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Favipiravir for the treatment of coronavirus disease 2019 pneumonia; a propensity score-matched cohort study

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ABSTRACT

We retrospectively investigated the clinical outcomes of favipiravir in patients with COVID-19 pneumonia. Patients who between 23 May 2020 and 18 July 2020 received ≥ 24 h of favipiravir were assigned to the favipiravir group, while those who did not formed the non-favipiravir group. The primary outcome was 28-day clinical improvement, defined as two-category improvement from baseline on an 8-point ordinal scale. Propensity scores (PS) for favipiravir therapy were used for 1:1 matching. The unmatched cohort included 1493 patients, of which 51.7% were in the favipiravir group, and 48.3% were not receiving supplemental oxygen at baseline. Significant baseline differences between the two unmatched groups existed, but not between the PS-matched groups (N = 774). After PS-matching, there were no significant differences between the two groups in the proportion with 28-day clinical improvement (93.3% versus 92.8%, P 0.780), or 28-day all-cause mortality (2.1% versus 3.1%, P 0.360). Favipiravir was associated with more viral clearance by day 28 (79.8% versus 64.1%, P < 0.001). Adverse events were common in both groups, but the 93.9% were Grades 1–3. Favipiravir therapy for COVID-19 pneumonia is well tolerated but is not associated with an increased likelihood of clinical improvement or reduced all-cause mortality by 28 days.

Background

Favipiravir inhibits RNA-dependent RNA polymerase with in vitro activity against influenza and SARS-CoV-2.[1] Early in the Coronavirus Disease 2019 (COVID-19) pandemic, it was suggested that favipiravir may be associated with shortened time to SARS-CoV-2 clearance, and with earlier radiological improvement.[2] The aim of this study was to investigate the clinical outcomes and safety of favipiravir in a large cohort of patients hospitalised COVID-19 pneumonia.

Methods

The study was undertaken at Hamad Medical Corporation (HMC), the provider of all COVID-19 medical care for the 2.8 million population of Qatar. Patients aged 18 years or more who were hospitalised with PCR-confirmed SARS-CoV-2 pneumonia during the period between 23 May 2020 and 18 July 2020 were included. Patients who received 24 h or more of favipiravir therapy were assigned to the favipiravir group (FVP group), while the non-favipiravir group (non-

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FVP group) included those who did not receive favipiravir. Favipiravir was administered orally, as two 1600 mg doses 12 hourly for one day, followed by 600 mg twice daily for up to nine more days. Treatment selection was according to the treating physicians at the time of the of initiation. All data, including treatment allocation and outcomes, were independently collected by two investigators, and concordance was verified by a third investigator. Radiological evidence of pneumonia was verified by two radiologists who were blinded to the patients' study allocation. COVID-19 severity was categorised according to the following eight-point ordinal scale: 1, not hospitalized and without limitations of activities; 2, not hospitalised but has limitation of activities, requiring oxygen, or both; 3, hospitalised, not requiring supplemental oxygen and no longer requiring ongoing medical; 4, hospitalised, not requiring supplemental oxygen but requiring ongoing medical care; 5, hospitalised and requiring any supplemental oxygen; 6, hospitalised and requiring non-invasive ventilation (NIV) or use of high-flow nasal oxygen (HFNO) devices; 7, hospitalised and receiving invasive mechanical ventilation (IMV) or extracorporeal membrane oxygenation (ECMO); and 8, death. [3].

The primary outcome was clinical improvement by day 28, defined as two-category improvement from baseline on the ordinal severity scale. Secondary outcomes included viral clearance, defined as one SARS-CoV-2 RT-PCR with a cycle threshold of > 30 on a respiratory tract sample taken ≥ 10 days from onset of symptoms. Adverse events were defined and graded according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, 2017.

