Original Article

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Efficacy and Safety of Arbidol in Treatment of Patients with COVID-19 Infection: A Randomized Clinical Trial

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Abstract

Background: COVID-19 has led to the demand for finding effective antiviral agents. Preliminary experiments showed Umifenovir inhibit replication in vivo. There is limited data on the clinical efficacy of COVID-19-infected pneumonia. Therefore, we aimed to evaluate this medication based on clinical findings.

Methods: The present study was designed to investigate the advantages and disadvantages of Umifenovir and compared to empirical treatments. For this purpose, multi-stage sampling was considered. 56 people who had mild-to-moderate symptoms without signs of pneumonia, were selected by accidental non-random sampling method and divided into two groups [(group A with Hydroxychloroquine (HCQ) and group B in combination with Umifenovir] by randomized block sampling (1:1). During the study, three patients left the case group. Their clinical signs and symptoms were evaluated on 3rd, 7th, and 14th day after taking these medicines in the disease course. The SPSS software was used for data analysis and the significance level was considered to be $p<0.05$.

Results: On the seventh day after visiting the patients, there were statistically significant differences in recuperation dry cough ($p=0.001$), weakness ($p=0.004$), gastrointestinal symptoms ($p=0.043$) and shortness of breath ($p=0.001$) between the two groups so that group B patients (HCQ and Umifenovir) had a faster recovery. In patients treated with HCQ and Umifenovir compared to the control group, myalgia ($p=0.03$), gastrointestinal symptoms ($p=0.047$) and weakness ($p=0.007$) improved significantly earlier during the illness.

Conclusion: Evaluation of the clinical findings in mild-to-moderate COVID-19 patients' symptoms was performed and it was shown that recuperation was faster in the group who received both HCQ and Umifenovir.

Keywords: COVID-19, Hydroxychloroquine, Umifenovir

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Introduction

The COVID-19 was identified following the epidemic of the "unknown flu virus" that occurred in Wuhan, China (1). The incidence of the infection is constantly increasing. The virus can easily be transmitted from one person to another with airborne, droplet, oral and fecal secretions (possibly even by asymptomatic patients) (2).This has become a major public health problem (3,4), with 270, 508, 964 million people infected (6,154,813 people in Iran) and more than 5, 324, 274 people died (130,722) so far (5). The prevalence of the infection has led to the empirical use of various antiviral therapies in infected patients (6). However, there still seems to be no treatment regimen with specific clinical efficacy and optimal effectiveness.

Umifenovir is a broad-spectrum antiviral drug that has been approved in several countries (7). The antiviral mechanism of this drug is mainly as follows: a) inhibition of the membrane fusion between viral particles and plasma membranes, b) regulation of the immune response by producing interferons and activating macrophages, c) modulation of the expression of inflammatory cytokines such as interleukin-6, interleukin-8, and TNF-α inhibitor (7-9). Recent studies have also shown that Umifenovir has antiviral effects on other viruses such as Herpes (10), Zika virus (11), and Ebola virus (12). In the laboratory, the efficacy of Umifenovir in inhibiting Severe Acute Respiratory Syndrome (SARS) coronavirus replication has been demonstrated (13,14), and observational studies have reported the positive effect of this medication on the treatment of COVID-19 (15,16).

Umifenovir has been used as an anti-influenza drug in various countries for several decades (17,18). In vitro studies have confirmed the antiviral effect of Umifenovir on coronavirus (13,14,17). Fever, cough, headache, shortness of breathing, fatigue, loss of taste or smell and gastrointestinal tract such as diarrhea, anorexia, nausea, and abdominal pain are common symptoms of COVID-19 (18).

The innate pathogenesis of the virus leads to mild symptoms in which antiviral therapy can quickly improve the primary symptoms. Then, increased cytokines in the lungs and bone marrow lead to worsening of the symptoms of influenza virus or SARS-CoV infections (17,20-22). Previous data have shown that there are two potential mechanisms involved in the process of lung damage caused by influenza virus, including viral pathogenesis and the host's innate immune responses to the disease (23).

