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Randomized controlled open label trial on the use of favipiravir combined with inhaled interferon beta-1b in hospitalized patients with moderate to severe COVID-19 pneumonia

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ABSTRACT

Objective: To evaluate the therapeutic effectiveness of favipiravir combined with inhaled interferon beta-1b in adult patients hospitalized with moderate to severe COVID-19 pneumonia.
Methods: A randomized, open-label controlled trial of oral favipiravir in adults hospitalized with moderate to severe COVID-19 pneumonia from June 22nd 2020 to August 13th 2020 was conducted. Patients were randomly assigned to receive either a combination of favipiravir with interferon beta-1b by inhalation aerosol or hydroxychloroquine (HCQ). The outcome endpoints included improvement in inflammatory markers, lower length of hospital stay (LOS), discharges and lower overall 14-day mortality.
Results: A total of 89 patients underwent randomization with 49% (n = 44) assigned to favipiravir and 51% (n = 45) assigned HCQ. The overall mean age was 55 ± 14 years and 58% (n = 52) were males. There were no significant differences in the inflammatory biomarkers at hospital discharge between the two groups; C-reactive protein (p = 0.413), ferritin (p = 0.968), lactate dehydrogenase (p = 0.259) and interleukin 6 (p = 0.410). There were also no significant differences between the two groups with regards to the overall LOS (7 *vs* 7 days; p = 0.948), transfers to the ICU (18.2% *vs* 17.8%; p = 0.960), discharges (65.9% *vs* 68.9%; p = 0.764) and overall mortality (11.4% *vs* 13.3%; p = 0.778).
Conclusions: No differences in clinical outcomes were found between favipiravir plus inhaled interferon beta-1b and hydroxychloroquine in adults hospitalized with moderate to severe COVID-19 pneumonia.

Introduction

In late December 2019, China reported the first case of atypical pneumonia and it did not take a long time before it spread throughout the country and subsequently worldwide. The causative organism was found to be a virus (Lee & Hsueh, 2020). It was quickly confirmed by molecular testing to be from the coronaviruses group, which are enveloped single stranded RNA viruses of zoonotic origin. Later in January 2020, it was denoted by the World Health Organization (WHO) as coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and was declared a global pandemic in March 2020 (World Health Organization, 2020).

In the Sultanate of Oman, the Ministry of Health reported the first two cases on 24th of February 2020 (Khamis et al., 2020). Since then, the number of reported cases has been increasing

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significantly. Up to September 2020, there have been more than 80,000 reported cases (Ministry of Health Oman, 2020)

As the current virus infectivity is much greater than with SARS-CoV, worldwide laboratories and hospitals are working day and night to find a possible cure by investigating potential drugs to treat SARS-CoV-2 infection. One efficient way to do so was by investigating the effectiveness of pre-existing drugs such as remdesivir, favipiravir, hydroxychloroquine (HCQ) alone or in combination with azithromycin and steroids. The combination of HCQ and azithromycin was advocated initially. However, with emerging data, safety and efficiency were of concern. Research sought alternative antivirals such as favipiravir as a potential agent that had demonstrated its efficacy in a few studies (Cai et al., 2020).

Favipiravir triphosphate is a purine nucleoside analogue, which acts as a competitive inhibitor of RNA-dependent RNA polymerase. Favipiravir is effective against different influenza virus strains and serotypes and has been licensed in Japan as an anti influenza drug (Shiraki and Daikoku, 2020). As it has the unique feature of broad-spectrum activity toward RNA viruses as reported earlier (Mentré et al., 2015), it was researched against COVID-19 infection in China and the results were promising (Cai et al., 2020; Shiraki and Daikoku, 2020). The open label, non-randomized study that was conducted by Cai et al. for mild to moderate COVID-19 pneumonia identified a significant reduction in the time to SARS-CoV-2 viral clearance in patients treated with favipiravir compared with historical controls treated with lopinavir/ritonavir (4 *versus* 11 days; $p < 0.001$). Furthermore, by day 14, 91.4% of patients in the favipiravir arm had radiographic improvement *versus* 62.2% in the lopinavir/ritonavir arm (Cai et al., 2020). Based on these data, several countries had adopted favipiravir in their treatment protocols and guidelines (Saudi Ministry of Health, 2020; United Arab Emirates Ministry of Health and Prevention, 2020).

