Clinical Evaluation of Umifenovir as a Potential Antiviral Therapy for COVID-19: A Multi-center, Randomized, Controlled Clinical Trial

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Abstract

Objectives: To evaluate the efficacy and safety of umifenovir as a potential antiviral therapy for COVID-19. This study aims to determine whether umifenovir can improve clinical outcomes, reduce hospitalization duration, and enhance recovery rates in patients diagnosed with COVID-19 compared to standard care.

Methods: A multicenter, open-label, randomized controlled trial was conducted involving 260 patients diagnosed with COVID-19. Participants were randomly assigned to receive either umifenovir (200 mg every six hours for seven days) or standard care. The primary outcome was clinical improvement assessed via the New Early Warning Signs 2 (NEWS-2) scoring system, while secondary outcomes included changes in CT scan scores, length of hospital stay, intensive care unit (ICU) admission rates, and mortality.

Results: Of the 260 enrolled patients, 193 completed the study. Both groups showed significant reductions in clinical symptoms, but myalgia was more prevalent in the umifenovir group. The intervention group demonstrated a significant decrease in CT scan scores; however, there were no significant differences in hospital stay duration, ICU admissions, or mortality rates between groups.

Conclusions: While umifenovir exhibited some immunological benefits in COVID-19 patients, it did not significantly improve broader patient-important outcomes compared to standard care. Therefore, its use in clinical practice for COVID-19 treatment is currently not justified, highlighting the need for further research to explore alternative therapeutic strategies.

Keywords: COVID-19; Umifenovir; Efficacy; Clinical Trial.

Introduction

A novel virus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is responsible for the infectious respiratory illness known as coronavirus disease 2019 (COVID-19). This virus has led to a global pandemic, resulting in over 5 million deaths.[1,2]

Evidence-based therapeutic modalities for COVID-19 management are currently insufficient.[3] Antiviral medications can mitigate the severity of the disease and its complications in individuals infected with SARS-CoV-2.[4] Recent efforts to prevent and treat SARS-CoV-2 have focused on various vaccines, immunotherapies, and pharmacological alternatives.[5]

Studies indicate that oral antiviral medications for patients at moderate to high risk of the disease may reduce hospitalization rates or prevent progression to severe forms, which is critical for healthcare systems during a pandemic.[6,7]

Although the precise cause of COVID-19 remains unknown, the spike protein of the virus binds to the angiotensin-converting enzyme 2 (ACE2) in the lower airways to facilitate entry into alveolar cells.[8,9] In older adults with acute COVID-19, dendritic cell (DC)-induced T-cell activation is delayed, and CD4+ and CD8+ T-cells exhibit a reduced capacity to produce gamma interferon (IFN-γ) and interleukin 2 (IL-2).[8] This impairment may hinder the effectiveness of the adaptive immune response. Suboptimal T-cell activation during SARS-CoV-2 infection is attributed to a decrease in DC populations in the lungs of older patients with severe disease, warranting further investigation.[8]

Umifenovir has demonstrated immunomodulatory properties and has been studied in vitro, in animal models, and in human subjects. Evidence suggests that it positively influences non-specific immune defense mechanisms, stimulates interferon production, and activates phagocytes. Immunological markers such as elevated blood immunoglobulin levels, increased B lymphocyte counts, and enhanced CD4+ and CD8+ cell counts improve in patients treated with umifenovir for viral respiratory tract infections characterized by reduced baseline immunity.[10]

Based on these findings, we propose that umifenovir may serve as a viable treatment option for SARS-CoV-2. Consequently, we conducted this multicenter, open-label, randomized controlled trial to evaluate the efficacy and safety of umifenovir in treating COVID-19 patients.

Methods

This investigation was conducted as a multicenter, controlled, open-label, parallel two-arm phase 3 randomized, clinical trial (RCT). It included 260 patients diagnosed with COVID-19 through RT-PCR and/or chest CT scan who provided informed consent for participation.

The research was conducted at Baqiyatallah Hospital (Baqiyatallah University of Medical Sciences (BMSU)) and Sina Hospital (Tehran University of Medical Sciences (TUMS)) in Tehran, Iran, from April 2020 to March 2021.

The ethics committee of BMSU approved this clinical trial (ethics committee code: IR.BMSU.REC.1399.037). Additionally, this study was registered with the Iranian Registry of Clinical Trials (IRCT20080901001165N46).