Umifenovir inhibits the viral fusion with the host cell and stimulates the immune system and increases the phagocytic activity of macrophages through interferon production. This drug has a hepatic metabolism and is administered at a dose of 200 *mg* every 8 hours. The active ingredient of this drug is non-toxic and rare side effects have been reported (17).

Pruritus and skin rashes are among the rare side effects of this medicine and no other serious side effects have been reported. However, it is contraindicated in children under two years of age and pregnant and lactating women. Careful monitoring of its side effects should be done in patients with liver and kidney failures. The LD50 dose of this drug it s 4 *g/kg* body weight (17). Therefore, due to the insufficient number of clinical trials and studies conducted on the treatment of this disease with this drug so far, as well as the lack of specific drug therapy, we aimed to examine the effects of this drug in a more detailed interventional study.

Materials and Methods

Participants

This study is an open-label clinical trial conducted on patients with definitive diagnosis of COVID-19 (PCR testing from nasopharyngeal and oropharyngeal secretions or a clear view on the chest CT scan) (definitive evidence for SARS-CoV-2 in chest CT, patchy and ground-glass opacities in lungs) who were referred to Imam Khomeini Hospital Complex, Tehran, Iran. This study was conducted from April 20 to June 4, 2020. In this study, multi-stage sampling was considered. In the first stage, 56 people were selected by accidental non-random sampling method. This sample size was subsequently divided into two groups by randomized block sampling (with a randomized block design, the experimenter divides subjects into subgroups called blocks, such that the variability within the blocks is less than the variability between the blocks. Then, subjects within each block were randomly assigned to treatment conditions (1:1). During the study, three patients left the case

group (two patients lost to follow up, one patient discontinued the intervention). These two groups included control (N=25) and case (N=28) arms. Their clinical symptoms were examined while taking these medicines in the disease course (14-day follow-up for each patient). The inclusion criteria for the study included patients with age greater than or equal to 18 years, oral tolerance, obtaining written informed consent from the patients and diagnosis of mild-to-moderate COVID-19 infection (adolescents or adults with clinical signs of pneumonia (fever, cough, dyspnea, fast breathing), fatigue, anorexia, myalgia. Other non-specific symptoms, such as sore throat, nasal congestion, headache, nausea and vomiting, have also been reported (1,24-26), but should be without signs of severe pneumonia (including SpO_2 ≥ 90% on room air, respiratory rate > 30 breaths/min; severe respiratory distress) (27). The exclusion criterion was the basal alanine Aminotransferase (ALT) value greater than five times the normal range (normal value for ALT in blood ranges from 29 to 33 *IU/L* for males and 19 to 25 *IU/L* for females).

The case group received hydroxychloroquine (HCQ) at a dose of 200 *mg* every 12 hours and Umifenovir at a dose of 200 *mg* every 8 hours for 10 days. The control group received the national treatment protocol proposed for COVID-19 (28), including HCQ every 12 hours for 10 days and acetaminophen and diphenhydramine oral syrup if needed.

With the exception of Umifenovir, all other standard interventions and treatments were the same for patients in both groups. Umifenovir was provided by the Center for Progress and Development (CPDI) of Iran Presidency and given to the infectious disease ward, and patients did not pay for it. Pharmstandard, one of the leading Russian pharmaceutical companies, is the manufacturer of this drug. Given the open-label nature of the trial, the department of pharmacotherapy was the research supervisor.

Measurements

After obtaining written informed consent from the patients, demographic and clinical characteristics such as age, gender, Body Mass Index (BMI), history of underlying diseases including COPD, asthma, Diabetes Mellitus (DM), hypertension, malignancy, HIV, and taking immunosuppressive drugs were extracted and recorded from the patients' medical history.

In the beginning, factors such as fever, heart rate, respiratory rate, oxygen saturation, and tests such as White Blood Cell count (WBC), C-Reactive Protein (CRP), liver enzymes, bilirubin, Creatine Phosphokinase (CPK), and electrolytes including sodium, magnesium, and potassium were recorded.

