A Randomized Controlled Study Of Favipiravir Vs Hydroxychloroquine In COVID-19 Management: What Have We Learned So Far?

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EDITORIAL NOTE:

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Abstract

Background: *Favipiravir* is considered a potential treatment for COVID-19 due its efficacy against different viral infections. We aimed to explore the safety and efficacy of *favipiravir* in treatment of COVID-19 mild and moderate cases.

Methods: A randomized-controlled open-label interventional phase 3 clinical trial [NCT04349241]. 100 patients were recruited from 18[th]April till 18[th]May. 50patients received *favipiravir* 3200mg at day1 followed by 600mg twice (day2-day10). 50patients received hydroxychloroquine 800mg at day1 followed by 200mg twice (day2- 10) and oral oseltamivir 75mg/12hour/day for 10 days. Patients were enrolled from Ain Shams University Hospital and Assiut University Hospital.

Results: Both arms were comparable as regards demographic characteristics and comorbidities. The average onset of SARS-CoV-2 PCR negativity was 8.1 and 8.3 days in HCQ-arm and favipiravir-arm respectively. 55.1% of those on HCQ-arm turned PCR negative at/or before 7th day from diagnosis compared to 48% in favipiravir-arm (p=0.7). Four patients in FVP arm developed transient transaminitis on the other hand heartburn and nausea were reported in about 20 patients in HCQ-arm. Only one patient in HCQ-arm died after developing acute myocarditis resulted in acute heart failure.

Conclusion: Favipiravir is a safe effective alternative for hydroxychloroquine in mild or moderate COVID-19 infected patients.

Introduction

At the end of 2019, the entire world encountered the first presentation of coronavirus disease 2019 (COVID-19) [1]; it was declared as a pandemic by the World Health Organization (WHO) by March 2020. Globally there are more than 19 millions cases of COVID-19 and more than 7 hundreds thousands deaths reported so far [2,3] . The first case registered in Egypt was in February 2020 and since that date, the numbers have been increasing and by early July 2020, Near one hundred thousand confirmed cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and about 5000 deaths have been reported by the Ministry of Health (MoH) [4] . The curve of new cases in Egypt prompted the investigation of different treatment options to find the most effective and safe choice for COVID-19 patients. *Favipiravir* (FPV) is one of the potential options according to a Chinese study considering the past history of its efficacy against viral influenza [5] . FPV is a novel RNA-dependent RNA polymerase (RdRp) inhibitor, which has also shown efficacy against the Ebola virus [6] . *Favipiravir*, also known as T-705 or Avigan, is a pyrazine derivative and guanine analog that causes chain termination and prevent RNA elongation . *Favipiravir* demonstrated anti-viral activity against a broad array of RNA viruses, including arenaviruses, bunyaviruses, and filoviruses [7] . In Japan, *favipiravir* is approved for influenza A resistant to neuraminidase inhibitors [8] . Also, an expert consensus group in China suggested that chloroquine improved lung imaging and shortened disease course [9] . However, a number of additional reports have since shown no positive impact with the addition of hydroxychloroquine (HCQ) [10]. The aim of the

current study was to explore the safety and efficacy of *favipiravir* in treatment of COVID-19 mild and moderate cases compared to hydroxychloroquine plus oseltamivir as the standard of care approved national protocol there.

Patients And Methods

Study Objectives:

The primary objective of the current study was to evaluate the SARS-CoV-2 viral clearance on days three, seven and 14 . While the secondary objectives were evaluation of the clinical outcomes on days three, seven and 14 and assessment of safety of *favipiravir* versus the standard of care (SOC); HCQ based therapy in the treatment of patients with mild or moderate COVID-19 .

End points:

The primary endpoints were achievement of two successive negative SARS-CoV-2 PCR analysis tests 48 hours apart by nasopharyngeal swab, normalization of body temperature for 48 hours, improvement of radiological abnormalities at day 14 and discharge rate out of the hospital . The secondary endpoints were normalization of C-reactive protein (CRP) and serum ferritin levels .

