Received: 4 July 2021 | Accepted: 9 July 2021

DOI: 10.1002/jmv.27195

RESEARCH ARTICLE

JOURNAL OF MEDICAL VIROLOGY WILEY

Comparing the effectiveness of Atazanavir/Ritonavir/Dolutegravir/Hydroxychloroquine and Lopinavir/Ritonavir/Hydroxychloroquine treatment regimens in COVID-19 patients

Saeed Kalantari[1,2] | Soheil R. Fard[1] | Donya Maleki[1,2] | Mahshid T. Taher[1,2] | Zeynab Yassin[1,2] | Yousef Alimohamadi[3] | Sara Minaeian[1]

[1]Antimicrobial Resistance Research Center, Institute of Immunology and Infectious Diseases, Iran University of Medical Sciences, Tehran, Iran

[2]Department of Infectious Diseases, School of Medicine, Iran University of Medical Sciences, Tehran, Iran

[3]Pars Advanced and Minimally Invasive Medical Manners Research Center, Pars Hospital, Iran University of Medical Sciences, Tehran, Iran

Correspondence

Sara Minaeian and Donya Maleki, Antimicrobial Resistance Research Center, Institute of Immunology and Infectious Diseases, Floor 3, Bldg no. 3, Hazrat-e Rasool General Hospital, Niyayesh St, Sattar Khan St, 1445613131 Tehran, Iran.
Email: sara.minaeian@gmail.com; minaeian.s@iums.ac.ir (S. M.) and dmaleki56@yahoo.com (D. M.)

Funding information

Iran University of Medical Sciences: 17671

Abstract

The purpose of this study was to compare the effectiveness of Atazanavir/Ritonavir/Dolutegravir/Hydroxychloroquine and Lopinavir/Ritonavir/Hydroxychloroquine treatment regimens in COVID-19 patients based on clinical and laboratory parameters. We prospectively evaluated the clinical and laboratory outcomes of 62 moderate to severe COVID-19 patients during a 10-day treatment plan. Patients were randomly assigned to either KH (receiving Lopinavir/Ritonavir [Kaletra] plus Hydroxychloroquine) or ADH (receiving Atazanavir/Ritonavir, Dolutegravir, and Hydroxychloroquine) groups. During this period, clinical and laboratory parameters and outcomes such as intensive care unit (ICU) admission or mortality rate were recorded. Compared to the KH group, after the treatment period, patients in the ADH group had higher activated partial thromboplastin time (aPTT) (12, [95% confidence interval [CI]: 6.97, 17.06), $p = <0.01$), international normalized ratio (INR) (0.17, [95% CI: 0.07, 0.27), $p = <0.01$) and lower C-reactive protein (CRP) (−14.29, (95% CI: −26.87, −1.71), $p = 0.03$) and potassium (−0.53, (95% CI: −1.03, −0.03), $p = 0.04$) values. Moreover, a higher number of patients in the KH group needed invasive ventilation (6 (20%) vs. 1 (3.1%), $p = 0.05$) and antibiotic administration (27 (90%) vs. 21(65.6), $p = 0.02$) during hospitalization while patients in the ADH group needed more corticosteroid administration (9 (28.1%) vs. 2 (6.7%), $p = 0.03$). There was no difference in mortality rate, ICU admission rate, and hospitalization period between the study groups. Our results suggest that the Atazanavir/Dolutegravir treatment regimen may result in a less severe disease course compared to the Lopinavir/Ritonavir treatment regimen and can be considered as an alternative treatment option beside standard care. However, to confirm our results, larger-scale studies are recommended.