Eligible patients were randomly assigned to either the intervention or control group. The intervention group received an oral Umifenovir (Arbidol®) capsule at a dosage of 200 mg every six hours for seven days. Both groups received standard care per national recommendations for treating novel coronaviruses at that time; this included favipiravir based on the moderate severity of eligible individuals.

Inclusion criteria were as follows: 1)Age greater than 18 years; 2) At least one clinical symptom associated with COVID-19: cough, fever over 37.5°C, shortness of breath, weakness, myalgia, arthralgia, diarrhea, nausea, or vomiting; 3) Confirmed diagnosis of COVID-19 via laboratory RT-PCR; 4) Confirmed diagnosis of COVID-19 pneumonia via lung CT scan indicative of pulmonary involvement; 5) Peripheral oxygen saturation in ambient air at rest below 93%; 6) Duration of symptom presentation and research participation less than ten days; 7) Written informed consent provided.

Exclusion criteria included: 1) Concurrent use of other medications with direct or potential antiviral activity against SARS-CoV-2; 2) Participation in any other clinical study involving investigational treatments for COVID-19; 3) Pregnancy or nursing.; 4) Previous hypersensitivity reaction to umifenovir; 5) Respiratory failure necessitating intubation or presence of shock state/multi-organ dysfunction at baseline; 6) Medical history including congenital heart disease, congestive heart failure, coronary artery disease, severe heart rhythm disorders, epilepsy, stroke, mental retardation, or spinal cord injury; 7) Immunodeficiency conditions such as organ transplants or HIV status.

Demographic information along with medical history and clinical symptoms were recorded using a data collection form at participation onset.

Vital signs (blood pressure (BP), respiratory rate (RR), heart rate (HR), O2 saturation (SpO2)) and laboratory findings (complete blood count (CBC), hemoglobin (Hgb), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), creatinine (Cr), urea) were collected at baseline and on day seven for all patients.

The New Early Warning Signs 2 (NEWS-2) score, length of hospital stays, need for transfer to the Intensive Care Unit (ICU), and patient status during hospitalization were recorded. Chest CT scans were performed at baseline and day fourteen; scores were estimated.

Participants were randomly assigned 1:1 to either the umifenovir group or control group using a four-block design via www.sealedenvelope.com. This method reduced selection bias and ensured balanced representation across treatment arms.

NEWS-2 score identifies patients at risk of clinical deterioration through measurements including RR, SpO2, supplementary oxygen requirements, systolic BP (SBP), HR, body temperature (T), and alert-verbal-pain-unresponsive (AVPU) ratings.

The AVPU score was calculated based on GCS values: A ranges from 14 to 15; V from 9 to 13; P from 4 to 8; U has a value of 3. Scores between 0 and 4 indicate low risk; scores of 5 or 6 indicate medium risk; scores of 7 or more indicate high risk.[11]

A semi-quantitative assessment for pulmonary involvement in COVID-19 pneumonia was established using a visual score ranging from 0 to 5 assigned to each lung lobe; total scores ranged from 0 to 25.[12]

The primary outcome was clinical improvement assessed via the NEWS-2 scoring system following World Health Organization (WHO) recommendations.

Secondary outcomes included changes in chest CT scan scores, duration of hospitalization, need for ICU transfer, and mortality rates.

Normality distribution was examined using Shapiro-Wilk testing. Continuous variables were reported as mean ± standard deviation (SD), while categorical features with normal distribution were presented as percentages (%). Interquartile range (IQR) and median values reported non-normally distributed continuous data. Chi-square tests and Fisher's exact tests compared categorical data; Mann-Whitney U tests compared non-normally distributed continuous variables. Statistical analysis utilized SPSS software version 21; significance was set at P-values less than 0.05.

Results

Of the initial cohort of 314 patients with positive RT-PCR results confirming COVID-19 pneumonia via chest CT scan enrolled in the trial; ultimately, 67 patients were excluded due to non-compliance or loss to follow-up. Of the remaining participants who completed the trial—193 patients—98 belonged to the control group while 95 were in the intervention group (Figure 1). The mean age was 56.24±14.86 years; males constituted 54.4% of participants. Except for age—significantly higher in the intervention group (P=0.008) but not clinically significant—demographics and medical histories showed no statistically significant differences between groups at baseline (Table 1).

