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Evaluating the Effects of Umifenovir Compared to Lopinavir/Ritonavir in the Management of Patients with COVID-19: A Randomized Controlled Trial

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Abstract

Background. Due to the lack of specific safe medications for the treatment of COVID-19, medications used for other similar conditions are being tested to alleviate the condition of COVID-19 patients, resulting in acceptable outcomes in some cases. Umifenovir (Arbidol®) is used to treat influenza viruses by inhibiting the fusion of the virus with the host cell. According to previous findings, umifenovir may inhibit SARS-CoV-2 infection by interfering with the release of SARS-CoV-2 from inside the cell. This study aimed to determine the effects of umifenovir, a fusion inhibitor, versus lopinavir/ritonavir in treating patients with COVID-19. **Methods**. This study was a randomized controlled trial consisting of 90 confirmed COVID-19 patients divided into the lopinavir/ritonavir group and the umifenovir group. The lopinavir/ritonavir group received 100/25 mg twice, while the umifenovir group was given 200 mg thrice a day, in both groups, for seven days. Outcomes included mortality rate and the need for mechanical ventilation or intensive care unit admission. Length of stay in the hospital and ICU and the lab tests trend were also assessed. **Results**. The mortality rate and the need for admission to the ICU were significantly lower in the umifenovir group (8% vs. 27.5%; P-value = 0.02). Moreover, The levels of white blood cells were also lower in the umifenovir group than in the control group by day 10 (6.2 (5.3-7.4) vs. 10.8 (9.9-13); P-value <0.001). **Conclusions**. Umifenovir may reduce the need for admission to the ICU and mortality rate in patients with COVID-19 compared with lopinavir/ritonavir. The lab test trends were also in favor of umifenovir use.

Keyword: COVID-19, lopinavir/ritonavir, SARS-CoV-2, umifenovir

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Introduction

On December 31, 2019, the World Health Organization was informed of the outbreak of pneumonia in Wuhan, Hubei Province (China), a city of 11 million people. In early 2020, the World Health Organization declared that the disease was an important medical emergency (1, 2). As of October 2022, more than 600 million COVID-19 cases have been confirmed worldwide, although the true rate of infections may be up to 10-times higher, with seroprevalence studies suggesting up to 80-90% of the global population has already been infected (3).

Currently, various SARS-CoV-2 vaccines have been approved for the prevention of COVID-19. There are some approved medications with promising effects regarding the management of COVID-19 induced by SARS-CoV-2, including tocilizumab or baricitinib (4). However, other beneficial medications with more favorable safety profiles still need to be improved. Many studies have been performed to assess novel treatments for SARS-CoV-2 (5). Repositioning the drugs being approved for other similar conditions is a fundamental and universal strategy in producing new medications, which reduces the cost and time to reach the market as some stages of clinical trials may not be required (6, 7). These medications

can be combined with other medications to improve clinical outcomes and discover new mechanisms of action for older and new classes of medications (8, 9).

Medications including human immunoglobulin, interferon, remdesivir, favipiravir, lopinavir, ritonavir, methylprednisolone, and ivermectin have been used in previous trials as adjunctive therapy for patients with COVID-19 (10-12).

Umifenovir (Arbidol®), a medication manufactured in Russia, is used to treat influenza viruses by inhibiting the fusion of the virus with the host cell. This medication is not well known in other countries. Umifenovir has been used against influenza A and B viruses and has recently been used to treat hepatitis C (13, 14). According to previous findings, umifenovir may inhibit SARS-CoV-2 infection by interfering with the release of SARS-CoV-2 from inside the cell (8, 15, 16). In a study that compared the efficacy of umifenovir with lopinavir/ritonavir, the authors showed clinical and laboratory improvement in the umifenovir group (17). However, A systematic review and meta-analysis performed in 2021 concluded no beneficial effects of umifenovir in COVID-19 treatment. The authors of the mentioned meta-analysis recommended conducting further well-designed trials (18). Lopinavir/ritonavir (Kaletra®) is a fixed-dose combination antiretroviral medication for treating and preventing Human Immunodeficiency Virus (HIV). It is generally recommended for use with other antiretrovirals. At the time of the study, lopinavir/ritonavir was considered part of the standard of care in managing COVID-19 patients.

Considering the potential inhibition of SARS-CoV-2 entry into the host cell by umifenovir, this study aimed to investigate the potential beneficial effects of umifenovir, compared to lopinavir/ritonavir, in the treatment of COVID-19 cases.

