be used in the pediatric population ($\geq$ 12 years) in COVID-19 pharmacotherapy (8). Although some ongoing clinical trials are performed to assess the therapeutic options for children, no published study has been released.

Favipiravir is a prodrug that converts to an active metabolite with broad-spectrum activity developed to treat influenza and used against Ebola (9, 10). Published clinical trials on the adult population reported benefits in patients diagnosed with COVID-19 (11); however, the data were not conclusive. Additionally, some warnings have been issued, and adverse reactions, including bone marrow suppression, hepatotoxicity, and hypersensitivity reaction, were reported (12).

With regard to limited available data about the safety

and efficacy of favipiravir in the pediatric population (13, 14) and no specific reported dosing recommendation for the pediatric population, the used dosage was derived from the limited data for this drug in the treatment of Ebola in children.

2. Objectives

This study aimed to assess the safety and efficacy of favipiravir in children who were admitted to a hospital due to severe COVID-19.

3. Methods

In this historical cohort study, the patients aged 1 - 18 years with a diagnosis of COVID-19 who were admitted to Mofid Children's Hospital, Tehran, Iran, were included within April 2020 to December 2020. The study was conducted in accordance with the Declaration of Helsinki and approved by the Board of Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (IR.SBMU.RICH.REC.1399.069). The inclusion criteria were patients with symptoms compatible with the disease, including fever, cough, peripheral capillary oxygen saturation (SpO_2) (measured using pulse oximeter) less than 93% or severe respiratory distress, cyanosis, and apnea. Furthermore, the patients with fever and/or malaise and/or upper respiratory disease and/or pneumonia were included. The patients who were symptom-free, with no pulmonary involvement in radiologic findings, or with a negative result for reverse transcription-polymerase chain reaction were excluded. Individual case report forms were completed for each patient. Moreover, the data regarding demographics, medical history, related laboratory data, clinical data on the course of hospitalization, and administered medications were recorded.

Favipiravir was administered based on the recommendation of the national guideline at a dosing of 60 mg/kg/day (max: 3200 mg/day) for 1 day followed by 23 mg/kg/day (max: 1200 mg/day) divided into three doses for 7 to 14 days (15). The patients in the control group (within February 2020 to March 2020) received a therapeutic regimen based on the national protocol except for the favipiravir (15). The patients in both groups received standard care, including oxygen supplementation, ventilation support, fluid and electrolyte correction, vasoactive agents and antibiotic administration, and renal replacement support if appropriate (15, 16).

The primary outcome was defined as the need for invasive mechanical ventilation. In addition, the patients were followed up for intensive care unit (ICU) admission, hospital stay, and mortality as secondary outcomes. The patients

were followed for the occurrence of potential drug reactions as safety outcomes. The criteria for admission to the ICU are defined as acute refractory hypoxia, acute hypercapnia, respiratory exhaustion, hemodynamic instability, and diagnosis of moderate to severe MIS-C (17).

Statistical analyses were performed using SPSS software (version 20.0). Continuous variables were expressed as mean $\pm$ standard deviation or median [interquartile range (IQR)] for variables with normal and nonnormal distributions, respectively. Categorical data were expressed as frequency (percentage). The independent samples t-test and Mann-Whitney U test were used to compare the differences in continuous variables for parametric and nonparametric ones, respectively. The differences in the categorical data were analyzed using the chi-square test (or Fisher's exact test if appropriate). Multivariable logistic regression was performed to evaluate the association between favipiravir administration and outcomes (i.e., need for invasive mechanical ventilation and in-hospital mortality). The model was adjusted for hypoxia (defined as SpO_2 < 94%) and high-risk conditions (i.e., malignancy, cardiac disease, immune deficiency, asthma, failure to thrive, and metabolic disease). Odds ratio (OR) plus 95% confidence interval (CI) were reported. P-values of 0.05 were considered statistically significant in the analysis.

4. Results

In this study, 25 patients received favipiravir, and 70 patients were included in the control group. The median age of the included patients was 6.00 years (IQR = 9.00), with a median weight of 22.00 kg (IQR = 25.00). In addition, 59 patients (62.10%) were male. The symptoms of the included patients were initiated 1 days (IQR = 4 days) before the first physician visit. The patients experienced fever (58.90%), dyspnea (44.20%), and nonproductive cough (36.80%) as their three most common signs and symptoms, respectively. The routine vaccination was performed for 93 patients (96.8%). Table 1 shows the patients' baseline demographics and related laboratory data in the case and control groups.