Clinical symptoms of patients with COVID-19 infection such as nausea, vomiting, diarrhea, cough, shortness of breath, fever, body aches, loss of appetite, and other symptoms were also monitored. The patients' symptoms were evaluated in terms of improvement or worsening, and the results on the third day after the onset of symptoms were reported "primary outcome", and on the seventh day as "secondary outcome", and on the 14th day as "final outcome". improvement or worsening were reported on the 3rd day after start in each as the primary outcome, on the 7th day as the secondary outcome, and on the 14th day as the final outcome.

The patients were also monitored for common side effects of Umifenovir such as skin rashes and gastrointestinal symptoms such as nausea and vomiting, diarrhea or abdominal pain, jaundice, and bradycardia.

Ethical considerations

This study was approved by the Ethics Committee of Tehran University of Medical Sciences (TUMS) according to the 2013 Declaration of Helsinki. The written informed consent was obtained from all the patients. The patients were informed that they could withdraw from the study at any time and continue their treatment according to the national protocol.

Statistical analysis

The Kolmogorov-Smirnov test was first used to assess whether the distribution of variables was normal. Continuous variables were expressed as median [Interquartile Range (IQR)] and their relationship was reported in the two groups using Mann-Whitney U test and Kruskal–Wallis test. Qualitative variables were expressed as numbers (percentages) and their relationship was analyzed using the Chi-square test

and Fisher's exact test. The Kaplan-Meier method was used to compare the improvement in disease symptoms during the treatment between the two groups. The statistical analysis was performed using the SPSS software (version 25) and p-values<0.05 were considered statistically significant.

Results

Demographic and clinical characteristics

The statistical population included 53 patients with COVID-19 disease. Among these patients, 25 received hydroxychloroquine and 28 received a combination of HCQ and Umifenovir (Figure 1). All patients were in the mild-to-moderate group, and none of them had fever. There were no statistically significant differences in demographic variables such as age, gender, body mass index (BMI), primary symptoms, and patients' lab tests between the two groups (Tables 1-3).

Myalgia was the most common symptom at the onset of the disease, and most of the patients (94.3%) had myalgia upon entering into the study. However, there was no significant difference in the frequency of myalgia between the two groups (p=0.46).

Treatment responses

On the third day of the disease, there were statistically significant differences in myalgia (p=0.002), dry cough (p=0.001), weakness (p=0.021), and gastrointestinal symptoms (p=0.001) between the two groups (Table 4) and the recovery rate was more in the Umifenovir group. On the seventh day, there were statistically significant differences in dry cough (p=0.001), weakness (p=0.004), gastrointestinal symptoms (p=0.043), and shortness of breath (p =0.001) between the two groups (Table 4) and the recovery rate was more in the Umifenovir group.