Categorical data were summarised as numbers and percentages and compared using Pearson's chi-squared or Fisher's exact test, as appropriate. Continuous data were presented as medians and interquartile ranges (IQR) and compared using Wilcoxon rank-sum test. Missing baseline variables were handled by using multiple imputation with chained equations. Propensity scores for receiving favipiravir, instead of non-favipiravir therapy, were calculated using a non-parsimonious multivariate logistic regression model that included all measured potential baseline predictors for treatment. A summary of mean bias across all covariates before and after matching was displayed using histogram. The propensity scores were used as a 1:1 matching variable for favipiravir/non-favipiravir, using 0.2 calliper and without replacement (data supplement file). Cox regression was used to examine the association of the study arm with the primary endpoint. Variables with an associated P < 0.0.5 in the univariate Cox regression model were included in the multivariate analysis by forward addition and adjusted by the propensity score after excluding collinearity. All P values were two-sided with a threshold of < 0.05 for statistical significance. Statistical analyses were performed using Stata Statistical Software Release 15.1 (StataCorp LLC, College Station, Texas).

Results

1493 patients were included (81.9% males, median age 46 years), of which 721 (51.7%) were in the FVP group. Notable baseline characteristics include diabetes (568, 38%), hypertension (518, 34.7%), and a median body mass index was 28 kg/m^2 [interquartile range (IQR) 25.2–31.5]. At baseline, 48.3% were not receiving supplemental oxygen, while 4.3% were on NIV, and 3.7% were on IMV. Hydroxychloroquine (696, 96.5%), lopinavir-ritonavir (558, 77.4%), and azithromycin (716, 99.3%) were the experimental anti-SARS-CoV-2 agents used in the non-FVP group. Significant baseline differences between the two groups were present, but not in propensity score-matched cohort (n = 694) (Table 1).

In the unmatched cohort, individuals in the FVP group were more likely to achieve clinical improvement within 28 days (93.7% versus 90.9%, P 0.042), and to have an ordinal scale category 3 or lower status by day 28 (93% versus 88.1%, P 0.001). However, the propensity score-matched groups did not differ significantly in the proportion with clinical improvement within 28 days (93.3% versus 92.8%, P 0.780), or the secondary endpoints of the proportion with category 3 status or less on day 28 (93% versus 91%, P 0.290), 28-day all-cause mortality (2.1% versus 3.1%, P 0.360), or hospital length of stay (median 9 days versus 9 days, P 0.440). Favipiravir was associated with a higher proportion of viral clearance by day 28 (79.8% versus 64.1%, P < 0.001). Sub-analysis by baseline need for oxygen support yielded similar results (Table 2, and Table S1 in the supplement). In the adjusted Cox proportional hazards model, receipt of favipiravir was not associated clinical improvement by day 28 (adjusted hazard ratio 0.978, 95% confidence interval 0.862 –1.109, P 0.726) (Table S2 in the supplement). The total number of adverse events was 1664, of which 55.3% occurred in individuals in the FVP group. Most adverse events were of Grades 1–3 (93.9%). The most frequently reported adverse events were alanine transaminase (ALT) increase (498, 33.4%), aspartate transaminase (AST) increase (336, 22.5%), and corrected QT interval (QTc) prolongation (162, 10.9%). ALT and AST increase were significantly more frequent in the FVP group (P < 0.001 for both), whereas QTc prolongation was more common in the non-FVP group (P 0.034) (Tables S3–S6 in the supplement).

Discussion

The lack of clinical benefit in our report is consistent with findings from previous studies. [2,4] While earlier SARS-CoV-2 clearance with favipiravir may seem desirable, the detection of SARS-CoV-2 by RT-PCR does not necessarily imply the presence of viable virus, and it is not clear that pharmacological interventions that reduce SARS-CoV-2 viral load result in improved clinical outcomes. [5].

Our negative clinical results could be related to our favipiravir dosing regimen, which is consistent with the approved favipiravir dose for influenza in Japan.[6] However, the half maximal effective concentration (EC_{50}) for favipiravir against SARS-CoV-2 is 61.88 μg/mL, which is substantially higher than influenza virus's EC_{50} of 0.01–3.53 μg/mL. [1] In this report, the median duration from onset of symptoms to starting favipiravir therapy was 5 days (IQR 3–7); hence the lack of effectiveness could not be explained by delayed antiviral therapy. [5,7].