In the course of the hospitalization, the patients received favipiravir for a median of 5.00 days (IQR = 4.00). After favipiravir initiation, potentially adverse reactions were reported in 13 patients (52.00%). Diarrhea, nausea, and vomiting were reported in 5 (20.00%), 11 (44.00%), and 3 (12.00%) patients in the favipiravir group, respectively. The aforementioned conditions were reported in 18 (25.7%), 22 (31.4%), and 21 (30.0%) patients in the control group, respectively. No significant differences were observed regarding the reactions between the two groups. Decreased appetite was reported in 19 (76.00%) and 20 (28.57%) patients

Table 1. Baseline Demographics and Related Laboratory Data [a, b]

Variables	Favipiravir Group (n = 25)	Control Group (n = 70)	P-Value
Age (y)	8.00 (IQR = 7.50)	6.00 (IQR = 10.00)	0.980
Gender			
Male	15 (60.0)	43 (61.4)	0.820
Female	10 (40.0)	27 (38.6)	
Medical history			
Malignancy	10 (40.0)	13 (18.6)	0.035
Cardiac disease	1 (4.0)	7 (10.0)	0.676
Immune deficiency	4 (16.0)	4 (57.1)	0.201
Asthma	2 (8.0)	2 (2.9)	0.282
Failure to thrive	1 (4.0)	6 (8.6)	0.671
Metabolic disease	0 (0.0)	3 (4.3)	0.564
Symptom initiation before admission	2.00 (IQR = 3.50)	1.00 (IQR = 3.00)	0.016
Baseline laboratory data			
White blood cell (cell/micL)	5500.00 (IQR = 8200.00)	7400.00 (IQR = 6900.00)	0.261
Lymphocyte (%)	26.67 ± 21.47	27.95 ± 11.38	0.450
Neutrophile (%)	66.89 ± 22.54	71.45 ± 7.70	0.331
Hemoglobin	10.35 ± 2.88	8.85 ± 0.64	0.904
Platelet	218.00 (IQR = 230.00)	203.00 (IQR = 201.00)	0.823
C-reactive protein	74.00 (IQR = 97.00)	34.00 (IQR = 90.00)	0.347
Erythrocyte sedimentation rate	41.00 (IQR = 53.50)	35.00 (IQR = 45.00)	0.437
Serum creatinine	0.60 (IQR = 0.19)	0.50 (IQR = 0.20)	0.380
Blood urea nitrogen	10.20 (IQR = 5.75)	10.00 (IQR = 9.40)	0.168
Na	136.48 ± 3.72	134.11 ± 5.11	0.038
K	4.13 ± 0.49	4.02 ± 0.73	0.487
P	4.45 ± 2.27	3.94 ± 1.44	0.315
Ca	8.36 ± 1.98	8.48 ± 0.97	0.773
Prothrombin time (PT)	13.00 (IQR = 2.50)	13.90 (IQR = 4.50)	0.109
International normalized ratio (INR)	1.10 (IQR = 0.30)	1.20 (IQR = 0.70)	0.144
Partial thromboplastin time (PTT), sec	32.00 (IQR = 9.50)	30.00 (IQR = 12.00)	0.327
Lactate dehydrogenase	421.00 (IQR = 256.50)	703.00 (IQR = 381.00)	0.005
Creatine phosphokinase	61.00 (IQR = 72.50)	80.00 (IQR = 91.00)	0.157
Aspartate aminotransferase	35.00 (IQR = 23.00)	34.50 (IQR = 34.25)	0.896
Alanine aminotransferase	29.00 (IQR = 14.00)	25.00 (IQR = 30.75)	0.553
Alkaline phosphatase	319.00 (IQR = 235.00)	298.00 (IQR = 186.00)	0.458
Total bill	0.60 (IQR = 0.40)	0.65 (IQR = 0.91)	0.724
Direct bill	0.40 (IQR = 0.40)	0.24 (IQR = 0.64)	0.814
Oxygen saturation (%)			0.009
> 94	12 (48)	12 (17)	
90 - 94	10 (40.0)	47 (67.1)	
< 90	3 (12.0)	11 (15.7)	
Ventilation support			
Room air (no support)	12 (48.0)	11 (15.7)	0.001
O₂ with mask	7 (28.0)	37 (52.9)	0.032
O₂ with hood	1 (4.0)	12 (17.1)	0.173
Noninvasive ventilation	1 (4.0)	0 (0.0)	0.263
Invasive ventilation (intubated)	4 (16.0)	10 (14.3)	1.000
Symptoms			
Fever	17 (68.0)	39 (55.7)	0.284
Cough	8 (32.0)	37 (52.9)	0.073
Dyspnea	26 (37.1)	4 (16.0)	0.051