Type I interferons (such as IFN-α, IFN-β) have been shown in clinical trials during the SARS epidemic to have the ability to inhibit the replication of SARS-CoV-1 and therefore improve clinical outcomes (Moriguchi and Sato, 2003). A recent study has shown that SARS-CoV-2 was sensitive to type I inhaled interferon pretreatment in vero cells (Lokugamage et al., 2020) and a small pilot non-randomized study on 33 patients with moderate COVID-19 pneumonia showed that the use of inhaled interferon IFN-κ combined with trefoil factor 2 (TFF2), a secreted polypeptide resistant to degradation and hydrolysis, protects the gastrointestinal tract from microbial or chemical induced injury, and was associated with clinical and radiological improvement and viral reversion, therefore resulting in shorter length of stay (Fu et al., 2020). A randomized double-blind placebo-controlled trial to determine the safety and efficacy of inhaled IFN-β1a (SNG001for nebulisation) for patients infected with SARS-CoV-2 is ongoing (ClinicalTrials.gov Identifier: NCT04385095).

Hence, we postulated that favipiravir might show similar promising results in our COVID-19 patients' treatment. To investigate this further, this open label randomized trial was conducted to assess the outcomes of favipiravir combined with inhaled interferon beta-1b among hospitalized patients with moderate to severe COVID-19 pneumonia.

Methods

An open label randomized controlled study was conducted at the Royal Hospital, Muscat, Oman, from June 22nd 2020 to August 13th 2020. The aim of the study was to evaluate the efficacy and safety of favipiravir combined with inhaled interferon beta-1b compared with the existing standard of care per "National COVID-19 Clinical Management Protocol, Ministry of Health, Oman-version 1″ for adult patients with moderate to severe COVID-19 pneumonia.

Patients within 10 days of COVID-19 symptoms onset were screened for eligibility and assigned the treatment (experimental arm or standard arm) by block randomization by a computer-generated random number list prepared by an investigator with no clinical involvement in the trial. The recruitment was within 24 h following the screening process. Trial participants, investigators, care givers, outcome assessors, and date analysts were not blinded to the group assignment.

Experimental Arm

This arm included the treatment with favipiravir 1600 mg on day 1 followed by 600 mg twice a day for a maximum of 10 days, and interferon beta-1b at a dose of 8 million IU (0.25 μg) twice a day was given for 5 days through a vibrating mesh aerogen nebulizer (Aerogen Solo). In case the patient experienced an adverse event related to liver injury of grade ≥3 (common terminology criteria for adverse events (CTCAE) v5.0, 2017), the dose was reduced to 800 mg on day 1 then 400 mg twice a day. The treatment was discontinued if the patient experienced any adverse event related to liver injury of grade ≥3 after dose reduction.

Standard Arm

The standard arm included the care based on the national guidelines that had HCQ 400 mg twice per day on day 1, then 200 mg twice per day for 7 days.

The primary endpoint measures were time from assignment to clinical recovery, the normalization of inflammatory markers and improvement in oxygen saturation that is maintained for at least 72 h. Secondary endpoint measures included deterioration/aggravation of pneumonia (defined as SpO2 of ≤93 % or PaO2/FiO2 of ≤300 mmHg or RR of ≥30/min without oxygen inhalation and requiring oxygen therapy or more advanced breath support); intensive care unit (ICU) admission rate, and mortality within 14 days of assignment.

The inclusion criteria were: age between 18–75 years, confirmed SARS-CoV-2 infection by RT-PCR test on respiratory tract specimens, moderate to severe COVID-19 pneumonia according to the WHO interim guidelines case definitions (WHO/2019 nCoV/ Surveillance Case Definition /2020.1), the interval between symptoms onset and randomization is not >10 days; for female subjects: evidence of post-menopause, or, for pre-menopause subjects, negative pre-treatment serum or urine pregnancy test, eligible subjects of child-bearing age (male or female) must agree to take effective contraceptive measures (including hormonal contraception, barrier methods or abstinence) with his/her partner during the study period and for at least 7 days following the last study treatment; not participating in any other interventional drug clinical study before completion of the present one.

The exclusion criteria were: age above 75, refractory nausea, vomiting, or chronic gastrointestinal disorders, inability to swallow the study drug or having undergone extensive bowel resection which may affect adequate absorption of favipiravir; severe liver disease: underlying liver cirrhosis or alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevated over 5 times the upper limit of normal; gout or history of gout or hyperuricemia; known severe renal impairment with creatinine clearance (CrCl) of <30 ml/min or having received continuous renal replacement therapy, hemodialysis or peritoneal dialysis, known allergy or hypersensitivity to favipiravir, or pregnant or lactating women.

