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Efficacy of umifenovir in the treatment of mild and moderate COVID-19 patients

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ABSTRACT



The coronavirus disease (COVID-19) outbreak was initially reported in Wuhan, China in December 2019. Many cases of pneumonia without any apparent cause were described to be associated with seafood and wet markets in Wuhan. At present, there are no effective antiviral drugs to treat COVID-19. Umifenovir is a broad-spectrum antiviral drug used for treating several viral infections, and it reportedly inhibits SARS-CoV replication *in vitro*. This exploratory randomized and controlled study recruited 30 COVID-19 patients admitted to the hospital until May 18, 2020. Fifteen (15) eligible patients randomly allocated underwent umifenovir therapy (600 mg/d). Time to clinical recovery (TTCR), clinical characteristics, and tomographic results were analyzed at baseline and five days after treatment to assess the effect of umifenovir. Thirty (30) COVID-19 patients (mean age: 36.5 years [SD: 12.1, range: 19-59]), including 18 (60%) males and 12 (40%) females, were recruited for the study. There were no significant differences in age or gender, but there were significant differences in TTCR among the two categories. Body temperature (BT) and cough recuperation time [2.8 (0.6) and 2.6 (0.6) days, respectively] were highly reduced in the umifenovir category at 2.4 and 2.1 days, respectively. Moreover, many patients treated with umifenovir exhibited no side effects. In this study, pneumonia was ameliorated in 76.6% (23/30) of the patients, with moderate and potential amelioration in 36.6% and 40% of the patients, respectively. In addition, 66.6% of the patients in the umifenovir category had potential pneumonia absorption.

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INTRODUCTION

The corona virus disease (COVID-19) outbreak was reported in Wuhan, China in December 2019. Many cases of pneumonia without any apparent cause were described to be associated with seafood and wet markets in Wuhan (Li *et al.*, 2020). COVID-19 has become a pandemic and is reportedly caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and continues to affect an increasing number of nations, which may lead to a possible socio - economic collapse.

At present, there are no effective antiviral drugs that effectively target SARS-CoV-2 attachment, its entry into host cells, or genomic replication. It is clear that using potent therapeutics is the only option to decrease COVID-19 morbidity and mortality before a vaccine becomes available; however, in recent times, patient therapy has mostly been limited to supportive care, varying from symptomatic management to critical care support.

Umifenovir is a broad-spectrum antiviral drug that is used for treating several viral infections, such as those caused by the severe acute respiratory syndrome coronavirus (SARS-CoV), and influenza, Ebola, Lassa, and paramyxoviruses (Shi *et al.*, 2007; Blaising *et al.*, 2013; Pécheur *et al.*, 2016). Umifenovir has shown potential effects against influenza A, B, and C viruses, although it mainly acts against influenza A viruses (eg H1N1, H2N2, and H3N3) causing less side effects and therefore enhancing safety (Leneva *et al.*, 2019). Additionally, umifenovir has been reported to inhibit SARS-CoV replication *in vitro* (Khamitov *et al.*, 2008).

In spite of the aforementioned precursory evidence, the precise efficacy of umifenovir against COVID-19 is unknown. The current study aimed to evaluate the efficacy of umifenovir in the treatment of mild and moderate COVID-19 patients.

MATERIALS AND METHODS

Study design and patients

This exploratory randomized and controlled study recruited 30 COVID-19 patients admitted to City Clinical Hospital No. 1 (Bishkek, Kyrgyzstan) until May 11, 2020. The inclusion criteria were as follows: 1) age 18–60 years; 2) SARS-CoV-2 infection confirmed by real-time reverse-transcription polymerase chain reaction (rRT-PCR) from naso and oropharyngeal swabs; 3) mild clinical status (mild clinical symptoms but no signs of pneumonia with chest computerized tomography [CT] scanning) and moderate clinical status (symptoms like pyrexia, respiratory symptoms, and pneumonia upon CT scanning); 4) body temperature (BT) > 37°C and oxygen saturation (SaO₂) > 93%; and 5) acceptance for recruitment in the study and providing written consent. The exclusion criteria were as follows: 1) severe/critical illness; 2) allergies to umifenovir; 3) exhibiting severe side effects, such as nausea, vomiting, diarrhea, or other gastrointestinal symptoms; 4) receiving other drugs that may interact with umifenovir; 5) pregnant or lactating women; 6) cardiac, liver, or renal disease; 7) gestation or lactation; and 8) enrollment in different drug trials within the previous 30 days.