[a] The independent samples *t*-test and Mann-Whitney U test were used to compare the differences in continuous variables for parametric and nonparametric ones, respectively. The differences in the categorical data were analyzed using the chi-square test (or Fisher's exact test if appropriate).
[b] Continuous variables were expressed as mean ± SD or median [interquartile range (IQR)] and categorical data were expressed as No. (%).

in the favipiravir and control groups, respectively (P < 0.001). Cardiovascular complications, including hypotension, tachycardia, and chest pain, occurred in 10 (40.00%), 10 (40.00%), and 7 (28.00%) patients in the case group and 9 (12.86%), 18 (25.71%), and 5 (7.14%) patients in the control group, respectively. Hypotension and chest pain were significantly higher in patients who received favipiravir than in the controls (P = 0.004 and P = 0.007, respectively). No significant differences were observed in the increase in liver transaminases (P = 0.694). Regarding electorate abnormalities, hyperuricemia was not reported in any patients. Neutropenia was observed in 5 (20.00%) and 10 (14.29) patients in the case and control groups, respectively (P = 0.501; Table 2).

There were several reported outcomes for the patients in this study. The need for invasive mechanical ventilation was reported in 4 (16.00%) and 11 (15.71%) patients in the favipiravir and control groups, respectively (P = 1.000). The median duration of hospital stay for the total population reported 8 days (IQR = 7.25) which was significantly higher in patients who received favipiravir (10 days; IQR = 16.00) than in the controls (6 days; IQR = 5.50) (P = 0.002). Moreover, 9 patients (36.00%) in the favipiravir group needed to be transferred to the ICU, compared to 2 (2.86%) patients in the control group (P < 0.001).

Mortality was reported in 4 (16.00%) and 9 (12.86%) patients in the favipiravir and control groups, respectively, which was not significantly different [OR = 1.29; 95% CI (0.36 - 4.63); P = 0.695]. The causes of death were reported as septic shock (n = 9; 9.50%) and acute cardiac event, and arrhythmia (n = 4; 4.20%). No significant difference was observed in the intubation rate between the two groups [16.00% and 15.71%; OR = 1.022; 95% CI (0.29 - 3.56); P = 0.973]. Table 3 shows the results of the logistic regression model regarding the evaluation of the effect of favipiravir and other variables on mortality and the need for mechanical ventilation.

5. Discussion

This cohort study reported the first data on the safety and efficacy of favipiravir in the pediatric population diagnosed with COVID-19. Previously, favipiravir was used to treat other viral infections in the pediatric population. In 2015, the first report on medication utilization was published from Africa. Favipiravir was used in weight-based dosing to treat Ebola in children older than 1 year (18). The dosing regimen which was considered to treat Ebola based on the patient's weight was used in the case group of the present study (19).

The first concern for the children receiving favipiravir is the safety profile and severe adverse drug reactions

(ADRs) during medication administration. Favipiravir administration as a direct viral replication inhibitor is associated with some severe adverse reactions (12). The present results are significant in major respects. The current study reported no significant increase in gastrointestinal ADRs, such as diarrhea, nausea, and vomiting, in favipiravir-receiving patients, compared to control patients. The favipiravir-receiving patients showed a higher rate of decreased appetite than the control patients. Other important concerns, such as bone marrow suppression as the most important adverse reaction associated with favipiravir use, were reported to be higher but not statistically significant in patients who received favipiravir.

Cardiovascular adverse reactions, such as hypotension and chest pain, were reported higher in patients who received favipiravir than the controls, which need some precautions in patients with underlying cardiovascular conditions. Furthermore, the prevalence of periorbital edema was higher in patients who received favipiravir than in the controls. The prevalence of other adverse reactions, including electrolyte abnormality and an increase in liver transaminase levels, was not significantly different between the two groups.

The early results from trials that examined the efficacy of favipiravir showed some beneficial outcomes, such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) clearance on the fourth day, in infected patients. In a pilot stage of phase II/III clinical trial, favipiravir administration was associated with SARS-CoV-2 viral clearance in 62.5% of patients within 4 days. Additionally, in another open-label randomized clinical trial with a sample size of 80 patients, favipiravir was associated with better clinical responses, including disease progression and viral clearance (20, 21). It is important to bear in mind the possible bias in these responses, which is constant of the impact of immunomodulatory agents.