Systemic corticosteroids are associated with improved survival in patients with COVID-19 who require oxygen support.[8] In our study, 48.7% of patients did not require any oxygen support at baseline. Similarly, tocilizumab was associated with reduced mortality in patients with severe COVID-19 who had C-reactive protein (CRP) levels of ≥ 75 mg/L. [9] The median baseline CRP in our study population was 46.3 mg/L (IQR 19.2–91.4). It is therefore not surprising that these two agents were not associated with improved rates of clinical recovery in this study.

Adverse events were frequent in both groups in our study. However, the vast majority were mild and did not result in premature treatment discontinuation. [6,10] ALT, AST and serum uric acid elevations are known common adverse events in association with favipiravir. [6,10] Of note, we reported QTc prolongation in 9.2% of patients in the FVP group, and 12.6% of those in the non-FVP group (P 0.034). This has been occasionally reported in favipiravir recipients, but a causal link has not been established.[11].

In this study, almost all patients in the comparator arm and nearly half of those in the favipiravir group had received hydroxychloroquine, azithromycin, and lopinavir-ritonavir. All of these have been shown to be futile in patients with COVID-19. [5] While the presence of those agents in the study may have contributed to the observed adverse events, it is unlikely that they influenced the assessment of favipiravir's clinical efficacy.

To the best of our knowledge, this is the largest reported study to investigate the role of favipiravir in the treatment of patients with

Table 1
Baseline characteristics before and after propensity-score matching.