In general, according to the Breslow (Generalized

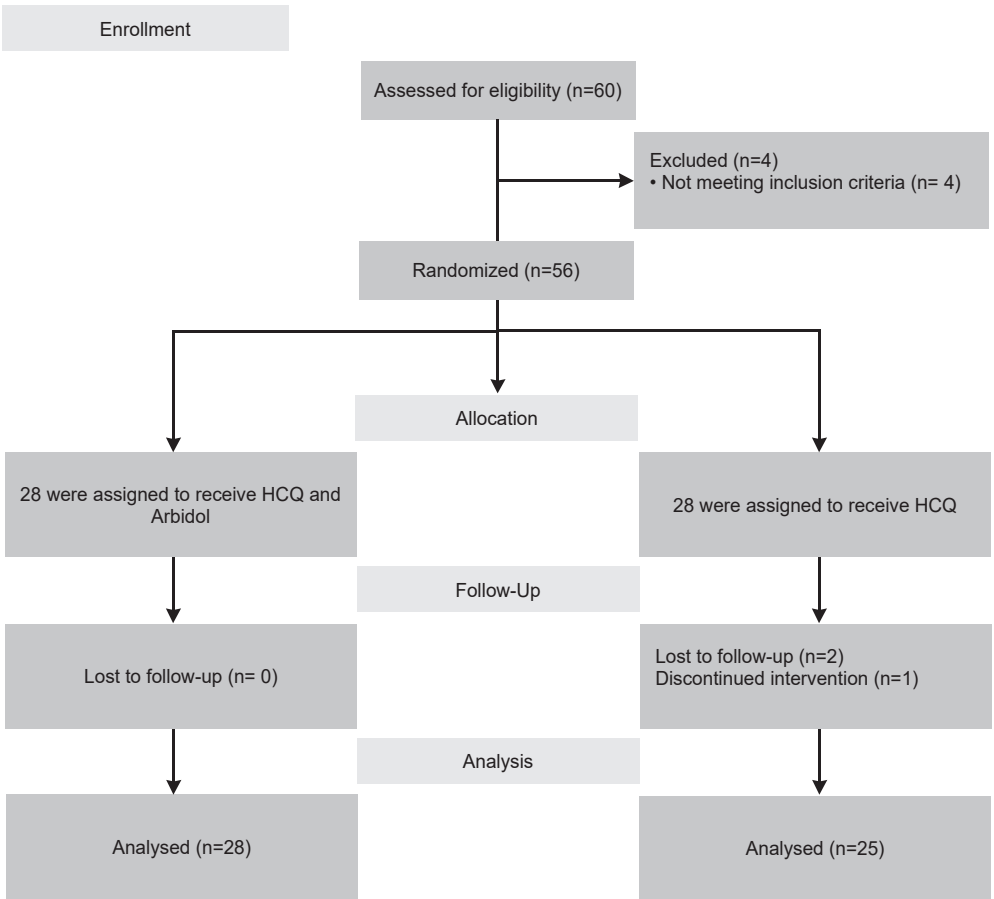

Figure 1. Consolidated standards of reporting trials (CONSORT) flow diagram.

Table 1. Demographic characteristics, symptoms, signs and chest CT scan findings in patients with Covid-19 on the first-day visit

Variables	HCQ/Arbidol N (%)	HCQ N (%)	p-value
Gender Male Female	 19(67.9) 9(32.1)	 13(52) 12(48)	
Sleep disorders*	4(14.3)	5(20)	0.421
Anosmia*	2(7.1)	4(16)	0.281
Sore throat	13(46.4)	14(56)	0.481
Conjunctivitis*	1(3.6)	0	0.531
Chest CT (Unilateral)*	7(25)	12(48)	0.131
Chest CT (Bilateral)	16(57.1)	11(44)	0.131
Dry cough	24(85.7)	17(68)	0.121
Myalgia	27(96.4)	23(92)	0.461
Dyspnea	22(78.6)	11(44)	0.011
Gastrointestinal symptoms	8(28.6)	12(48)	0.141
Weakness	27(96.4)	25(100)	0.531
Chest pain*	5(17.9)	12(48)	0.021

*Fisher's exact test; HCQ: Hydroxychloroquine

Table 2. Laboratory findings of mild to moderate Covid-19 patients on the first day, Tehran, 2020

Variables	HCQ/Umifenovir (n=28) Median (IQR), N (%)	HCQ (n=25) Median (IQR), N (%)	p-value
Age (yrs.)	46.5(36-57.5)	42(34-50.5)	0.533
BMI	25.05(23.75-25.6)	25.23(23.95-26.15)	0.061
Symptom duration before admission (day)	4(3-5)	4(3-5)	0.971
RR	22(21-23.75)	22(20-23)	0.351
PR	99.5(90.25-104.75)	91(86.5-100)	0.161
O_2 saturation (%)	95(94.25-97)	96(95-97)	0.281
T (*°C*)	37.05(36.9-37.3)	37(36.9-37.5)	0.971
CRP (*mg/L*)	16.5(6.75-60)	14(7-29.5)	0.521
AST (*IU/L*)	27(18.25-36.25)	25(19.5-30)	0.221
ALT (*IU/L*)	27(18.25-36.25)	30(25.5-33)	0.211
Alk phosphatase (*IU/L*)	174(150-190.5)	202(170.5-233.5)	0.016
Cr (*mg/dL*)	0.95(0.825-1.1)	0.9(0.8-1.05)	0.311
Troponin (*ng/L*)	1.5(1.5-2.1)	1.5(1.5-1.5)	0.511