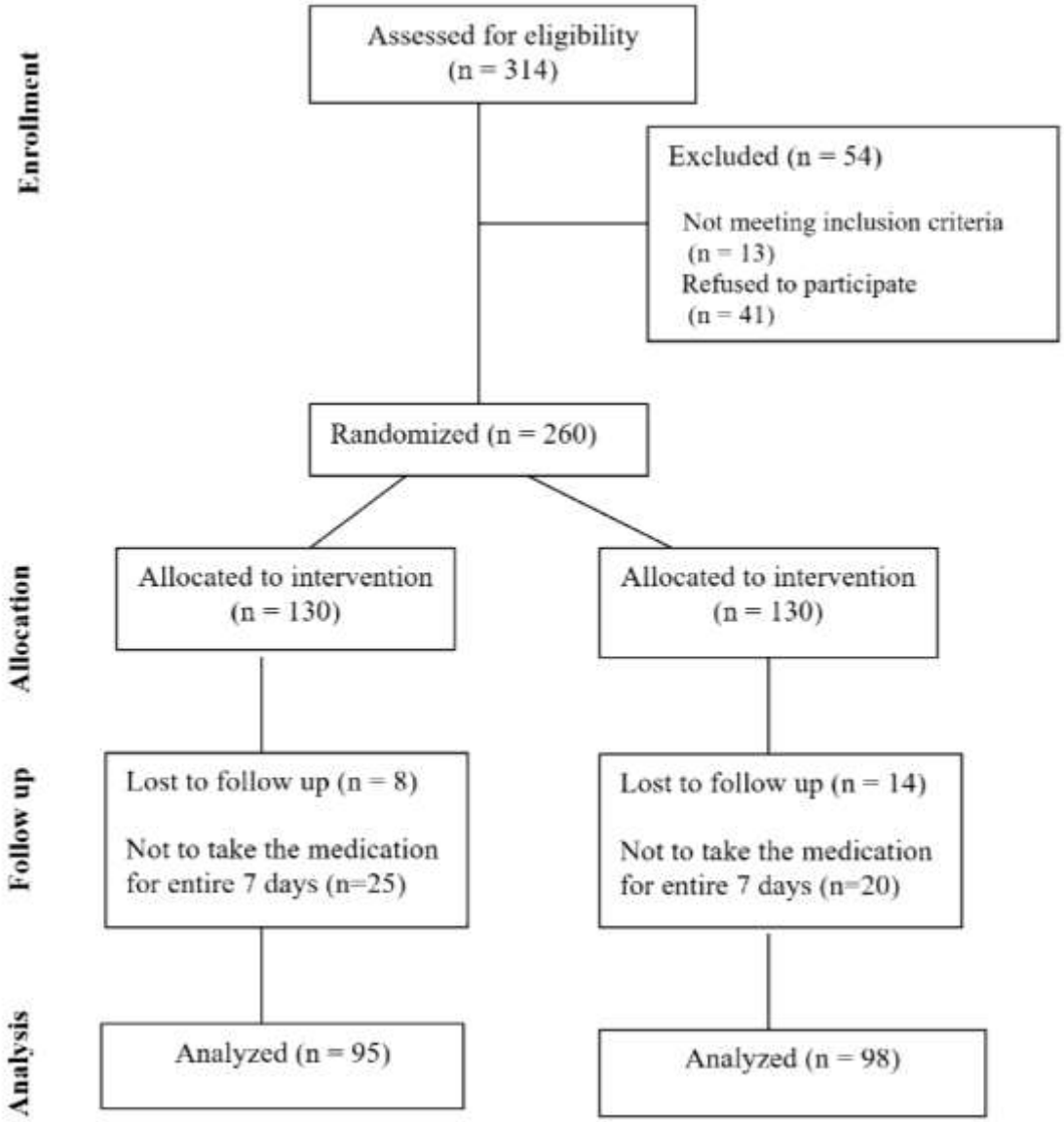

Figure 1: Trial flowchart diagram.

Table 1: Comparison of demographic information, symptoms, and characteristics between two study groups.