KEYWORDS

Atazanavir, COVID-19, Dolutegravir, Hydroxychloroquine, Lopinavir, Ritonavir

1 | INTRODUCTION

More than a year after its emergence, the COVID-19 pandemic is still raging around the world and shows no signs of stopping. The disease that first emerged from Wuhan, China in December 2019,[1] has now infected more than 100 million people and caused more than two million deaths.[2]

Based on the disease characteristics and virus lineage, the first worldwide line of treatment was considered to be the drugs that had shown positive outcomes in the treatment of similar conditions like severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS); drugs such as Ribavirin, Interferon, Lopinavir/Ritonavir, and Arbidol.[3–7] Unfortunately, these drugs were not quite successful in lowering the mortality rate of COVID-19, thus genomic characterization of the virus initiated an international effort to find a cure for the disease.[8]

The virus responsible for the disease, first named 2019-nCOV and later officially designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a member of Coronaviridae family of viruses. SARS-CoV-2 is the seventh coronavirus strain that has been associated with human diseases including common cold (HCoV-229E, HCoV-HKU1, and HCoV-OC43), respiratory tract infections and bronchitis (HCoV-NL63), SARS (SARS-CoV), and MERS (MERS-CoV).[9–13]

SARS-CoV-2 contains four different structural proteins: Envelope (E) protein that facilitates virus assembly and budding, Membrane (M) that is associated with maturity and the final form of the virus, Nucleocapsid (N) which is involved in virus assembly by binding to RNA and Spike (S) that is responsible for virus entry to the host cell via the angiotensin-converting enzyme 2 (ACE2) receptor and is vital to its infectivity.[14–16] After cell entry, the viral genome will be translated into two major polypeptide chains and subsequently truncated into 16 nonstructural proteins (nsp1–nsp16) by viral proteases such as coronaviral principal protease (3CLpro) and papain-like protease (PLpro). These proteins are responsible for virus production and assembly.[17–19]

One of the more common treatment regimens for COVID-19 is Lopinavir/Ritonavir that is generally used in human immunodeficiency virus (HIV) treatment. Lopinavir is an aspartate protease inhibitor for HIV-1 and has the ability to inhibit 3CLpro activity, a major enzyme in viral replication, and Ritonavir is responsible for extending Lopinavir half-life in plasma via inhibiting cytochrome p450.[20,21] There is also evidence regarding their effectiveness against SARS-CoV and MERS-CoV.[4,22] Using Ritonavir/Lopinavir for COVID-19 has resulted in contradicting outcomes in different studies,[23–25] thus like many other treatment options, Lopinavir/Ritonavir cannot be considered as a definitive treatment for COVID-19.

Atazanavir is another HIV/AIDS targeting drug that is seeing more and more use as a COVID-19 treatment option. It is one of the 10 Food and Drug Administration-approved protease inhibitors of HIV and can effectively reduce HIV viral load to undetectable levels.[26] Bioinformatics studies show that this drug might be able to inhibit vital SARS-CoV-2 enzymes such as helicase and 3CLpro[27,28] thus making it a viable treatment candidate for COVID-19.

Dolutegravir, like previously mentioned drugs, is primarily used in HIV treatment. This relatively new drug is an integrase strand transfer inhibitor (INSTI) and is able to prevent the integration process of viral DNA into the host genome.[29] Recent findings suggest that Dolutegravir is capable of inhibiting SARS-CoV-2's 3CLpro protease by binding to the enzyme active sites.[27]

Additionally, there are studies suggesting that people with HIV that also contracted COVID-19, may have favorable outcomes[30] or suffer from less severe hypoxemia[31] compared to the general population. These results in addition to in silico and *in vitro* effects of anti-retroviral drugs such as atazanavir or dolutegravir suggest that these drugs might have the ability to manage or treat the COVID-19 infection.

Thus, as current treatment options are clearly not efficient in lowering the COVID-19 mortality rate, to examine these new treatment candidates, in this study we compared the effects of the national treatment regimen (Lopinavir/Ritonavir plus hydroxychloroquine) with a treatment regimen consisting of Atazanavir/Ritonavir/Dolutegravir plus hydroxychloroquine.