Study design:

A computer based randomized controlled interventional clinical trial phase 3 to assess the safety and efficacy of *favipiravir* versus HCQ based therapy (SOC) in the treatment of 100 patients with mild or moderate COVID-19 confirmed by reverse transcription polymerase chain reaction (RT-PCR) nasopharyngeal swab . A block-randomization scheme was generated by computer software; patients were randomized between *favipiravir* and HCQ based therapy in a 1:1 ratio. All patients were enrolled from day zero of presentation to the isolation hospital. Group one included 50 patients who received *oseltamivir* 75 mg 12 hourly for 10 days and *hydroxychloroquine* 400 mg 12 hourly on day-one followed by 200 mg 12 hourly daily on day-2 to10days conforming to the national standard of care therapy. Group two included 50 patients who received the investigational drug *favipiravir* in a regimen of 3200 mg (1600 mg 12 hourly) loading dose on day-one followed by 1200 mg maintenance dose (600 mg 12 hourly daily) on day-2 to 10 .

The procedures applied in this study were approved by the Ethical Committee of Human Experimentation of Ain Shams University [FMASU   P14 / 2020] and registered on clinicaltrials.gov [NCT04349241] and was in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments in humans, 2013. Recruitment started on 18th Apr 2020 .

Study setting:

Patients with COVID-19 were randomized to either therapy protocols in two University isolation hospitals. Among 243 COVID-19 patients presented to the two participating isolation hospitals, 100 patients met

the inclusion criteria and agreed to participate in the trial. In the first hospital, Obour Ain Shams University Specialized Hospital (situated in Cairo), 40 patients received *favipiravir* and 46 HCQ based therapy. While in the second hospital, Assiut University Hospital (situated in Upper Egypt) the rest of two groups.

Study population:

Included patients were adults between 18 and 80 years with confirmed COVID-19 documented by a diagnostic laboratory test (e.g. nasopharyngeal swab) at the time of illness and having mild to moderate symptoms according to the national protocol classification . Patients who had severe disease defined as presence of dyspnea, respiratory rate ≥ 30/min, blood oxygen saturation ≤ 93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300, and/or lung infiltrates > 50% within 24 to 48 hours or life-threatening disease defined as respiratory failure, septic shock, and/or multiple organ dysfunction or failure were excluded . Also pregnant or lactating females or those participating in any investigational clinical study, other than observational, within the previous 30 days were excluded.

Study Procedures:

Screening phase:

A written signed and dated informed consent form (ICF) was obtained from each patient before inclusion in the study . Patient clinical report forms included demographic data, full medical history, comorbidities and concurrent medications . In addition, physical examination, body weight, height, body mass index, vital signs (blood pressure, heart rate and temperature) and blood oxygen saturation were assessed and recorded .

Baseline Laboratory investigations included complete blood count (CBC), liver (alanine amino transferase (ALT), aspartate amino transferase (AST), total and direct bilirubin) and kidney function tests (serum creatinine), CRP, serum ferritin , HIV antibody, HCV antibody, HBV surface antigen (HBsAg) and urine pregnancy test for females. Creatine kinase (CK) total and creatine kinase-MB (CK-MB), lactate dehydrogenase (LDH) and coagulation test (D-dimer, prothrombin time and INR) were assessed. COVID -19 was confirmed by SARS-CoV-2 RT-PCR test by nasopharyngeal swab. Chest X-ray or computed tomography (CT) scan of the chest was performed beside electrocardiogram on admission (ECG).

Treatment phase:

Once eligibility was confirmed, patients were randomized and medications started . The patients received information regarding the identification and notification of adverse events and recording the concomitant medications . The patients were advised to record the daily dosing of the study medications in diaries. If the patients were fatigued or uneducated the clinical pharmacist or the treating physician would be responsible for recording . Clinical assessment and vital signs were documented daily and adverse events

were recorded . Follow-up laboratory results for liver function tests, SARS-CoV2 RT-PCR tests by nasopharyngeal swab, CRP and serum ferritin levels were repeated on days 3, 7, and 14 of treatment. Follow-up chest X-ray and /or CT scan were performed at day 14. All patients in both arms received anticoagulation in the form of enoxaparin 40mg SC for 14 days or 1mg/kg every 12 hours in case D-dimers> 1000ng/ml for one month.