	Unmatched cohort (n = 1493)			Propensity-score matched cohort (n = 774)		
Variable	**Favipiravir group (n = 772)**	**Non-favipiravir group (n = 721)**	**P value**	**Favipiravir group (n = 387)**	**Non-favipiravir group (n = 387)**	**P value**
Male sex	624 (80.8%)	599 (83.1%)	0.260*	312 (80.6%)	312 (80.6%)	1.000*
Age (years)	48 (39.50–57)	44 (37–54)	< 0.001§	47 (38–55)	46 (38–57)	0.950§
Nationality by WHO region			< 0.001†			0.35†
African Region	6 (0.8%)	10 (1.4%)		4 (1%)	3 (0.8%)	
Eastern Mediterranean Region	281 (36.4%)	221 (30.7%)		123 (31.8%)	126 (32.6%)	
European Region	6 (0.8%)	5 (0.7%)		3 (0.8%)	2 (0.5%)	
Region of the Americas	6 (0.8%)	2 (0.3%)		3 (0.8%)	0	
South-East Asian Region	345 (44.7%)	398 (55.2%)		192 (49.6%)	208 (53.8%)	
Western Pacific Region	128 (16.6%)	85 (11.8%)		62 (16%)	48 (12.4%)	
Diabetes mellitus	286 (37.1%)	282 (39.1%)	0.410*	146 (37.7%)	138 (35.7%)	0.550*
Hypertension	278 (36%)	240 (33.3%)	0.270*	123 (31.8%)	126 (32.6%)	0.820*
Ischaemic heart disease	32 (4.2%)	28 (3.9%)	0.800*	15 (3.9%)	13 (3.4%)	0.700*
Chronic lung disease	37 (4.8%)	49 (6.8%)	0.097*	24 (6.2%)	22 (5.7%)	0.760*
Chronic liver disease	5 (0.7%)	8 (1.1%)	0.340†	3 (0.8%)	3 (0.8%)	1.000†
Chronic kidney disease	31 (4%)	54 (7.5%)	0.004*	20 (5.2%)	25 (6.5%)	0.440*
Cancer	15 (1.9%)	3 (0.4%)	0.008†	1 (0.3%)	1 (0.3%)	1.000†
Current or past smoker	72 (9.3%)	50 (6.9%)	0.250*	32 (8.3%)	30 (7.8%)	1.000*
Body mass index (Kg/m^2)	27.8 (25–31.2)	28.4 (25.6–32)	0.024§	27.9 (24.9–31.2)	28.4 (25.3–31.9)	0.260§
Dyspnoea	380 (49.2%)	327 (45.4%)	0.13*	186 (48.1%)	193 (49.9%)	0.610*
Systolic blood pressure (mmHg)	115 (106–126)	108 (100–119)	< 0.001§	111 (104–121)	112 (102–122)	0.800§
Temperature (Celsius)	38 (37.2–38.6)	38 (37.4–38.9)	< 0.001§	38 (37.2–38.6)	37.9 (37.2–38.7)	0.940§
Heart rate (per minute)	98 (88–110)	97 (89–108)	0.420§	99 (89–110)	98 (90–108)	0.950§
Respiratory rate (per minute)	21 (20–26)	23 (20–28)	< 0.001§	22 (20–28)	22 (20–26)	0.240§
Oxygen saturation	0.96 (0.94–0.97)	0.94 (0.91–0.96)	< 0.001§	0.95 (0.92–0.97)	0.95 (0.93–0.97)	0.570§
Hydroxychloroquine therapy	37 (4.8%)	696 (96.5%)	< 0.001*	24 (6.2%)	372 (96.1%)	< 0.001*
Azithromycin therapy	354 (45.85%)	716 (99.3%)	< 0.001*	184 (47.6%)	386 (99.7%)	< 0.001*
Lopinavir/ritonavir therapy	68 (8.8%)	558 (77.4%)	< 0.001	34 (8.8%)	302 (78%)	< 0.001
Tocilizumab therapy	50 (6.5%)	99 (13.7%)	< 0.001*	31 (8%)	27 (7%)	0.590*
Systemic corticosteroids	488 (63.2%)	283 (39.3%)	< 0.001*	169 (43.7%)	176 (45.5%)	0.610*
Renal replacement therapy	26 (3.4%)	43 (6%)	0.017*	13 (3.4%)	21 (5.4%)	0.160*
Haemoglobin (g/dL)	14 (12.7–15.1)	14.1 (13.1–15)	0.140§	14 (12.8–15.2)	14.2 (13.1–15)	0.720§
White blood cells (x10^9/L)	6.1 (4.8–7.9)	6.40 (5.1–8.2)	0.070§	6.2 (4.9–7.9)	6.10 (4.8–7.8)	0.710§
Lymphocyte count (x10^9/L)	1.2 (0.8–1.6)	1.2 (0.9–1.6)	0.023§	1.2 (0.8–1.6)	1.3 (1–1.7)	0.200§
Platelets (x10^9/L)	218 (176.5–273.5)	219 (178–282)	0.590§	220 (180–274)	218 (174–286)	0.710§
Serum creatinine (µmol/L)	85 (71–99)	84 (69–98)	0.230§	86 (71–99)	82 (67–95)	0.026§
Alaine transaminase (IU/L)	32.1 (22–55)	34 (23.4–53)	0.073§	33 (23–56)	32 (22–50)	0.68§
Aspartate transaminase (IU/L)	36 (25–56)	39 (28–58)	0.009§	37 (26–58)	37 (27–53)	0.81§
C-reactive protein (mg/L)	45.9 (18.4–93.5)	53 (22.5–110)	0.017§	46.3 (20–95.2)	45.7 (18.6–88.5)	0.370§
Ferritin (µg/L)	580 (293–995)	602 (300–965)	0.740§	609 (310–961)	563 (289–951)	0.500§
D–dimer (mg/L)	0.49 (0.34–0.83)	0.54 (0.36–1)	0.002§	0.52 (0.35–0.89)	0.53 (0.35–0.94)	0.330§
Bilateral pneumonia	603 (78.1%)	655 (90.9%)	< 0.001*	333 (86.1%)	330 (85.3%)	0.760*
Baseline ordinal scale category			0.910*			0.130*
Category 4 (no supplemental oxygen)	376 (48.7%)	345 (47.9%)		201 (51.9%)	215 (55.6%)	
Category 5 (supplemental oxygen)	336 (43.5%)	317 (44%)		153 (39.5%)	153 (39.5%)	
Category 6 (HFNO or NIV)	34 (4.4%)	30 (4.2%)		18 (4.7%)	7 (1.8%)	
Category 7 (IMV or ECMO)	26 (3.4%)	29 (4%)		15 (3.9%)	12 (3.1%)	