Thirty (30) eligible patients were randomly allocated following substantively demarcating the accuracy of the enrollment criteria into two categories as follows. In Category 1 (umifenovir category), 15 patients were treated with umifenovir (orally administered, 200 mg three times per day for 1–5 days). In Category 2 (control category), 15 patients underwent standard treatment. Notably, all patients underwent the standard treatment (antivirals, antibiotics, immunoglobulin, and corticosteroids). Confidentiality was maintained concerning the data collected from the patients who provided voluntary consent. This study was approved by the Ethics Committee of the City Clinical Hospital No. 1 (Bishkek, Kyrgyzstan).

Procedures

The naso and oropharyngeal samples, collected between March 12 and May 11, 2020, were positive for SARS-CoV-2 when tested using rRT-PCR, and 30 confirmed COVID-19 patients were enrolled. The following data were collected: 1) main dates, such as pyrexia onset, enrollment, amelioration established by CT scanning, and discharge; 2) predisposing factors (ex hypertension and diabetes mellitus); 3) everyday analysis of clinical parameters (ex BT, SaO₂, heart rate, and respiration rate); and 4) side effects.

Endpoints

The examination endpoints were five days after admission or when side effects were seen. Differences in TTCR and clinical features of patients were assessed following delivery. TTCR is a composite of BT and cough amelioration over 72 h. The following normalization and alleviation criteria were considered: 1) BT > 37°C; 2) cough description from patient case sheets being insignificant or absent with no symptoms. BT and cough were checked three times per day to establish the average. To analyze tomographic differences, chest CT reports before one day (day 0) and one day after the study (day 6) were evaluated. Lung recovery was determined in three stages: aggravated, unaffected, and ameliorated; pneumonia was considered moderately ameliorated if no patches were observed < 50% of the lungs, whereas no patches in > 50% of the lungs indicated potentially ameliorated pneumonia.

Statistical Analysis

Data are presented as the mean (\pm standard deviation, SD) and n (%). Student's t-test was used for comparisons between the two categories. A two-sided p-value of < 0.05 was considered statistically significant. All analyses were performed with

Table 1: Patients characteristics in this study

Characteristics	All	Control	Umifenovir	P value
Cases, n	30	15	15	
Age, mean (SD)	36.5 (12.1)	37.3 (12.2)	35.7 (12.6)	0.0464
Gender, n (%)				0.0399
Male	18 (60 %)	8 (54.4%)	10 (66.6%)	
Female	12 (40%)	7 (46.6%)	5 (33.3%)	
Pyrexia, day (SD) ¹	2.8 (0.6)	3.3 (0.4)	2.4 (0.5)	0.0515
Cough, day (SD) ²	2.6 (0.6)	3.2 (0.4)	2.1 (0.3)	0.0527
Side effects	1 (3.3 %)	0	1 (6.6 %)	

¹ 11 and nine patients in the umifenovir and control categories experienced pyrexia before one day intervention. ² 11 and seven patients in the umifenovir and control categories experienced cough before one day intervention. SD: standard deviation

Table 2: Pneumonia absorption on chest computed tomography

Category	All	Aggravated	Unaffected	Moderate	Ameliorated Potential	Total
All	30	4 (13.3%)	3 (10%)	11 (36.6%)	12 (40%)	23 (76.6%)
Control, n (%)	15	3 (20%)	2 (13.3%)	8 (53.3%)	2 (13.3%)	10 (66.6%)
Umifenovir, n (%)	15	1 (6.6%)	1 (6.6%)	3 (20%)	10 (66.6%)	13 (86.6%)
P value	0.0438					

GraphPad Prism, v6.0.