Follow-Up Phase:

Patients were followed-up for a period up to 30 days following the end of treatment for any newly developed symptoms, signs or adverse events.

Theory:

The aim of the current study was to explore the safety and efficacy of favipiravir in treatment of COVID-19 mild and moderate cases compared to hydroxychloroquine plus oseltamivir as the standard of care approved national protocol there.

Results

One hundred confirmed COVID-19 patients, according to the standard case definition were randomly allocated into either FPV or HCQ based therapy arm.

Table 1 illustrates the base line characteristics of the two study groups with COVID-19. Both FPV and HCQ based therapy groups were comparable as regards demographic characteristics and comorbidities. Healthcare workers represented 70% in the FPV arm and 62% in the HCQ based therapy arm. Direct contact with a confirmed case was reported by 74% and 72% and of patients treated in the FPV arm and HCQ based therapy respectively. Comorbidities in the form of hypertension, diabetes and ischemic heart diseases were equally manifested in both groups. Patients treated in HCQ based arm reported 1 extra hospital stay day in average, but the difference was not statistically significant (12.4 vs 11.5 days in HCQ based arm and FPV arm respectively).

As regards the laboratory safety profile; three patients (6%) in the HCQ based arm reported a D-dimer level above 1000 compared to seven patients in the FPV (14%) but the difference was not significant. Average platelets count was relatively lower in the HCQ based group compared to the FPV arm and the difference was significant (p=0.029). Radiologically, 24% of those who received the HCQ based therapy showed bilateral basal peripheral ground glass opacities in chest CT compared to 20% of those who received FPV (P>0.05). Serum ferritin, LDH, CK total and CKMB showed no significant difference between both groups.

The main presenting symptoms and signs reported in the 2 groups were fever and dry cough as illustrated in Table 2. Although more frequently reported in the FPV arm (36% vs 38% respectively) than the HCQ based therapy (24% and 30% respectively), the difference was not significant (p>0.05). Expectoration, dyspnea, sore throat, diarrhea, rhinorrhea, anosmia and loss of taste were rarely reported

by patients from either group. Oxygen saturation was within an average of 97% on room air in both groups.

The average onset of SARS-CoV-2 PCR negativity was 8·1 days in the HCQ based therapy and 8.3 days in the FPV arm. More than half of the patients on HCQ based therapy (55.1%) turned PCR negative at or before the 7th day from diagnosis compared to 48% in FPV arm, however, the difference was not statistically significant(P=0.7). Figure 1 displays percentage of the onset of SARS-CoV2 PCR negativity that started from the 3rd till the 14th day.

The efficacy of the two treatment regimens were assessed with respect to improvement in the laboratory tests; D-dimer and serum ferritin as well as the radiological improvement are illustrated in Table 3. The two regimens were comparable in relation to viral clearance before the 7th day, in term of the 3 parameters; D-dimer, serum ferritin and radiological findings. For COVID-19 patients with D-dimer ≤250 ng/ml, 68·2% (n=15) cleared the virus before the 7th day in the HCQ based therapy compared to only 45.5% (n=5) in the FPV arm (p=0.379).

Both regimens displayed a different safety profile. Four patients (8%) in the FPV arm experienced elevated liver transaminases between 3-5 times the upper normal limit between day 7 and day 14 which did not necessitate withholding therapy and improved within two weeks after end of treatment. There was a single mortality among the COVID-19 patients in the HCQ based arm due to acute heart failure resulting from myocarditis at day 8.

Discussion

Early in the pandemic, hydroxychloroquine was suggested as a potential antiviral medication based on the medications' cellular interaction with the virus and in vitro data [11,12]. Initial anecdotal evidence suggested that HCQ helps with pneumonia in regards to shortening of disease course and improvement of lung imaging [13] . This led the Centers for Disease Control and Prevention (CDC) to suggest the use of HCQ and the Food and Drug Administration (FDA) enacting its emergency use without rigorous clinical trials followed by revoking its emergency use in mid June 2020 [14,15] . This has led to much controversy given the potential for cardiac complications, prompting medical experts to advocate for caution [16] .