2 | MATERIALS AND METHODS

2.1 | Ethics statement

This study was reviewed and approved by scientific advisory and ethical committees of the Iran University of medical sciences (Registration number: IR.IUMS.REC.1399.1149) and before signing written informed consent forms, all patients were given a complete explanation about the study procedures and protocol.

2.2 | Study population

All the subjects for this study were selected among patients who were referred to the Rasool-e-Akram general teaching hospital with COVID-19 symptoms between January 30 and February 14, 2021. Selected patients had confirmed moderate to severe COVID-19 infection and needed hospitalization.

COVID-19 disease confirmation was in accordance with published national guidelines with criteria consisting of three or more of the following conditions: (1) cough, (2) weakness, (3) fever of ≥38.5°C, (4) intense fatigue, (5) myalgia, (6) sore throat, (7) dyspnea, (8) low appetite/Diarrhea/nausea, and (9) decreased awareness. Additionally, COVID-19 would also be confirmed if the patient had one or more of the following disease characteristics: (1) oxygen saturation value of less than 93%, (2) disease confirmation based on chest imaging results, and (3) a respiratory rate greater than 24 breaths per minute.

After clinical confirmation, nasopharyngeal swab samples were collected and SARS-CoV-2 specific reverse-transcriptase polymerase

TABLE 1 Baseline characteristics, comorbidities, and admission symptoms of patients

	KH	ADH	*p* value
Age, mean ± SD	58.77 ± 19.49	57.00 ± 17.10	0.70
Gender (male), *n* (%)	12 (40)	16 (50)	0.43
Days with symptom before admission, mean ± SD	6.90 ± 3.58	6.72 ± 4.74	0.87
Vital signs, mean ± SD			
Temperature	37.00 ± 0.68	37.08 ± 0.68	0.68
Heart rate	94.96 ± 9.99	89.89 ± 9.35	0.06
Respiratory rate	28.36 ± 24.98	20.50 ± 2.94	0.12
Bp-S	117.67 ± 15.6-9	119.67 ± 26.1-6	0.72
Bp-D	71.67 ± 11.09	71.77 ± 8.97	0.97
SpO_2	89.03 ± 6.59	89.31 ± 6.38	0.87
GCS	17.00 ± 14.40	14.47 ± 1.32	0.33
Admission criteria, *n* (%)			
Fever (≥38.5°C)	16 (55.2)	18 (60)	0.71
Cough	26 (86.7)	27 (87.1)	0.96
Dyspnea/tachypnea	25 (83.3)	20 (69)	0.19
ARI possibility	0 (0)	4 (14.8)	0.05
History of diseases, *n* (%)			
Chronic cardiac disease	6 (21.4)	6 (19.4)	0.84
Hypertension	7 (24.1)	11 (34.4)	0.38
Chronic pulmonary disease	1 (3.4)	2 (6.5)	1
Asthma	3 (10.3)	1 (3.2)	0.35
Chronic kidney disease	0 (0)	2 (6.5)	0.49
Chronic liver disease	0 (0)	1 (3.2)	1
Diabetes	11 (37.9)	9 (28.1)	0.41
Chronic neurological disorder	3 (10.3)	1 (3.2)	0.35
Hypothyroid	0 (0)	1 (3.3)	1
History of drugs, *n* (%)			
ACE inhibitors	2 (6.9)	4 (12.5)	0.67
ARBs	0 (0)	2 (6.5)	0.49
NSAIDs	0 (0)	3 (9.7)	0.24
Symptoms during hospitalization, *n* (%)			
Fever	18 (62.1)	19 (59.4)	0.83
Cough with sputum	5 (17.2)	4 (13.3)	0.73
Cough with hemoptysis	2 (6.9)	2 (6.7)	0.73
Sore throat	1 (3.4)	4 (12.5)	0.36
Chest pain	1 (3.4)	2 (6.3)	1
Muscle aches	18 (62.1)	22 (68.8)	0.58
Fatigue/Malaise	17 (58.6)	22 (68.8)	0.41
Inability to walk	6 (20.7)	6 (18.8)	1

(Continues)