In a multicenter randomized open-labeled clinical trial conducted with a sample size of 380 patients in Iran, the results demonstrated that favipiravir add-on therapy resulted in no clinical benefits (i.e., ICU admission, intubation, or in-hospital mortality) in patients with moderate to severe COVID-19 (22). In the pediatric population, to date, there have been no clinical results on the efficacy of favipiravir in COVID-19 treatment. In the present study, no significant effect was observed regarding the need for mechanical ventilation in patients who received favipiravir. The median hospitalization and ICU admission duration was significantly higher in patients who received favipiravir than in the controls. Additionally, the results of the present study showed no significant difference between the case and control groups concerning the mortality rate.

In interpreting the above-mentioned results, it should

Table 2. Potentially Adverse Reactions in Patients of Case and Control Groups [a]

Variables	Favipiravir Group (n = 25)	Control Group (n = 70)	OR (95% CI)	P-Value
Decreased appetite	19 (76.00)	20 (28.57)	6.92 (2.76 - 22.72)	< 0.001
Diarrhea	5 (20.00)	18 (25.71)	0.72 (0.24 - 2.20)	0.567
Nausea	11 (44.00)	22 (31.43)	1.71 (0.67 - 4.38)	0.257
Vomiting	3 (12.00)	21 (30.00)	0.32 (0.09 - 1.18)	0.075
Liver transaminases elevation				
< 3 × ULN [b]	4 (16.00)	11 (15.70)	1.02 (0.29 - 3.56)	0.973
3 - 5 × ULN	0	2 (2.90)	-	0.393
> 5 × ULN	0	0	-	-
Acute kidney injury	0	0	-	-
Neutropenia	5 (20.00)	10 (14.29)	1.50 (0.46 - 4.91)	0.501
Hypotension	10 (40.00)	9 (12.86)	5.52 (1.56 - 13.08)	0.004
Tachycardia	10 (40.00)	18 (25.71)	1.93 (0.73 - 5.05)	0.179
Chest pain	7 (32.00)	5 (7.14)	5.06 (1.43 - 17.84)	0.007
Periorbital edema	2 (8.00)	0 (0)	-	0.071
Headache	5 (20.00)	5 (7.14)	3.25 (0.85 - 12.38)	0.072
Hyperuricemia	0 (0)	3 (4.29)	-	0.293
Hypokalemia	2 (8.00)	8 (11.43)	0.67 (0.13 - 3.41)	0.632

Abbreviations: OR, odds ratio; CI, confidence interval.
[a] Values are exspressed as No. (%).
[b] Upper limit of normal = 40 units/L.

Table 3. Association of Favipiravir Administration with Need for Invasive Mechanical Ventilation and Mortality Based on Logistic Regression Model

Variables	OR* (95% CI)	P-Value
Need for invasive mechanical ventilation*	1.29 (0.18 - 9.40)	0.804
In-hospital mortality#	2.13 (0.38 - 11.90)	0.388

Abbreviations: OR, odds ratio; CI, confidence interval.
[a] The model was adjusted for high-risk conditions, hypoxia, and C-reactive protein level.
[b] High-risk conditions including Malignancy, cardiac disease, immune deficiency, asthma, failure to thrive, and metabolic disease.

be considered that patients who received favipiravir had a better oxygenation profile than the controls. About half of the patients in the favipiravir group received no oxygenation support at the baseline, which was significantly higher than the control group. This phenomenon shows that although these patients had a better oxygenation profile at the baseline, the result of efficacy outcome after the adjustment of the effect of hypoxia was not significant, and the medication had no significant effect on the patients' outcomes. The initiation of the disease symptoms among patients in the favipiravir group before hospital admission was longer than the control group; nevertheless, in both groups, it could be considered that patients were in the viral phase of the disease.

Therefore, it can be considered that favipiravir as a ribonucleic acid-polymerase inhibitor could be used in the pediatric population; however, cautions about adverse reactions should be exercised. Due to favipiravir administration, the pediatric population is more susceptible to adverse cardiovascular reactions. This finding is important as COVID-19 could be associated with cardiac complications that complicate the disease course (23). In patients with a severe course of the disease, the occurrence of shock, hypotension, and cardiac complication could result in serious conditions which might be fatal.