There is currently a race for detecting effective treatment for COVID-19 Management and there is a lot of uncertainties concerning the benefit of treatment with HCQ. Putting in the consideration the median duration of SARS-Cov-2 viremia in survivors was 20 days and till death in patients who died [17] . These results directed the researchers all over the world to test different treatment options to decrease the median duration of viremia to get better outcome .

The current study aimed to explore an antiviral molecule that could be effective in the management of mild and moderate COVID-19 patients. Favipiravir inhibits SARS-CoV-2 *in vitro* [18] . According to the limited published data regarding its use in COVID-19 management , The need for different studies evaluating its efficacy and safety in such situation. A randomized study, Favipiravir versus Arbidol,

showed a better outcome with favipiravir in patients with moderate severity [19]. This prospective Chinese trial multicenter, randomized open-label, Studying 236 patients compared favipiravir and Arbidol demonstrated a higher clinical recovery rate at day seven in moderately ill patients receiving favipiravir (71.4% vs. 55.9%, p = 0.0199). Clinical recovery was defined as three or more days of improvement in respiratory rate, oxygenation, cough, and fever. There was no placebo group for comparison and this study has not been peer reviewed [19] .The clinical improvement mainly as fever resolution mainly was achieved mainly at Day 3 and dry cough at day 7 in FPV group in the current study beside improvement of the other presenting symptoms . Our data compared age, sex-matched groups, randomized to SOC (HCQ and Oseltamivir) and FPV showed similar efficacy regarding time to viral clearance (P=0.7), mean hospital stay (P=0.4) and safety . When favipiravir compared to other antivirals like lopinavir/ritonavir, FPV demonstrated reduced median viral clearance and radiographic improvement with average 4 days which is shorter than the current study (8.3 days) in FVP arm [5] . These may be due to the higher number of their recruited patients .

The current study one of the first randomized controlled trial assessing HCQ and Oseltamivir (the national standard protocol) versus FPV for treatment of mild to moderate COVID-19 disease . Nearly 90% of both groups of patients achieved viral clearance by day 14 and a single case mortality in the HCQ based group . Tang and colleagues found that the probability of negative SARS-CoV-2 testing by day 28 was 85.4% in the HCQ group and 81.3% in the SOC group (difference 4·1%, 95% CI -10·3 to 18.5%) and adverse effects were more common in the HCQ group (30% vs. 9%) which was superior to that reported in the current study HCQ-arm based therapy about 40% gastrointestinal tracts symptoms [20] .

Despite that Favipiravir resulted in moderate elevation of hepatic transaminases (8%) which is higher than which reported by Cai and his colleagues in only one patient (2.86%), it dropped back to normal levels within two weeks and there was no discontinuation of treatment. Being a backbone of treatment protocol is minimizing the risk of adverse events and drug-drug interactions . HCQ receiving group of patients reported in twenty patients different gastrointestinal symptoms including epigastric pain, nausea and diarrhea which needed symptomatic treatment in half of them.

Despite the comparable efficacy of both arms of treatment in the current study we should put in the consideration the international debate regarding the HCQ safety. Two small non-peer reviewed randomized studies have shown seemingly contradictory results. In one study, HCQ did not exhibit any difference in fever improvement or viral clearance with negative SARS-CoV-2 PCR [21]. In another study, HCQ showed significant improvement in symptoms and radiological CT scan findings [22] . One recent non-randomized study failed to demonstrate a benefit among patients hospitalized with an oxygen requirement [23] while an open-label randomized controlled trail (RCT) involving 150 patients demonstrated modest alleviation of symptoms [24] .

A retrospective analysis of data from patients hospitalized with confirmed SARS-CoV-2 infection in all U.S. Veterans Health Administration medical centers until April 11, 2020 concluded that no clear evidence that the use of HCQ, either with or without azithromycin, reduced the risk of mechanical ventilation in

patients hospitalized with COVID-19 [25]. An association of increased overall mortality was identified in patients treated with HCQ alone [26] .