Data collected included baseline demographics, co-morbidity, signs and symptoms on presentation, radiological features, laboratory parameters collected at day 0 and on discharge:

complete blood count (CBC), renal function tests, liver function tests, ferritin, lactate dehydrogenase (LDH), C-reactive protein (CRP), D-dimers, troponin, bone profile, interleukin 6 (IL-6) and other therapeutic interventions including antibiotics, steroids, tocilizumab and convalescent plasma.

Statistical analysis

Descriptive statistics was used to describe the data. For categorical variables, frequencies and percentages were reported. Differences between groups were analyzed using Pearson's $\chi 2$ tests (or Fisher's exact tests for expected cells of <5). For continuous variables, mean and standard deviation were used to summarize the data while analyses were performed using Student's *t*-test. Continuous but abnormal distributed variables were presented as median and interquartile range and analyzed using Wilcoxon-Mann-Whitney test. Statistical analyses were performed using STATA version 16.1 (STATA Corporation, College Station, TX, USA).

Power analysis

A total 190 patients was needed (95 on each arm) to have *90%* power to detect a difference of a 50% of improvement in either clinical recovery, normalization of inflammatory markers and improvement in oxygen saturation that is maintained for at least 72 h, overall length of hospital stay, discharges or overall mortality between the favipiravir arm and the standard control group (50% *vs* 25%) at the 5% alpha (significance) level. Because of missing data and losses to follow-up, an additional 10 subjects were required (5 in each arm) for a total of 200 COVID-19 subjects.

Results

Due to logistical and financial constraints, only a total of 89 COVID-19 patients were enrolled into the study with 49% (n = 44) randomly assigned to the treatment arm, favipiravir and interferon beta-1b, and 51% (n = 45) assigned to HCQ as a standard of care treatment group. The findings represent an interim analysis. The overall mean age was 55 ± 14 years and 58% (n = 52) were males. Fever (82%; n = 73), shortness of breath (79%; n = 70), and sore throat (39%; n = 35), were the three most prominent symptoms observed or reported.

The three most prevalent comorbidities were hypertension (54%; n = 48), diabetes mellitus (45%; n = 40), and heart disease (15%; n = 13). A total of 75% (n = 67) of the patients had chronic kidney disease (CKD), with 9% (n = 8) of them having a severe or end stage CKD. The study cohort was mostly managed with antibiotics (97%; n = 86), steroids (67%; n = 60) and convalescent plasma (58%; n = 52). There were no significant differences among the groups regarding the demographic and clinical characteristics; however, those on favipiravir were more likely to be associated with severe and end stage CKD compared to those on standard

Table 1
Demographic and clinical characteristics, signs and symptoms at presentation as well as other therapeutic modalities use stratified by Favipiravir.