Characteristic	**Control N = 98 n (%)**	**Intervention N = 98 n (%)**	***P*-value**
Demographic information			
Age (year), mean±SD	58.97±13.91	53.39±14.99	0.08
Male sex	51 (52.04)	54 (56.84)	0.56
BMI (kg/m2), mean±SD	27.30±6.79	27.62±4.63	0.69
Past medical and habitual history			
smoking	7 (7.14)	6 (6.32)	1
Diabetes Mellitus	20 (20.41)	22 (23.16)	0.72
Hypertension	23 (23.47)	28 (29.47)	0.41
Chronic kidney disease	7 (7.14)	9 (9.47)	0.6
Ischemic heart disease	15 (15.31)	10 (10.64)	0.39
Malignancy	2 (2.04)	1 (1.05)	1
Asthma	5 (5.1)	1 (1.05)	0.21

COPD	2 (2.04)	1 (1.05)	1
Symptoms			
Fever (Temperature >38)	51 (52.04)	40 (42.11)	0.19
Chills	46 (46.94)	46 (48.42)	0.88
Dyspnea	54 (55.1)	53 (51.68)	0.88
Chest pain	28 (28.57)	24 (25.53)	0.74
Cough	55 (56.12)	59 (62.11)	0.46
Myalgia	43 (43.88)	56 (58.95)	**0.04**
Weakness	36 (36.73)	43 (45.26)	0.24

Abbreviation: BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease; P-value>0.05 were considered as statistically significant.

At baseline, no significant differences existed between groups regarding clinical symptoms such as fever, chills, dyspnea, chest pain, or weakness (P>0.05), except myalgia which was significantly greater in the intervention group initially (Table 2). Both groups exhibited substantial reductions in clinical symptoms by study end; however, no statistically significant differences emerged regarding symptom reduction magnitude between groups.

Table 2: Comparison of vital signs, laboratory findings, and scores at the baseline and after the intervention between two groups of study.

Parameter	**Baseline**		**Post-intervention changes (Δ)**		***P*-value*,⁑**
	Control (N = 98) mean±SD	**Intervention (N = 95) mean±SD**	**Control (N = 98) mean±SD**	**Intervention (N = 95) mean±SD**	
SBP (mmHg)	127.92±16.46	130.45±17.91	-4.82±14.82	-3.72±15.52	0.615
DBP (mmHg)	81.37±10.78	81.76± 11.85	-1.45±9.34	-1.57±12.20	0.938
HR (beats/minute	96.54±13.42	93.97±13.68	-10.22±15.05	-8.73±13.96	0.477
RR (beats/minute)	17.55±2.91	18.76±3.95	-3.79±3.67	-2.66±2.47	**0.01**
SpO2 (%)	92.74±2.67	91.53± 4.25	1.19±3.43	2.42±4.18	**0.026**
Laboratory findings					
WBC count (×1000)	8.81±6.85	7.69±3.69	-1.27±4.84	0.66±4.13	**0.003**
Neutrophil count (×1000)	80.79±8.7	77.6±11.03	-11.97±14.73	-8.91±15.97	0.168
Lymphocyte count (×1000)	7.47±4.01	12.80±8.37	16.17±11.36	10.35±13.42	**0.0013**
Hgb (g/dl)	13.39±2.33	13.82±1.85	-1.24±1.68	-0.9±1.35	0.114
Platelet count (×1000)	212.32±81.18	216.56±85.35	44.54±95.07	46.63±93.45	0.87
ESR (mm/hr)	35.10±23.95	40.69±31.35	-17.01±22.57	-11.46±28.27	0.1331
CRP (mg/dl)	35.56±40.98	36.62±43.53	-20.97±33.70	-12.37±24.75	**0.045**
Cr (mg/dL)	1.37±1.25	1.24±0.66	-0.184±1.15	-0.45±0.4	0.274
Urea (mg/dL)	40.07±33.22	28.54±31.06	-11.94±23.10	3.20±20.92	**0.000**
Scores changes					
CT-scan score control: N = 68 intervention: N = 63	9.71±4.62	8.94±5.91	-4.14±3.75	-2.18±4.40	**0.001**
NEWS2 score	5.22±2.63	4.77±2.05	-2.48±3.56	-2.88±2.23	0.359

*Abbreviation: Δ: mean2-mean2; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; RR: respiratory rate; SpO2: oxygen saturation; WBC: white blood cell; Hgb: hemoglobin; ESR: estimated sedimentation rate; CRP: C-reactive protein; NEWS2 score: new early warning signs 2 score; *P-value>0.05 were considered as statistically significant.; ⁑ The p-value is related to the significant comparison of changes after the intervention in two groups.*

Baseline vital signs revealed no significant differences between groups except for a higher respiratory rate in the intervention group and higher SpO2 in controls—both clinically insignificant differences (Table 2).

Significant differences emerged post-trial regarding changes in WBC counts (P=0.003), lymphocytes (P=0.001), CRP (P=0.045), RR (P=0.01), and SpO2 (P=0.026) between groups while other variable changes remained statistically equal.