Methods

Setting

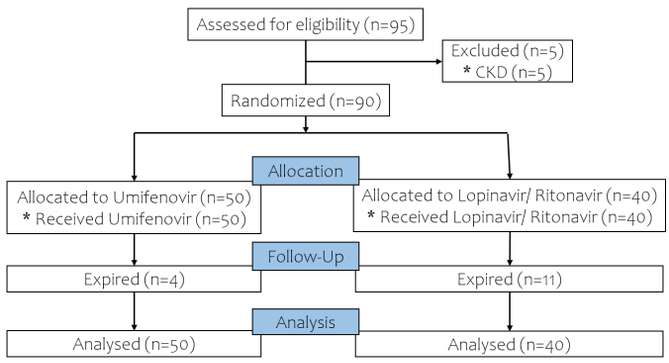
The study was a randomized controlled trial conducted at Dr Masih Daneshvari hospital, Tehran, Iran.

Patients

Ninety patients aged 18 and 100 with symptomatic COVID-19, confirmed by Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) test, were included in the study (Figure 1). The patients were admitted to Dr. Masih Daneshvari hospital, a referral center for COVID-19 cases in Iran. The inclusion criteria were equal to or more than 30 breaths/min, SpO2 93% at room air, and PaO2/FiO2 300 mmHg. The exclusion criteria were a history of allergy to this class of medications, prior use of umifenovir or lopinavir/ritonavir before hospitalization, pregnant or lactating women, acute or chronic kidney disease, and liver failure (child-pugh stage C or D).

Figure 1

CONSORT flowchart of the study



Ethics and approval

Before the trial, the informed consent form was signed by the patients. This research was conducted according to the declaration of Helsinki and was approved with the ethics code number of **IR.SBMU.RETECH.REC.1399.030** by the ethics committee of Shahid Beheshti University of Medical Sciences. The trial was also registered in the Iranian Registry of Clinical Trials with the registration number **IRCT20151227025726N15**.

Interventions

Ninety patients were included in this study and randomly assigned to the umifenovir group (N = 50) or the lopinavir/ritonavir group (n = 40). The screening process was performed at admission. Patients were recruited if they had fulfilled the eligibility criteria. The umifenovir group received umifenovir (Arbidol®) (200 mg three times daily for seven days) while the lopinavir/ritonavir group received Kaletra® (100/25 mg twice daily for seven days). In addition to these interventions, both groups received dexamethasone 6 mg daily for seven days, oxygen and fluid support, enoxaparin 40 mg daily for deep vein thrombosis, and pantoprazole 40 mg daily for stress ulcer prophylaxis.

Outcomes

The primary outcomes were the need for mechanical ventilation, admission to the Intensive Care Unit (ICU), and the mortality rate. Secondary outcomes included length of stay in the ICU and hospital. The whole outcome was assessed over seven days. Data were collected from the patient's medical records, including demographic data, underlying diseases, and laboratory test results.

Randomization and blinding

Randomization and treatment allocation occurred after primary screenings and confirmation of patients' eligibility. Randomization was carried out in a 1:1 ratio, with permuted blocks with lengths of two. The physicians were masked to the study intervention.

Sample size and Statistical analysis

The sample size was calculated using G power software. Given that there is a 50% probability of mortality rate for the lopinavir/ritonavir group to occur, the use of umifenovir might reduce the incidence to 20%. Assuming the first type error of 0.05 and 80% power, 39 patients were

calculated in each group. Considering the potential drop-out rate, 50 patients were enrolled in the umifenovir group, and 40 patients were recruited in the lopinavir-ritonavir group.

Missing data were not imputed, and no multiplicity adjustments were made in this study. The Shapiro-Wilk test was conducted to assess the normality of data distribution. To compare the differences between the quantitative variables of both groups, the student-t or Mann-Whitney U test was done. Categorical data were assessed using logistic regression. Multivariate logistic regression was performed to assess the effects of age on the primary outcomes. The odds ratio (OR) was considered the standard effect size. An OR lower than 0.24 was considered a large effect (19).

We considered p-values of less than 0.05 as significant. The results were analyzed using SPSS v.25.0 software (IBM Corp., Armonk, NY, USA) and STATA 14.

Results

Table 1 shows the demographics and baseline characteristics of the patients. The mean age of the patients in the umifenovir and lopinavir/ritonavir groups was 52 ± 18 years and 58 ± 14 years, respectively.