Cont Table 2

CPK (*mg/dL*)	100.5(66.5-156.5)	120(91.5-151)	0.571
Na (*mEq/L*)	140(139-141)	141(139-142)	0.151
K (*mEq/L*)	4.2(3.925-4.4)	4.1(4-4.2)	0.411
WBC (*$10^3/\mu l$*)	6.6 (5.2-7.652)	5.5 (4.85-6.55)	0.111
Lymphocytes (*$10^3/\mu l$*)	1.674(1.29-2.38)	1.53(1.281-1.874)	0.281
PLT (*$10^3/\mu l$*)	222(180.25-282)	215(199-246.5)	0.871
Need for hospitalization (yes)	1(3.6)	1(4)	0.981

HCQ: Hydroxychloroquine

Table 3. Primary outcome (survival of symptoms three days after the onset of illness) and secondary outcome (survival of symptoms seven days after the onset of illness) of mild to moderate Covid-19 patients separately into two study groups, Tehran, 2020

Symptoms	HCQ/Umifenovir N (%)	HCQ N (%)	p-value
Myalgia 3th day	2(7.1)	11(44)	0.002
7th day	0(0)	1(4)	0.471
Dry cough 3th day	21(75)	22(88)	0.001
7th day	1(3.6)	17(68)	0.001
Chest pain 3th day	3(10.7)	12(48)	0.003
7th day	0(0)	5(20)	0.191
Weakness 3th day	7(25)	14(56)	0.021
7th day	2(7.1)	10(40)	0.004
Gastrointestinal symptoms 3th day	0(0)	8(32)	0.001
7th day	0(0)	4(16)	0.043
Dyspnea 3th day	11(29.3)	16(64)	0.072
7th day	2(7.1)	12(48)	0.001

HCQ: Hydroxychloroquine

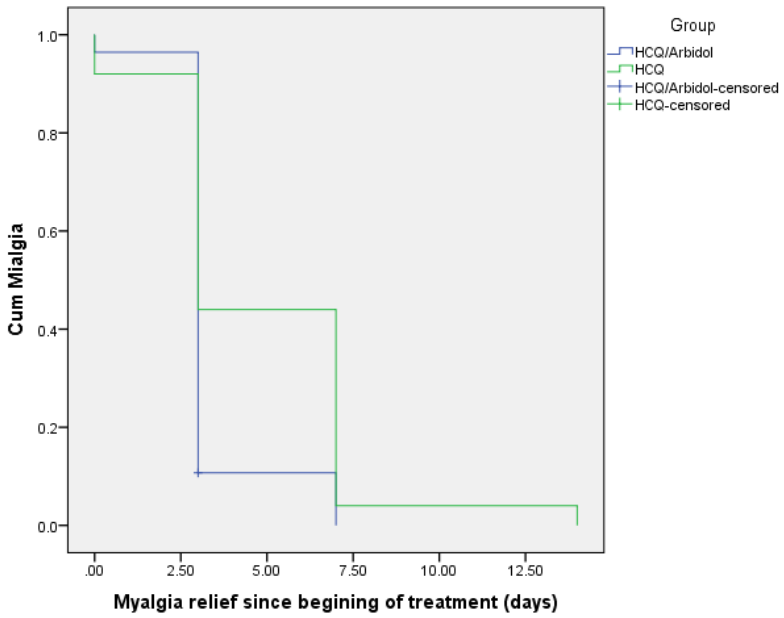

Figure 2. Kaplan-Meier analysis of recuperation Mialgiabetween two groups (who were treated with Umifenovir and HCQ and those treated only with HCQ).