RESULTS

Thirty (30) COVID-19 patients (mean age: 36.5 years [SD: 12.1, range: 19-59]), including 18 (60%) males and 12 (40%) females, were recruited for the study. Through randomization, patients were allocated to the group that underwent treatment with umifenovir (n=15) or the control (n=15) with follow up for 21 days. There was no significant difference in age or gender characteristics, but there were significant differences in TTCR between the two categories. With respect to pyrexia, nine patients in the control and 11 patients in the umifenovir category experienced pyrexia on day 0. When compared with the control category [3.3 (0.4) days], BT recuperation time was highly reduced in the umifenovir category [2.4 (0.5) days]. In terms of cough, seven patients in the control category and 11 patients in the umifenovir category experienced cough on day 0, and cough recuperation time was highly decreased in the umifenovir category [2.1 (0.3) days]. In fact, no patient progressed toward severe and critical illness in either category. Only one patient presented with mild side effects in the umifenovir category, while one patient had cephalalgia; notably, no patient experienced severe side effects (Table 1).

To assess the impact of umifenovir on pneumonia,

we compared the chest CT scans of the patients on days 0 and 6. In this study, pneumonia was ameliorated in 76.6% (23/30) of the patients, with moderate and potential amelioration in 36.6% and 40% of the patients, respectively. Further, many patients were observed to have significantly ameliorated pneumonia in the umifenovir category (86.6%, 13 of 15) compared to the control category (66.6%, 10 of 15). In addition, 66.6% of patients in the umifenovir category had potential pneumonia absorption (Table 2).

DISCUSSION

Thirty (30) COVID-19 patients were recruited as per the inclusion and exclusion criteria in this study. Through randomization, 15 patients were allocated to undergo umifenovir treatment, while 15 underwent standard treatment with an antiviral drug as the control. The results indicated that BT and cough recuperation time [2.8 (0.6) and 2.6 (0.6) days, respectively] were highly reduced in the umifenovir category to 2.4 and 2.1 days. Moreover, many patients treated with umifenovir exhibited no side effects.

The results of our study are consistent with those of a Chinese study comparing the efficacy of favipiravir (116 patients) and umifenovir (120 patients) for COVID-19 patients. The clinical recovery rate at day 7 and a reduced incidence of fever and cough were

both 55.8% in the umifenovir group (Chen *et al.*, 2020). In a previous study, 94 ordinary and severe COVID-19 patients who were treated with umifenovir and moxifloxacin showed decreasing viral load and inflammation; therefore, these drugs notably negatively regulated inflammation in severe COVID-19 patients (Xi *et al.*, 2020). Despite the small sample size, our study shows that umifenovir treatment ameliorates symptoms in mild and moderate COVID-19 patients.

In the present study, no patient developed severe or critical illness, which demonstrates that the condition was not aggravated following hospitalization. At the endpoint, all 30 patients were recovered and discharged from the hospital. Even with the lack of availability of specific antiviral drugs, all 30 patients did not progress to a severe or critical clinical condition and recovered after treatment with umifenovir.

Although this study demonstrated the efficacy of umifenovir in COVID-19 patients, there were some limitations. The sample size of the study was small, and we did not recruit severe or critically ill patients. Additionally, susceptible patients with comorbidities were also not recruited. Furthermore, the study was conducted at a single center. Interestingly, all 30 patients who received treatment with umifenovir in this study recovered and were observed to be healthy at follow-up.

CONCLUSION

In conclusion, our study found that umifenovir presents advantages for ameliorating mild and moderate COVID-19 in patients who were symptomatic in combination with supportive treatment, and no side effects were reported. Additional future studies are required to verify these results.

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Conflict of Interest

None.

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