Geleris and colleagues retrospectively reviewed 1,376 COVID-19 patients hospitalized in New York City, 811 of whom received HCQ (dosed at 600 mg bid day 1, then 400 mg daily for five days). There was no significant association between HCQ use and need for invasive ventilation or death [27] .

In conclusion, Favipiravir is a safe and effective alternative for Hydroxychloroquine in patients with mild or moderate COVID-19 . Favipiravir can be used safely during home isolation for mild to moderate cases , however safety od hydroxychloroquine for home treatment isolation is still questionable . Further studies for the role of favipiravir in Severe COVID 19 patients management are recommended.

Declarations

Conflict of interests: nothing to disclose ,

Funding: This study was funded by Rameda Pharmaceutical Company.

Limitations of the study: The low number of included patients due to the limited availability of favipiravir.

Contributors: H Dabbous shared in the protocol of the study, data collection and writing the manuscript. AF Sherief data collection and writing the manuscript. All other authors contributed equally in Management and follow up of patients beside data collection . By M Elgaafary statistical analysis was done .Study design and revision of the manuscript by M El-Sayed and F Ebeid were done

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Tables

Table 1: Baseline Demographic, Clinical and Laboratory Characteristics of the two COVID-19 Study Groups

	Hydroxychloroquine and Oseltamivir N=50	Favipiravir N=50	P value
Age (Years): *Mean (SD)*	36.4 (11.5)	36.3 (12.5)	0.984
Male Sex: *N (%)*	25 (50.0)	25 (50.0)	1.000
Health care worker: *N (%)*	31 (62.0)	35 (70.0)	0.527
Contact with confirmed case: *N (%)*	36 (72.0)	37 (74.0)	1.000
Direct care of patients: N (%)	29 (58.0)	34 (68.0)	0.407
Comorbidities: *N (%)*	9 (18.0)	6 (12.0)	0.575
Relevant CT Chest findings: *N (%)*	12 (24.0)	10 (20.0)	0.809
Hospital stays in days: *Mean (SD)*	12.4 (5.5)	11.5 (5.3)	0·408
Haemoglobin (g/dL): *Mean (SD)*	13.4 (1.6)	13.7 (1.7)	0.424
Total leukocyte count(x 10^9/L): *Mean (SD)*	5.5 (1.8)	5.7 (2.2)	0.512
Neutrophils count (x 10^9/L): *Mean (SD)*	6.6 (13.9)	5.8 (11.4)	0.741
Lymphocytes count (x 10^9/L): *Mean (SD)*	3.9 (7.6)	3.1 (6.8)	0.627
Platelets count (x 10^9/L): *Mean (SD)*	265.4 (95.4)	229.2 (64.1)	0.029
Serum ferritin (µg/L): *Mean (SD)*	280.7 (296.0)	201.5 (197.3)	0.118
Serum ferritin >200/300: *N (%)*	15 (30.0)	14 (28.0)	1.00
D-dimer (ng/mL): *Mean (SD)*	390.0 (359.3)	785.7 (1103.1)	0.018
D-Dimer >250: *N (%)*	28 (56.0)	39 (78.0)	0.033
Lactate dehydrogenase (IU/L):*Mean (SD)*	205.7 (48.9)	195.7 (54.9)	0.337
CK Total (U/L): *Mean (SD)*	111.1 (74.1)	94.2 (55.0)	0.469
creatine kinase-MB(U/L): *Mean (SD)*	12.4 (6.3)	14.2 (5.4)	0.405