Table 1
Baseline characteristics of the patients

Characteristics	Umifenovir (N=50)	Lopinavir/ ritonavir (N=40)
Sex — n (%)		
Male	28 (56)	24 (60)
Age (y) — mean ± SD	52 ± 18	58 ± 14
Comorbidity — n (%)		
Smoking	1 (2)	1 (3)
Addiction	1 (2)	0 (0)
Diabetes mellitus	11 (22)	10 (25)
Hypertension	17 (34)	14 (35)
Ischemic heart disease	4 (8)	7 (18)
Rheumatoid arthritis	1 (2)	0 (0)
Chronic kidney diseases	1 (2)	0 (0)
Malignancy	1 (2)	0 (0)
Chronic obstructive pulmonary disease	2 (4)	1 (3)

The clinical outcomes of the patients are presented in Table 2. As the Table shows, 20% of the patients in the lopinavir/ritonavir group needed invasive mechanical ventilation versus 6% of those in the umifenovir group. However, the age-adjusted difference between the two groups was not statistically significant and only marginally significant (P-value = 0.08).

Among patients with severe COVID-19 who received umifenovir or lopinavir/ritonavir, there was a significant difference between the two groups regarding age-adjusted mortality rate. The mortality rate was significantly lower in the umifenovir group (8 % vs. 27.5% (P = 0.02)) (Table 2).

27.5% of the patients in the lopinavir/ritonavir group needed admission to the ICU versus 8% of those in the umifenovir group (P-value = 0.02).

The length of hospital stay in the umifenovir group was significantly higher than that in the lopinavir/ritonavir group (10 (8-13) versus 7(5-11) days; P-value = 0.005). On the contrary, the number of patients needing oxygenation with nasal or face masks in the umifenovir group was higher than in the lopinavir/ritonavir group. However, this difference was marginally significant (P-value = 0.05).

Table 2
Clinical outcomes of the patients

	Umifenovir (N=50)	Lopinavir/ ritonavir (N=40)	OR Crude	OR Age-adjusted	P-value
The need for admission to the ICU; n (%)	4 (8)	11 (27.5)	0.22	0.25	0.03
Mortality; n (%)	4 (8)	11 (27.5)	0.22	0.19	0.02
The need for mechanical ventilation; n (%)	3 (6)	8 (20)	-	-	0.08
Nasal or face mask oxygen therapy; n (%)	45 (90)	29 (72.5)	-	-	0.05
The need for non-invasive mechanical ventilation; n (%)	2 (4)	3 (7.5)	-	-	0.65
Length of hospital stay (day); median (IQR)	10 (8-13)	7 (5-11)	-	-	0.01
Length of ICU stay (day); median (IQR)	12 (7-19)	7 (4-22)	-	-	0.02

Multivariate logistic regression was performed for the need for admission to the ICU and mortality rate. ICU: intensive care unit

Table 3 shows the trend of lab tests between the two groups. As evident in the table, there was no significant difference in the baseline values of the two groups. The levels of white blood cells were significantly lower in the umifenovir group by day 10. Urea levels were much lower in the umifenovir group by Days 5 and 10 (P-value = 0.004, P-value = 0.023) (Table 3).

Table 3

Comparison of laboratory parameters for baseline, fifth and tenth day in two groups

Laboratory parameters	Group		P Value
	Umifenovir (n=50)	Lopinavir/ Ritonavir (n=40)	
WBC Baseline; median (IQR)	7.1 (4.5-9.6)	5.4 (4.6-8)	0.288
WBC day 5; median (IQR)	6.9 (4.8-10)	7 (5.7-11.2)	0.509
WBC day 10; median (IQR)	6.2 (5.3-7.4)	10.8 (9.9-13)	0
Urea Baseline; median (IQR)	29.5 (22-39)	31.5 (23-42.5)	0.516
Urea day 5; median (IQR)	23 (21-36)	55 (33-67)	0.023
Urea day 10; median (IQR)	27.5 (23-40.5)	78 (39-99)	0.004
Cr Baseline; median (IQR)	1 (0.9-1.3)	1.1 (1-1.2)	0.618
Cr day 5; median (IQR)	1 (0.9-1.2)	1.2 (0.9-1.4)	0.227
Cr day 10; median (IQR)	1 (0.8-1.1)	1 (1-1.4)	0.289
ALT Baseline; median (IQR)	23 (16-32)	28 (19-40)	0.11
ALT day 5; median (IQR)	16.5 (15-21.5)	30.5 (16-49)	0.137
ALT day 10; median (IQR)	28 (28-28)	32 (23.5-35)	0.48
ALP Baseline; median (IQR)	181.5 (147-233)	163.5 (132-215.5)	0.27
ALP day 5; median (IQR)	139 (113.5-187)	167 (148-205)	0.258
ALP day 10; median (IQR)	179 (179-179)	179 (157.5-241)	1

Data are presented as median (IQR); IQR: Interquartile range; WBC: white blood cells; Cr: creatinine; ALT: Alanine transaminase; ALP: alkaline phosphatase

Discussion

The present study shows that umifenovir may have clinical benefits in treating COVID-19 patients. The results of our study are consistent with those achieved in 2020, which concluded that umifenovir monotherapy might be superior to lopinavir/ritonavir as the patients in the umifenovir group had a shorter duration of positive RT-PCR test (15).