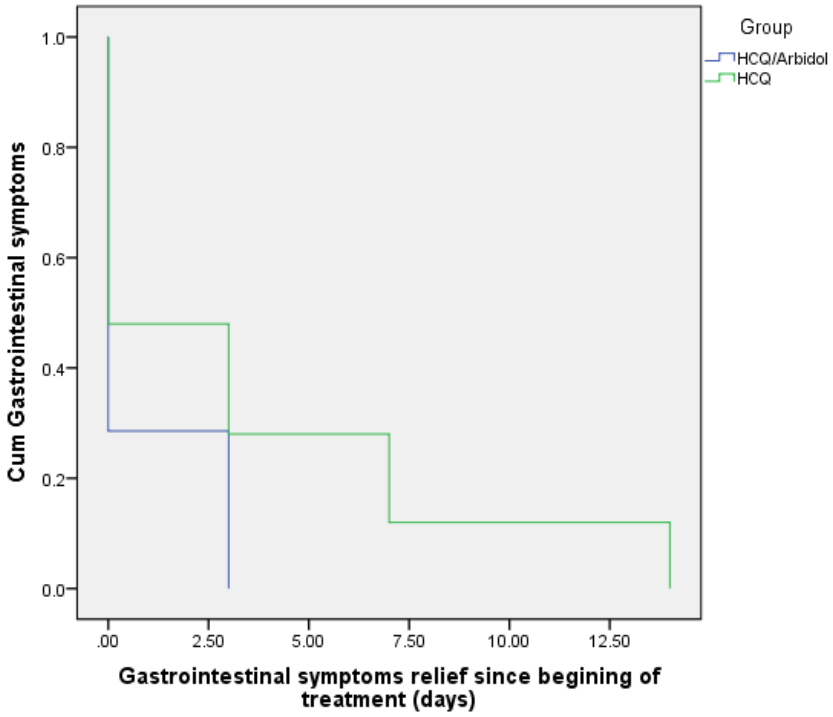

Figure 3. Kaplan-Meier analysis of recuperation GI symptoms between two groups (who were treated with Umifenovir and HCQ and those treated only with HCQ).

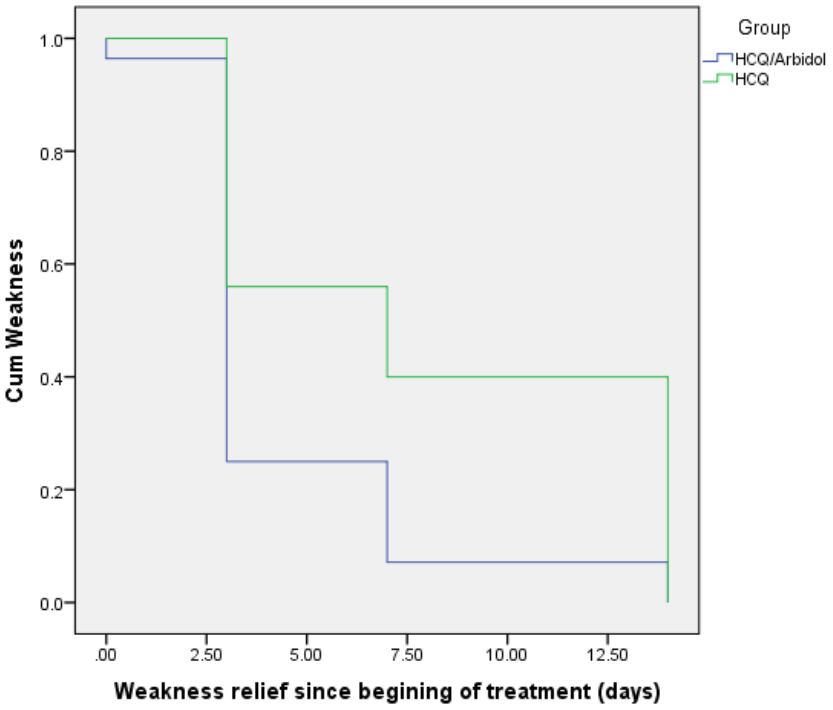

Figure 4. Kaplan-Meier analysis of recuperation weakness between two groups (who were treated with Umifenovir and HCQ and those treated only with HCQ).

Wilcoxon) test and Kaplan-Maier curves (Figures 2-4) during the disease course, there were statistically significant differences in myalgia (p=0.03), gastrointestinal symptoms (p=0.047), and weakness (p=0.007) between the two groups. However, there were no statistically significant differences in shortness of breath (p=0.29) and dry cough (p=0.81) between the two groups during the disease course.

Side effects

Side effects include dermatitis, gastrointestinal symptoms (such as nausea and diarrhea), jaundice, and neurological symptoms every three days but they were not observed in any of the patients after 14 days.