Table 2: The Presenting Clinical Manifestations in the two COVID-19 study groups

	Hydroxychloroquine and Oseltamivir N=50	Favipiravir N=50	P value
Fever: *N (%)*	12 (24.0)	18 (36.0)	0.275
Dry cough: *N (%)*	15 (30.6)	19 (38.0)	0.574
Expectoration: *N (%)*	2 (4.0)	1 (2.0)	1.000
Dyspnea: *N (%)*	0 (0.0)	2 (4.5)	0.216
Sore Throat: *N (%)*	1 (2.0)	3 (6.8)	0.337
Rhinorrhea: *N (%)*	1 (2.0)	0 (0.0)	1.000
Headache: *N (%)*	1 (2.0)	2 (4.7)	0.594
Diarrhea: *N (%)*	1 (2.0)	2 (4.5)	0.598
Anosmia: *N (%)*	1 (2.0)	1 (2.3)	1.000
Loss of taste: *N (%)*	2 (4.0)	1 (2.3)	1.000
Temperature (°C):*Mean (SD)*	37.2 (0.3)	37.1 (0.5)	0.211
Oxygen Saturation (%): *Mean (SD)*	97.5 (0.9)	97.6 (0.9)	0.645

Table 3: Clearance of SARS-CoV2 by PCR at day 7 of treatment in relation to D-dimer, ferritin and relevant CT chest findings in the two COVID-19 study groups

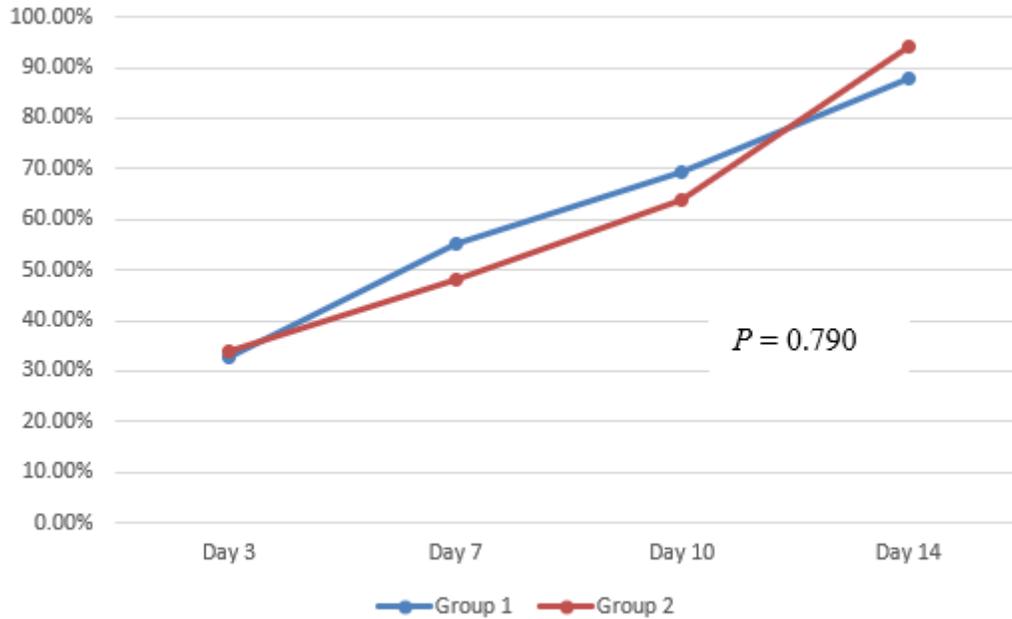|	Hydroxychloroquine and Oseltamivir N (%)	Favipiravir N (%)	P value
Elevated D-dimer (>250 ng/ml) before Day 7	12 (44.4)	19 (48.7)	0.927
Normal D-dimer (≤250 ng/ml) before Day 7	15 (68.2)	5 (45.5)	0.378
Ferritin >200/300 ng/ml before Day 7	10 (66.7)	7 (50·0)	0.462
Ferritin ≤200/300 ng/ml before Day 7	17 (50.0)	17 (47.2)	1.000
Normal CT chest before Day 7	21 (56.8)	21 (52.5)	0.884
Relevant CT chest finding before Day 7	6 (50.0)	3 (30.0)	0.415

Figures

$P = 0.790$

Figure 1

The Percentage of Onset of Viral Clearance (SARS-CoV-2 PCR Negative Conversion) in the two COVID-19 study groups; Group 1 (hydroxychloroquine and oseltamivir) and Group 2 (Favipiravir) within two weeks of treatment.