TABLE 1 (Continued)

	KH	ADH	*p* value
Headache	5 (17.9)	5 (15.6)	1
Altered consciousness	6 (16.7)	5 (15.6)	0.82
Vomiting/Nausea	7 (25)	8 (25)	1
Conjunctivitis	1 (3.6)	1 (3.1)	1

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; ARI, acute respiratory infection; Bp-S, blood pressure-systolic; Bp-D, blood pressure-diastolic; GCS, Glasgow Coma Scale; NSAIDs, nonsteroidal anti-inflammatory drugs; SpO_2, oxygen saturation.

chain reaction (RT-PCR) tests were performed for all patients. Patients with negative RT-PCR test results were excluded from the study. The discharge criteria during the study were: (1) general improvement in signs and symptoms, (2) SpO_2 greater than 93%, and (3) being consistently afebrile for 48 h without the use of antipyretics.

2.3 | Drug administration

Patients were randomly assigned to two treatment groups and received the designated medications for a period of 10 days: (1) KH group received Kaletra (Lopinavir 400 mg/Ritonavir 100 mg tablets twice a day) and Hydroxychloroquine (400 mg BD on the first day and then 200 mg BD) and (2) ADH group received Atazanavir 300 mg/Ritonavir 100 mg tablet once a day, Dolutegravir 500 mg tablet once a day and Hydroxychloroquine 400 mg BD on the first day and then 200 mg BD).

2.4 | Laboratory analysis

Multiple biochemical parameters were measured both at the time of the admission and discharge using routine methods and commercial kits. These parameters include complete blood count (CBC), creatinine, sodium, potassium, activated partial thromboplastin time (aPTT), prothrombin time (PT), INR, alanine aminotransferase (ALT), aspartate aminotransaminase (AST), creatine kinase, total bilirubin, urea (BUN), lactate dehydrogenase (LDH), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR).

2.5 | Data collection

All demographics, clinical presentations, comorbidities, and drug history were collected from patients. Clinical and laboratory parameters were recorded both at the time of admission and discharge. During hospitalization, additional necessary administered drugs and procedures were also recorded. If patients were stable enough to be discharged before the completion of the 10-day treatment period, their well-being and drug consumption were monitored daily.

2.6 | Statistical analysis

The descriptive statistics such as mean ± standard deviation and simple proportion were used to present continuous and categorical variables respectively. To compare baseline characteristics the Student *t* test or Mann–Whitney *U* test (in non-parametric distribution) and the χ^2 (fisher exact test) test was used for continuous and categorical variables respectively. The pair *t* test or Wilcoxon test was used to assess the treatment effects on different laboratory parameters within groups. To compare treatment efficacy between the two groups by adjusting baseline effects, the analysis of covariance (ANCOVA) test was used. The $\alpha = 0.05$ was considered as a statistically significant level. All statistical analysis was performed using the SPSS 20.0 software (SPSS).

3 | RESULTS

3.1 | Patients and baseline analysis

From January 3 and February 14, 2021, suspected COVID-19 patients referred to Rasool-e-Akram General-Teaching hospital were consecutively screened and eligible patients with laboratory-confirmed COVID-19 were included in this study. Overall, 62 patients entered the study. The mean age ± SD of all patients was 57.85 ± 18.17 and the frequency of females was slightly higher than males (34 (55%) vs. 28 (45%)). One or more comorbidities were present in 37 (59.7%) of patients at the time of admission. During the study, patients were randomly assigned to either KH or ADH treatment groups. As shown in Table 1, baseline characteristics such as age, gender, vital signs, admission symptoms, history of drugs, history of pre-existing conditions, and also symptoms during the hospitalization period, were not significantly different between study groups.