The represented data of this study should be interpreted with the consideration of the study's limitations. Firstly, randomized controlled clinical trials with a larger sample size should be performed to assess the whole aspects of the safety of favipiravir in the pediatric population. Secondly, this study was designed as a retrospective single-center cohort. It is required to obtain the data on the efficacy of favipiravir from multicentric clinical trials. Despite the results obtained from the present study, there is much room for further investigation to determine the effectiveness of favipiravir in the pediatric population, and more prospective randomized trials are needed in this re-

gard. In addition, it might be possible to use other dosing regimens in future investigations.

5.1. Conclusion

In conclusion, the use of favipiravir in the pediatric population is associated with more cardiovascular adverse effects (i.e., hypotension and chest pain). There was no significant increase in other adverse reactions, such as bone marrow suppression, increase in liver transaminase, and electrolyte abnormality. No efficacy was observed in the administration of favipiravir in the pediatric population. The administration of favipiravir did not result in better outcomes, such as the need for mechanical ventilation, duration of hospitalization, and mortality rate.

Acknowledgments

Footnotes

References

1. World Health Organization. *WHO Coronavirus (COVID-19) Dashboard.* Geneva, Switzerland: World Health Organization; 2021, [cited 9th Sep 2021]. Available from: https://covid19.who.int/.

2. Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. *Acta Paediatr.* 2020;**109**(6):1088–95. doi: 10.1111/apa.15270. [PubMed: 32202343]. [PubMed Central: PMC7228328].

3. Tagarro A, Epalza C, Santos M, Sanz-Santaeufemia FJ, Otheo E, Moraleda C, et al. Screening and Severity of Coronavirus Disease 2019 (COVID-19) in Children in Madrid, Spain. *JAMA Pediatr.* 2020. doi: 10.1001/jamapediatrics.2020.1346. [PubMed: 32267485]. [PubMed Central: PMC7142799].

4. Sun D, Li H, Lu XX, Xiao H, Ren J, Zhang FR, et al. Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center's observational study. *World J Pediatr.* 2020;**16**(3):251–9. doi: 10.1007/s12519-020-00354-4. [PubMed: 32193831]. [PubMed Central: PMC7091225].

5. Toubiana J, Poirault C, Corsia A, Bajolle F, Fourgeaud J, Angoulvant F, et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. *BMJ.* 2020;**369**:m2094. doi: 10.1136/bmj.m2094. [PubMed: 32493739]. [PubMed Central: PMC7500538].

6. Venturini E, Montagnani C, Garazzino S, Dona D, Pierantoni L, Lo Vecchio A, et al. Treatment of children with COVID-19: position paper of the Italian Society of Pediatric Infectious Disease. *Ital J Pediatr.* 2020;**46**(1):139. doi: 10.1186/s13052-020-00900-w. [PubMed: 32972435]. [PubMed Central: PMC7512208].

7. Vivekanandhan K, Shanmugam P, Barabadi H, Arumugam V, Daniel Raj Daniel Paul Raj D, Sivasubramanian M, et al. Emerging Therapeutic Approaches to Combat COVID-19: Present Status and Future Perspectives. *Front Mol Biosci.* 2021;**8**:604447. doi: 10.3389/fmolb.2021.604447. [PubMed: 33763450]. [PubMed Central: PMC7983051].

8. Frauenfelder C, Brierley J, Whittaker E, Perucca G, Bamford A. Infant With SARS-CoV-2 Infection Causing Severe Lung Disease Treated With Remdesivir. *Pediatrics.* 2020;**146**(3). doi: 10.1542/peds.2020-1701. [PubMed: 32554811].

9. Zyryanov SK, Butranova OI, Gaidai DS, Kryshen KL. [Pharmacotherapy for acute respiratory infections caused by influenza viruses: current possibilities]. *Ter Arkh.* 2021;**93**(1):114–24. doi: 10.26442/00403660.2021.01.200551. [PubMed: 33720636].

10. Guedj J, Piorkowski G, Jacquot F, Madelain V, Nguyen THT, Rodallec A, et al. Antiviral efficacy of favipiravir against Ebola virus: A translational study in cynomolgus macaques. *PLoS Med.* 2018;**15**(3). e1002535. doi: 10.1371/journal.pmed.1002535. [PubMed: 29584730]. [PubMed Central: PMC5870946].

11. Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). *Drug Discov Ther.* 2020;**14**(1):58–60. doi: 10.5582/ddt.2020.01012. [PubMed: 32147628].