Data are shown as number (%) or median (interquartile range). *Pearson's chi-squared test, †Fisher's exact test, §Wilcoxon rank-sum test. ECMO, extracorporeal membrane oxygenation; HFNO, high-flow nasal oxygen; IMV, invasive mechanical ventilation; NIV, non-invasive ventilation; WHO, World Health Organization

Table 2
Clinical outcomes before and after propensity-score matching.

	Unmatched cohort (n = 1493)			Propensity-score matched cohort (n = 774)		
	Favipiravir group (n = 772)	**Non-favipiravir group (n = 721)**	**P value**	**Favipiravir group (n = 387)**	**Non-favipiravir group (n = 387)**	**P value**
Clinical improvement within 28 days	723 (93.7%)	655 (90.9%)	0.042	361 (93.3%)	359 (92.8%)	0.780
Days to clinical improvement	8.50 (6–11.3)	8 (5–12)	0.130§	8.5 (6–11)	8 (5–12)	0.072§
All-cause mortality at 28 days	20 (2.6%)	24 (3.3%)	0.400*	8 (2.1%)	12 (3.1%)	0.360*
Ordinal scale category ≤ 3 on day 28	718 (93%)	635 (88.1%)	0.001*	360 (93%)	352 (91%)	0.290*
Hospital length of stay	9 (6–13)	10 (5–16)	0.420§	9 (6–12)	9 (5–14.5)	0.440§
Viral clearance	606 (78.5%)	457 (63.4%)	< 0.001†	309 (79.8%)	248 (64.1%)	< 0.001†
Status on day 28			0.014*			0.570*
Died	20 (2.6%)	24 (3.3%)		8 (2.1%)	12 (3.1%)	
Hospital floor	19 (2.5%)	31 (4.3%)		12 (3.1%)	11 (2.8%)	
Intensive care unit	20 (2.6%)	35 (4.9%)		9 (2.3%)	14 (3.6%)	
Discharged	713 (92.4%)	631 (87.5%)		358 (92.5%)	350 (90.4%)	

Data are shown as number (%) or median (interquartile range). *Pearson's chi-squared test, †Fisher's exact test, §Wilcoxon rank-sum test

COVID-19 pneumonia, and the first to examine outcomes after 28 days of follow up. Nevertheless, our findings are limited by the retrospective nature of the investigation. We used propensity score matching to reduce treatment allocation bias, and multivariate Cox proportional hazards to investigate the relationship between favipiravir and the study outcomes. However, we cannot rule out residual confounding.

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Ethical approval

The study was approved by the Institutional Review Board at Hamad Medical Corporation (MRC-01–20–994), with a waiver of informed consent.

CRediT authorship contribution statement

Conceptualization and study design: **RA Alattar and AS Omrani**. Data curation: **S Abdalla, TAK Abdallah, R Kazman, A Qadmour, TBH Ibrahim, B Alhariri, SH Shaar, A Bajwa, AB Alimam, R Qazi, F Ben Abid, AM Eldeeb, K Shurkri, A Elsayed, M Alsamawi, A Abdelmajid, MAP Basulto, AAR Cobian, A Alkhal, M Abukhattab, and MA Almaslamani**. Formal analysis and interpretation: **J Daghfal and AS Omrani**. Resources: **F Rustom**,. Writing – original draft preparation: **RA Alattar and AS Omrani**. All authors approved the version submitted for publication.

Data availability statement

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Declaration of Competing Interest

None

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jiph.2022.08.011.

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