3.2 | Effect of antiviral therapy on laboratory parameters within each group

Comparison between admission and discharge laboratory data revealed that KH treatment resulted in decreased LDH (455.91 ± 123.2 vs. 711.09 ± 155.42, $p = <0.01$) and ESR (25.9 ± 26.17 vs. 54.8 ± 21.06,

TABLE 2 Comparison between admission and discharge laboratory results within treatment groups

	KH (admission)	KH (discharge)	*p* value	ADH (admission)	ADH (discharge)	*p* value
Hb	12.72 ± 1.91	12.46 ± 2.30	0.32	12.58 ± 1.35	12.87 ± 1.73	0.70
WBC	7.79 ± 4.06	7.93 ± 3.58	0.88	8.06 ± 4.37	8.88 ± 4.77	0.26
Hematocrit	37.15 ± 6.02	37.32 ± 5.85	0.87	36.30 ± 6.48	38.28 ± 5.03	0.12
Platelets	195.78 ± 59.88	227.57 ± 120.4-8	0.18	224.08 ± 95.12	290.08 ± 113.03	0.01
APTT	40.95 ± 24.10	31.90 ± 8.79	0.08	38.78 ± 17.19	42.86 ± 20.16	0.47
PT	14.59 ± 1.46	14.53 ± 2.06	0.84	14.94 ± 4.13	14.06 ± 3.50	0.58
INR	1.18 ± 0.171	1.11 ± 0.14	0.12	1.24 ± 0.69	1.16 ± 0.25	0.73
ALT	29.33 ± 15.19	44.25 ± 33.01	0.16	32.73 ± 17.94	45.63 ± 29.70	0.18
Total bilirubin	0.72 ± 0.38	0.66 ± 0.46	0.26	1.07 ± 0.54	1.65 ± 1.16	0.06
AST	37.25 ± 8.45	40.33 ± 28.78	0.75	37.46 ± 13.76	35.46 ± 15.58	0.58
Urea	22.69 ± 21.70	26.46 ± 28.93	0.22	22.54 ± 26.41	30.02 ± 32.64	0.01
Creatinine	1.32 ± 0.57	1.31 ± 0.84	0.07	1.28 ± 0.90	1.25 ± 0.72	0.43
Sodium	138.11 ± 4.09	138.14 ± 4.81	0.98	137.44 ± 3.15	138.35 ± 2.72	0.32
Potassium	4.49 ± 0.68	4.51 ± 0.79	0.94	4.33 ± 0.61	4.02 ± 0.97	0.30
CRP	44.73 ± 10.85	31.64 ± 19.37	0.07	43.88 ± 9.50	16.88 ± 14.27	<0.01
LDH	711.09 ± 155.4-2	455.91 ± 123.2-0	<0.01	709.13 ± 337.71	418.13 ± 137.21	<0.01
CK	169.50 ± 143.6-5	127.00 ± 147.5-9	0.33	175.12 ± 178.95	64.23 ± 46.97	<0.01
ESR	54.80 ± 21.06	25.90 ± 26.17	0.01	54.41 ± 27.57	39.82 ± 28.64	0.03
SpO_2	88.26 ± 6.48	94.04 ± 6.29	<0.01	89.06 ± 6.33	93.10 ± 6.32	<0.01

Abbreviations: aPTT, activated partial thromboplastin time; ALT, alanine Transaminase; AST, aspartate aminotransferase; CK, creatine kinase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; INR, international normalized ratio; LDH, lactate dehydrogenase; PT, prothrombin time; SpO_2, oxygen saturation; WBC, white blood cells.

$p = 0.01$) and ADH treatment resulted in increased platelet count (290.08 ± 113.03 vs. 224.08 ± 95.12, $p = 0.01$), urea (30.02 ± 32.64 vs. 22.54 ± 26.41, $p = 0.01$) and decreased CRP (16.88 ± 14.27 vs. 43.88 ± 9.50, $p < 0.01$), LDH (418.13 ± 137.21 vs. 709.13 ± 337.71, $p < 0.01$), creatine kinase (64.23 ± 46.97 vs. 175.12 ± 178.95, $p = <0.01$) and ESR (39.82 ± 28.64 vs. 54.41 ± 27.57, $p = 0.03$) (Table 2).