Post-intervention CT scan scores decreased significantly within each group compared to pre-intervention scores (4.14±3.75 vs 2.18±4.4 for controls; 2.48±3.56 vs 2.88±2.23 for intervention), with statistically significant reductions noted in CT scan scores among intervention participants compared to controls (P=0.001). However, no significant difference appeared regarding NEWS-2 score reductions between groups (P=0.359). Lengths of hospital stay (P=0.28), ICU admission requirements (P=1), and mortality rates (P=0.873) showed no significant differences between groups (Table 3). No expected umifenovir side effects occurred within the intervention cohort.

Table 3: Comparison of changes in secondary outcomes at the end of the study between the two groups.

Parameter	Control (N = 98)	Intervention (N = 95)	*P*-value*
Mortality, no (%)	7 (7.14)	8 (8.42)	0.873
length of hospital admission day mean ± SD	6.37 ± 3.60	6.95 ± 3.87	0.284
Need for ICU admission, no (%)	13 (13.26)	12 (12.63)	1

**P-value>0.05 were considered as statistically significant.*

Discussion

The study evaluated the efficacy of umifenovir in treating COVID-19 by analyzing 193 patients who completed the treatment. The baseline characteristics revealed no significant differences between the intervention and control groups, except for RR and oxygen SpO2. Both groups showed a significant reduction in clinical symptoms by the end of the study, although myalgia was initially more prevalent in the intervention group. The intervention group also demonstrated a statistically significant decrease in CT scan scores. However, there were no notable differences in hospital stay duration, ICU admission rates, or mortality rates between the two groups.

Umifenovir has been shown to be effective against influenza in some Russian studies but lacks approval in many other countries, including the United States, where the FDA has not sanctioned it for influenza treatment or prevention.[10] Besides its antiviral properties against influenza A and B, umifenovir also exerts regulatory effects on the immune system by stimulating humoral immunity, interferon production, and macrophage xenophagy.[13]

A 2015 study conducted in Russia compared oseltamivir and umifenovir for influenza treatment, revealing similar mortality reduction rates. Umifenovir's advantage lies in its effectiveness against neuraminidase inhibitor-resistant viral strains due to its distinct mechanism of action.[14]

In a retrospective cohort study assessing umifenovir's impact on COVID-19 patients, those receiving a combination of oral umifenovir and lopinavir/ritonavir showed improved chest CT scans after seven days compared to those on monotherapy.[15] A systematic review by Huang et al. found that umifenovir significantly reduced viral load and length of hospital stay while being safe regarding side effects; however, it did not lower mortality rates. In contrast, the current study did not find statistically significant reductions in hospital stay length or mortality.[16]

The clinical efficacy of umifenovir remains uncertain due to a lack of large-scale RCTs. Some smaller studies have produced conflicting results; for instance, Wang et al. suggested that umifenovir improved discharge rates and reduced mortality, which was not observed in our findings.[17] Conversely, Huang et al. concluded that umifenovir treatment did not lead to better outcomes.[18]

Reports indicate that umifenovir is not superior to conventional supportive therapies regarding radiological improvement or clinical recovery rates. While our study noted a significant reduction in CT scan scores for patients taking umifenovir, there was no corresponding difference in clinical improvement or cure rates between groups.[16]

Chen's research also indicated that umifenovir does not shorten hospitalization time, consistent with our results.[18]

Additionally, another study found that levels of CRP, LDH, and D-dimer decreased after treatment with umifenovir in patients who improved but remained unchanged or increased in those who did not improve.[19] This

suggests that these markers may correlate with disease severity and progression. In our study, WBC count, lymphocyte count, and CRP levels significantly decreased in the intervention group.

Overall, considering the results—especially those related to patient-important outcomes—there is currently insufficient justification for using umifenovir in COVID-19 patients. Limitations of this study include a small sample size and the absence of conditions necessary for conducting a double-masked design. Variability in patients' time spent at the hospital also poses another limitation.

Conclusion

While umifenovir may show some efficacy against COVID-19 through improvements in certain immunological markers among treated participants, the overall findings suggest limited utility concerning broader patient-important outcomes. Further investigation into long-term implications is warranted for therapies targeting similar patient cohorts experiencing varying degrees of severity related to COVID-19.

Disclosure

The authors declare that there is no conflict of interest regarding this publication. Part of the study, which was run at Sina Hospital, was funded by the Tehran University of Medical Sciences, grant number 99-1-104-47199.

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