12. Kaur RJ, Charan J, Dutta S, Sharma P, Bhardwaj P, Sharma P, et al. Favipiravir Use in COVID-19: Analysis of Suspected Adverse Drug Events Reported in the WHO Database. *Infect Drug Resist.* 2020;**13**:4427–38. doi: 10.2147/IDR.S287934. [PubMed: 33364790]. [PubMed Central: PMC7751706].

13. Ozsurekci Y, Oygar PD, Gurlevik SL, Kesici S, Ozen S, Kurt Sukur ED, et al. Favipiravir use in children with COVID-19 and acute kidney injury: is it safe? *Pediatr Nephrol.* 2021;**36**(11):3771–6. doi: 10.1007/s00467-021-05111-x. [PubMed: 34021797]. [PubMed Central: PMC8140325].

14. Moolasart V, Wongsawat J, Phokhom P, Thienthong V. Favipiravir-based regimen for coronavirus disease 2019 pneumonia for a 47-day-old male newborn. *SAGE Open Med Case Rep.* 2020;**8**:2050313X20964046. doi: 10.1177/2050313X20964046. [PubMed: 33117539]. [PubMed Central: PMC7570769].

15. Karimi A, Rafiei Tabatabaei S, Rajabnejad M, Pourmoghaddas Z, Rahimi H, Armin S, et al. An Algorithmic Approach to Diagnosis and Treatment of Coronavirus Disease 2019 (COVID-19) in Children: Iranian Expert's Consensus Statement. *Arch Pediatr Infect Dis.* 2020;**8**(2). doi: 10.5812/pedinfect.102400.

16. Weiss SL, Peters MJ, Alhazzani W, Agus MSD, Flori HR, Inwald DP, et al. Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. *Intensive Care Med*. 2020;**46**(Suppl 1):10–67. doi: 10.1007/s00134-019-05878-6. [PubMed: 32030529]. [PubMed Central: PMC7095013].

17. Henderson LA, Canna SW, Friedman KG, Gorelik M, Lapidus SK, Bassiri H, et al. American College of Rheumatology Clinical Guidance for Multisystem Inflammatory Syndrome in Children Associated With SARS-CoV-2 and Hyperinflammation in Pediatric COVID-19: Version 2. *Arthritis Rheumatol*. 2021;**73**(4):e13–29. doi: 10.1002/art.41616. [PubMed: 33277976]. [PubMed Central: PMC8559788].

18. Bouazza N, Treluyer JM, Foissac F, Mentre F, Taburet AM, Guedj J, et al. Favipiravir for children with Ebola. *Lancet*. 2015;**385**(9968):603–4. doi: 10.1016/S0140-6736(15)60232-X. [PubMed: 25706078].

19. Mentre F, Taburet AM, Guedj J, Anglaret X, Keita S, de Lamballerie X, et al. Dose regimen of favipiravir for Ebola virus disease. *Lancet Infect Dis*. 2015;**15**(2):150–1. doi: 10.1016/S1473-3099(14)71047-3. [PubMed: 25435054].

20. Ivashchenko AA, Dmitriev KA, Vostokova NV, Azarova VN, Blinow AA, Egorova AN, et al. AVIFAVIR for Treatment of Patients With Moderate Coronavirus Disease 2019 (COVID-19): Interim Results of a Phase II/III Multicenter Randomized Clinical Trial. *Clin Infect Dis*. 2021;**73**(3):531–4. doi: 10.1093/cid/ciaa1176. [PubMed: 32770240]. [PubMed Central: PMC7454388].

21. Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, et al. Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. *Engineering (Beijing)*. 2020;**6**(10):1192–8. doi: 10.1016/j.eng.2020.03.007. [PubMed: 32346491]. [PubMed Central: PMC7185795].

22. Solaymani-Dodaran M, Ghanei M, Bagheri M, Qazvini A, Vahedi E, Hassan Saadat S, et al. Safety and efficacy of Favipiravir in moderate to severe SARS-CoV-2 pneumonia. *Int Immunopharmacol*. 2021;**95**:107522. doi: 10.1016/j.intimp.2021.107522. [PubMed: 33735712]. [PubMed Central: PMC7951885].

23. Long B, Brady WJ, Koyfman A, Gottlieb M. Cardiovascular complications in COVID-19. *Am J Emerg Med*. 2020;**38**(7):1504–7. doi: 10.1016/j.ajem.2020.04.048. [PubMed: 32317203]. [PubMed Central: PMC7165109].