Discussion

In this study, patients with mild-to-moderate disease symptoms (such as myalgia and fatigue) receiving Umifenovir in their treatment regimen improved quickly. Given the COVID-19 infection pandemic, there is an urgent need for an effective and specialized antiviral regimen to treat the clinical symptoms of the disease. In the absence of definitive treatment protocols, treatment strategies are proposed to accelerate the recovery of COVID-19 patients, which may be in the early stages of testing; however, future preclinical and clinical trials are necessary for possible studies. In systematic review studies, it was shown that lopinavir/ritonavir, remdesivir, convalescent plasma, chloroquine, ribavirin, hydroxychloroquine sulfate, traditional Chinese medicine, and arbidol were the most widely used therapies for the treatment of Covid-19 patients (29).

To this end, due to the limited number of clinical trial studies, we decided to use a medicine that has had favorable primary outcomes in animals as well as case studies. Based on the results of the present study, adding Umifenovir (due to its antiviral and anti-inflammatory effects) to empirical regimens accelerated the recovery process of patients' clinical symptoms.

In the current study, on the third day of the disease, there were statistically significant differences in myalgia, dry cough, weakness, and gastrointestinal symptoms between the two groups, and the recovery rate was better in the Umifenovir group. This means that primary symptoms can be controlled in the patients by adding Umifenovir.

In addition to its antiviral mechanism, Umifenovir has potential immunomodulatory and anti-inflammatory effects on the expression of inflammatory cytokines. In vitro studies have demonstrated that pro-inflammatory cytokines such as TNF-α, IL-8, and IL-6 decreased after treatment with Umifenovir (9). Acute respiratory distress syndrome (ARDS) caused by increased response to inflammatory cytokines/chemokine has also been shown to be one of the main mechanisms of SARS-CoV and MERS-CoV infections (17,30). It seems that the effects of Umifenovir should be reflected in the secondary symptoms of the disease. In our study, on the seventh day, there were statistically significant differences in dry cough, weakness, gastrointestinal symptoms, and shortness of breath between the two groups, and the group receiving HCQ addition to Umifenovir had a faster recovery.

Another study reported an early improvement in radiological evidence of COVID-19 infected pneumonia patients taking Umifenovir. This research also highlighted the antiviral and anti-inflammatory effects of the drug (9). However, another investigation claimed that Umifenovir had no positive effect on clinical and radiological improvement or even virus removal, and that the clinical efficacy of this drug differs from the severity of the disease (17).

Due to inconsistency in the results, the findings of the present study demonstrated that gradually there were statistically significant differences in myalgia, gastrointestinal symptoms, and weakness between the case group (Umifenovir) and the control group. This means that with the use of Umifenovir, patients had significantly fewer symptoms over time so that Umifenovir can be effective as antiviral and anti-inflammatory against this infection.

There were some limitations in this study. First of all, since there is no effective treatment for this disease, we used empirical treatment along with HCQ for the control group. Second, due to ethical considerations, the effect of Umifenovir was not assessed individually, thus we added Umifenovir to the empirical treatment. Third, due to the limited sample size and insufficient data in treatment of severe patients, we cannot extrapolate the results to all the patients with COVID-19. Lastly, due to the high cost and a limited number of PCR test

kits, we could not use this test to prove the disease and evaluate the response to the treatment.

Conclusion

In this study, we concluded that the primary symptoms of patients with mild-to-moderate COVID-19 may be controlled by adding Umifenovir to the empirical treatment. This drug had similar effects on secondary symptoms. By using this method, patients may be recovered faster, therefore it was shown that Umifenovir could have antiviral and anti-inflammatory effects.

Ethics approval

This study was approved by the Ethics Committee of Tehran University of Medical Sciences (TUMS) according to the 2013 Declaration of Helsinki (IR.TUMS.VCR.REC.1399.204). The written informed consent was obtained from all the patients. The patients were informed that they could withdraw from the study at any time and continue their treatment according to the national protocol.

Availability of data and material

Data could be available upon a reasonable request and with the permission of Tehran University of Medical Science ethical committee.

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Conflict of Interest

The authors have no conflict of interest.

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