Variable, *n (%) unless specified otherwise*	All (N = 89)	Favipiravir		*p*-value
		No (n = 45)	Yes (n = 44)	
Demographic				
Age, mean ± SD, years	55 ± 14	56 ± 16	54 ± 15	0.426
Male gender	52 (58 %)	24 (53 %)	28 (64 %)	0.324
Omani	77 (87 %)	40 (89 %)	37 (84 %)	0.508
Co morbidity				
Diabetes mellitus	40 (45 %)	23 (51 %)	17 (39 %)	0.237
Hypertension	48 (54 %)	24 (53 %)	24 (55 %)	0.909
Heart disease	13 (15 %)	6 (13 %)	7 (16 %)	0.772
Lung disease	5 (5.6 %)	2 (2.4 %)	3 (6.8 %)	0.677
Chronic kidney disease (CKD)				
Stage 1 – eGFR>90	22 (25 %)	15 (33 %)	7 (16 %)	0.009
Stage 2 – mild CKD	49 (55 %)	17 (38 %)	32 (73 %)	
Stage 3 – moderate CKD	10 (11%)	6 (13 %)	4 (9.1 %)	
Stage 4 – severe CKD	2 (2.3 %)	2 (4.4 %)	0	
Stage 5 – end stage CKD	6 (6.7 %)	5 (11 %)	1 (2.3 %)	
Signs and symptoms				
Fever	73 (82 %)	36 (80 %)	37 (84 %)	0.784
Sore throat	35 (39 %)	12 (27 %)	23 (52 %)	0.017
Shortness of breath	70 (79 %)	37 (82 %)	33 (75 %)	0.447
Diarrhea	24 (27 %)	8 (18 %)	16 (36%)	0.048
Fatigue	14 (16%)	6 (13 %)	8 (18 %)	0.573
Laboratory/chest X-ray findings on day 1, mean ± SD unless specified otherwise				
Bilateral infiltrates	71 (80 %)	33 (73 %)	38 (86 %)	0.126
WBC count, $x10^9$/L [88/89]	6.9 ± 3.3	6.9 ± 3.4	6.9 ± 3.3	0.899
ALC, $x10^9$/L [88/89]	1.1 ± 0.6	1.1 ± 0.7	1.1 ± 0.5	0.817
LDH, U/L [83/89]	431 ± 169	441 ± 161	421 ± 178	0.586
CRP, mg/dL [88/89]	117 ± 72	121 ± 72	113 ± 73	0.644
Ferritin, μg/L [82/89]	1367 ± 1851	1371 ± 1833	1364 ± 1891	0.986
ALT, IU/L [82/89]	45 ± 39	41 ± 30	50 ± 47	0.321
D-dimer, μg/L [78/89]	5.2 ± 17	5.6 ± 17	4.8 ± 18	0.842
IL-6, pg/mL [44/89]	110 ± 289	136 ± 370	73 ± 90	0.489
Other therapeutic modalities				
Antibiotic	86 (97 %)	44 (98 %)	42 (95 %)	0.616
Tocilizumab	31 (35 %)	17 (38 %)	14 (32 %)	0.658
Steroid	60 (67 %)	34 (76 %)	26 (59 %)	0.117
Convalescent plasma	52 (58 %)	29 (64 %)	23 (52 %)	0.286

SD = standard deviation; IQR = interquartile range; WBC = white blood cell; ALC = absolute lymphocyte count; LDH = lactate dehydrogenase; CRP = C-reactive protein; ALT = alanine transaminase; IL-6 = interleukin 6.

treatment regimens (p = 0.009). Other demographic and clinical characteristics as well as laboratory parameters and management are outlined in Table 1.

Table 2 outlines the inflammatory markers at hospital discharge as well as clinical outcomes of the study cohort stratified by favipiravir. There were no significant differences in the inflammatory biomarkers at hospital discharge between the two groups; CRP (50 *vs* 38 mg/dL; p = 0.413), ferritin (1107 *vs* 993 μg/L; p = 0.968), LDH (452 *vs* 366 U/L; p = 0.259) and IL-6 (138 *vs* 143 pg/mL; p = 0.410). There were also no significant differences between the two groups regarding the overall length of hospital stay (7 *vs* 7 days; p = 0.948), transfers to the ICU (18.2% *vs* 17.8%; p = 0.960), discharges (65.9% *vs* 68.9%; p = 0.764), oxygen saturation at discharge (94% *vs* 95%; p = 0.324) and overall mortality (11.4% *vs* 13.3%; p = 0.778).

Discussion

Our study focuses on the use of favipiravir and inhaled interferon as a potential drug therapy for COVID-19 infection with the hope to establish effectiveness and to test the existing published reports favoring the use of favipiravir. Favipiravir was not significantly different compared to HCQ with regards to overall length of hospital stay, ICU transfers, discharges, oxygen saturation at discharge, overall mortality as well as changes in the inflammatory cytokine storm biomarkers at discharge.

Favipiravir has been studied in animal models and found to be effective against influenza virus, Ebola virus and coronavirus, due to its unique feature of broad-spectrum activity toward RNA viruses (Mentré et al., 2015; Madelain et al., 2016; Madelain et al. 2015; Oestereich et al., 2014; Sissoko et al., 2016; Nguyen et al. 2017; MDVI, LLC, 2020; Fang and Wang, 2020). High concentration of the drug has shown *in vitro* activity against SARS-CoV-2 in infected Vero E6 cells (Furuta et al., 2013). In a recent study conducted by Cai et al. on the early use of favipiravir (within 7 days of illness), in patients with mild to moderate COVID-19 illness, the effectiveness was significant in terms of clinical improvement and reduction in the median time to viral clearance when compared with lopinavir/ritonavir (4 *versus* 11 days; $p < 0.001$) (Cai et al., 2020). Furthermore, by day14 of treatment, 91.4% of patients in the favipiravir arm had radiographic improvement *versus* 62.2% in the lopinavir/ritonavir arm. There was a significantly lower rate of adverse events in patients receiving favipiravir (11.4% *versus* 55.6%; $p < 0.01$). Patients received favipiravir 1600 mg orally twice daily on day 1 followed by 600 mg orally twice daily on days 2–14. Both arms were co-treated with inhaled interferon beta-1b 60 μg twice daily and therapy was continued up to 14 days. In our study, despite using similar doses for favipiravir, no differences were seen between the two arms, potentially as most patients in our cohort had moderate to severe pneumonia.