The need for admission to the ICU was significantly lower in the umifenovir group. Considering the lower age of the patients in the umifenovir group, age values were adjusted, and OR was increased to 0.25 from 0.22. Hence, after adjusting the age values, the protective effects of umifenovir vs. lopinavir/ritonavir in preventing admission to the ICU reduced to 75% from 78%. This difference was still significant, while the effect was modified. The protective effects of umifenovir vs. lopinavir/ritonavir in preventing mortality is 78%. Interestingly, this effect was increased to 81% when adjusting for age.

The length of hospital stay in the lopinavir/ritonavir group was significantly shorter than in the umifenovir group. However, this effect must be interpreted cautiously as this might be due to the lower mortality rate in the umifenovir group and not due to the improved outcomes of the patients.

We found that those who took umifenovir had lower levels of white blood cells and urea by day ten than the control group, which may improve outcomes in the umifenovir group. Umifenovir may have beneficial effects in reducing inflammation during COVID-19. Considering the above evidence, re-evaluation of this medication for treating COVID-19 should be considered. In another study, Li et al. investigated the safety and efficacy of umifenovir in treating mild to moderate COVID-19 patients. These patients experienced clinical and radiological improvements after the initiation of treatment (12). In another study in China, Huang et al. reported that umifenovir could decrease the viral shedding interval and duration of hospitalization (20). Our results are consistent with those of the above studies.

In another retrospective cohort study conducted in China at the University of Zhejiang, Kaijin Xu et al. concluded that after administering umifenovir, patients needed High Flow Nasal Catheter (HFNC) oxygen therapy was reduced by a greater degree than the control group (21). This indicates that umifenovir could accelerate viral clearance, improve radiological changes, and reduce the demand for oxygen therapy in hospitalized patients. In a study on the clinical effects of umifenovir, Chen et al. combined these with adjuvant therapy in China and concluded that the clinical symptoms in patients infected with SARS-CoV-2 were relieved faster, and the duration of hospitalization was considerably reduced in the umifenovir group, compared to the controls ($P < 0.05$) (22).

Our data are inconsistent with the study by Alavi Darazam et al., who concluded that umifenovir is ineffective in shortening the duration of COVID-19 or mortality. However, the primary outcome of that study was time to clinical improvement, which was different from ours (23).

The main limitation of our study was that we evaluated the potential beneficial effects of umifenovir in combination with dexamethasone only, and the efficacy of umifenovir as single-agent therapy was not evaluated. Hence, the effects of umifenovir may be overestimated in this regard. Another main point to consider is that the effects of umifenovir were compared to lopinavir/ritonavir, which has yet to be proven to have considerable beneficial effects.

Considering the large effect size of the umifenovir in comparison with lopinavir/ritonavir, in terms of the need for mechanical ventilation, it is recommended to perform the trial with a larger sample size to detect this effect in this regard.

Conclusion

Umifenovir, in combination with dexamethasone, may have beneficial effects in treating severe COVID-19 patients. The mortality rate and the need for admission to the ICU were significantly lower in the umifenovir group. The lab test trends were also in favor of umifenovir use.

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Conflicts of interest

None.

Ethics approval

Before the trial, the informed consent form was signed by the patients. This research was conducted according to the declaration of Helsinki and was approved with the ethics code number of **IR.SBMU.RETECH.REC.1399.030** by the ethics committee of Shahid Beheshti University of Medical Sciences. The trial was also registered in Iranian Registry of Clinical Trials with the registration number of **IRCT20151227025726N15**.

Authors contribution

Study conception and design: Saghar Barati, Farzaneh Dastan; Data collection: Seyed Alireza Nadji, Sahar Yousefian, Sara haseli; Analysis and interpretation of the results: Saghar Barati, Farzaneh Dastan, Jalal Heshmatnia, Payam Tabarsi, Afshin Zarghi; Draft manuscript preparation: Saghar Barati, Alireza Dastan; All authors reviewed the results and approved the final version of the manuscript. All authors agreed to be responsible for all aspects of the work to ensure the accuracy and integrity of the published manuscript.

Data availability

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

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