In this study, a potential reason for lack of clinical response could be the timing of administration of favipiravir in relation to the course of the illness, in particular during early phases of the disease. Gonçalves et al. (2020) modeled the pharmacokinetics /pharmacodynamic and viral kinetics of 13 untreated patients infected with SARS-CoV-2 to anticipate the effects of a number of antivirals such as lopinavir/ritonavir, HCQ, IFN-β-1a, and remdesivir. An efficacy of >90% was required to reduce peak viral load by greater than two logs if antivirals were given after onset of symptoms; while an efficacy of 60% was adequate if the antiviral was initiated prior to symptom onset. The efficacy based on the pharmacokinetics/pharmacodynamic parameters of these drugs is in a range of 6–87% making them unlikely to have a major effect on viral load kinetics if they are not administered very early before symptoms develop (as a pre-exposure or post-exposure prophylaxis).

Combination therapy and aggressive dosing, including providing loading doses to rapidly reach high therapeutic concentration, may be helpful to increase the efficacy of these antiviral therapies (Smith et al., 2020). In a case series on 11 patients with severe COVID-19 pneumonia, combination treatment with nafamostat mesylate for 10–14 days and favipiravir at higher doses (3600 mg on day 1 and at 1600 mg per day on day 2 for 14 days) was found to be effective. Seven patients were successfully weaned from mechanical ventilation with a median duration of 16 (10–19) days and 9 and 7 patients were discharged from the ICU and the hospital, respectively (Doi et al., 2020). It is possible that higher doses could have potentially achieved the needed clinical benefit. In an animal model, high doses of favipiravir had potent antiviral activity against SARS-CoV-2 (Kaptein et al., 2020). However, the most appropriate dosage of favipiravir to control SARS-CoV-2 virus in human remains unknown. Thus, conducting randomized clinical trials with focus on the effective doses to achieve viral clearance are critically warranted.

We opted to use the combination of inhaled interferon and favipiravir. Dong et al. and Lu et al. recommended the combination of interferon alfa by vapor inhalation in combination with other medications such as ribavirin or lopinavir/ritonavir to treat COVID-19 (Dong et al., 2020; Lu, 2020; Agrawal et al., 2020; Kumari et al., 2020). The administration by vapor inhalation has the advantage of specifically targeting the respiratory tract; however, contrary to the intravenous and subcutaneous modes of administration, the pharmacodynamics and pharmacokinetics of this mode of administration are not well studied. Interferon treatments (including interferon alfa and interferon beta) had a mixed efficiency against MERS-CoV and SARS-CoV viruses, but *in vitro*

Table 2
Inflammatory mediators at hospital discharge as well as clinical outcomes of the study cohort stratified by Favipiravir.

Variable, *median (IQR) unless specified otherwise*	All (N = 89)	Favipiravir		*p*-value
		No (n = 45)	Yes (n = 44)	
Inflammatory parameters				
CRP, mg/dL [69/89]	41 (14–98)	33 (14–79)	50 (14–130)	0.413
Ferritin, μg/L [53/89]	1055 (439–1454)	993 (295–1650)	1107 (539–1404)	0.968
LDH, U/L [49/89]	380 (339–484)	366 (338–427)	452 (351–554)	0.259
IL-6, pg/mL [26/89]	143 (44–547)	143 (113–478)	138 (25–742)	0.410
LOS, days [87/89]	7 (4–11)	7 (3–11)	7 (4–12)	0.948
Outcomes, n (%)				
Transferred to ICU	16 (18.0 %)	8 (17.8 %)	8 (18.2 %)	0.960
Discharged home	60 (67.4 %)	31 (68.9 %)	29 (65.9 %)	0.764
SaO2 on discharge	94 (93–96)	95 (93–96)	94 (93–96)	0.324
Died	11 (12.4 %)	6 (13.3 %)	5 (11.4 %)	0.778

IQR = interquartile range; CRP = C-reactive protein; LDH = lactate dehydrogenase; IL-6 = interleukin 6; LOS = length of hospital stay; ICU = intensive care unit; SaO2 = oxygen saturation (%).

studies in human lung tissue suggest that SARS-CoV-2 could be substantially more sensitive to interferon than other coronaviruses (Sallard et al., 2020). Nevertheless, the potential benefit was not seen in our cohort. In an open-label, randomized, phase 2 trial study by Ivan Fan-Ngai Hung and colleagues, a triple combination regimen of interferon beta-1b 8 million international units (0·25 mg) on alternate days, lopinavir 400 mg plus ritonavir 100 mg every 12 h, and ribavirin 400 mg every 12 h was compared with lopinavir 400 mg plus ritonavir 100 mg every 12 h alone. Triple therapy was associated with a significant reduction in the duration of viral shedding (7 *versus* 12 days in the control group; hazard ratio [HR] 4·37 [95% CI: 1·86–10·24]), symptom alleviation (4 *versus* 8 days; HR 3·92 [95% CI: 1·66–9·23]), and duration of hospital stay (9·0 *versus*14·5 days; HR 2·72 [95% CI: 1·2–6·13]). These significant differences were sustained in a subgroup analysis of patients who were enrolled within less than 7 days of symptom onset and in patients who received interferon beta-1b (Shalhoub, 2020; Hung et al., 2020).

Interferon beta-1b is safe (Hurwitz et al., 2008; Lampl et al., 2013; Freedman et al., 2013) and may be an effective treatment against COVID-19 in the early stages of infection but not in advanced cases. Conducting clinical trials should give more accurate information on the relevance of this therapy. The outcomes in the current study between favipiravir and standard of care arms were similar. The baseline differences and the use of other concomitant co-therapies that could have impacted the results were also similar in both the favipiravir and the standard arms. This included antibiotics (42% *vs* 44%; $p = 0.616$), tocilizumab (32% *vs* 38%; $p = 0.658$), steroids (59% *vs* 76%; $p = 0.117$) and convalescent plasma (52 *vs* 64; $p = 0.286$).

In the current study, no major side effects such as hyperuricemia, deranged liver enzymes or QTc prolongation were reported from the use of favipiravir. In a review by Pilkington et al. where the follow-up ranged from 5 to 21 days, the authors concluded that favipiravir had a favorable safety profile regarding total and serious adverse events (Pilkington et al., 2020). Favipiravir has been shown to be safe and tolerable in short-term use (Malvy et al., 2020), but more evidence is required to evaluate the long-term effects and until then caution is advised in its use outside of the clinical trials setting.

Our study has several limitations. First, time to viral clearance was not measured as repeating nasopharyngeal swabs were not done due to limited resources, nor the radiological imaging to assess improvement. Second, the exclusion criteria did not include other experimental therapeutic agents such as IL-6R-antagonist, steroids and convalescent plasma. The quite frequent use of these experimental interventions, although fairly equally distributed between the randomization arms, could have affected selection criteria and caused potential bias. In fact, any effects of favipiravir may have been subdued by these potentially effective therapies rather than HCQ. Furthermore, due to logistical constraints, this study was not able to accrue the subjects as laid down by the power analysis and hence the findings should be interpreted with caution. However, this study is unique as it is randomized and assessed the response to favipiravir combined with inhaled interferon beta-1b treatment in moderate to severe COVID-19 pneumonia. In addition similar to several recent studies, this study further confirms that HCQ has no proven clinical effects (Tang et al., 2020; Geleris et al., 2020).

Conclusion

This randomized open-label controlled study showed no differences in inflammatory markers or clinical outcomes in COVID-19 patients with moderate to severe pneumonia treated with favipiravir and inhaled interferon beta-1b against HCQ. Further randomized placebo controlled double blinded and well-powered studies are warranted to corroborate or refute our findings.

Ethical statement

Ethical approval was obtained through the Center of Research and Ethical Review and Approval Committee (RERAC ID/CSR/20/23,686) as well as through the Royal Hospital Research and Ethics Committee (SRC#71/2020). All patients were requested to provide a written informed consent. Adverse events were reported immediately to the Royal Hospital Research and Ethics Committee.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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