Furthermore, O_2 saturation on discharge was significantly improved in both KH and ADH groups compared to values at admission date (94.05 vs. 88.26, $p < 0.01$ and 93.1 vs. 89.06, $p < 0.01$) although ANCOVA analysis showed no differences between the treatment groups (−1.489, (95% CI: −3.92, 0.941) $p = 0.22$) (Table 3).

3.3 | Laboratory parameter differences between study groups

ANCOVA analysis of the admission and discharge laboratory data (Table 3) revealed that compared to KH treatment, ADH treatment resulted in a slightly elevated aPTT (mean difference: 12 [95% CI, 6.97, 17.06], $p = <0.01$) and INR (mean difference: 0.17 [95% CI, 0.07, 0.27], $p < 0.01$) values and decreased CRP (mean difference: −14.29 [95% CI, −26.87, −1.71], $p = 0.03$) and potassium (mean difference: −0.53 [95% CI, −1.03, −0.03], $p = 0.04$) values.

Additionally, compared to the KH group, we observed that ADH treated patients generally had higher platelets count (mean difference: 59.80 [95% CI, −3.10, 122.70], $p = 0.06$) and lower creatine kinase values (mean difference: −64.46 [95% CI, −132.18, 3.25], $p = 0.06$), although these differences did not reach statistical significance.

3.4 | Outcome and supplementary treatment differences between study groups

During the hospitalization period, additional required treatment and procedures were recorded. Comparing the data from both treatment groups showed that a higher number of patients in the KH group

TABLE 3 ANCOVA analysis of treatment efficacy between ADH and KH treatment groups regarding the laboratory parameters from before and after the treatment period

	Mean difference (ADH–KH)–CI 95%	*F*	*p* value	Partial eta squared
Hb	0.26 (95% CI: −0.57, 1.1)	0.48	0.50	0.04
WBC	0.77 (95% CI: −0.99, 2.54)	0.77	0.38	0.01
Hematocrit	1.27 (95% CI: −1.43, 4.01)	0.87	0.35	0.02
Platelets	59.80 (95% CI: −3.10, 122.70)	6.97	0.06	0.63
aPTT	12 (95% CI: 6.97, 17.06)	30.1-5	<0.01	0.79
PT	−0.14 (95% CI: −2.01, 1.73)	0.02	0.88	0.001
INR	0.17 (95% CI: 0.07, 0.27)	12.6-4	<0.01	0.36
ALT	−0.02 (95% CI: −21.62, 21.57)	0.00-0	1	0.001
Total bilirubin	0.64 (95% CI: −0.1, 1.39)	3.2	0.09	0.12
AST	−4.88 (95% CI: −19.63, 9.87)	0.45	0.51	0.01
Urea	3.70 (95% CI: −8.97, 16.36)	0.34	0.56	0.01
Creatinine	−0.02 (95% CI: −0.34, 0.30)	0.02	0.90	.0001
Sodium	−10.28 (95% CI: −24.86, 4.30)	2.00	0.16	0.04
Potassium	−0.53 (95% CI: −1.03, −0.03)	4.54	0.04	0.09
CRP	−14.29 (95% CI: −26.87, −1.71)	5.47	0.03	0.18
LDH	−37.70 (95% CI: −138.36, 62.95)	0.58	0.45	0.02
CK	−64.46 (95% CI: −132.18, 3.25)	3.9	0.06	0.15
ESR	14.10 (95% CI: −5.80, 34.00)	2.10	0.16	0.07
SpO_2	−1.489 (95% CI: −3.92, 0.941)	1.51	0.22	0.03

Abbreviations: ALT, alanine transaminase; ANOVA, analysis of variance; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CK, creatine kinase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; INR, international normalized ratio, LDH, lactate dehydrogenase; PT, prothrombin time; SpO_2, oxygen saturation; WBC, white blood cells.

required invasive ventilation (6 (20%) vs. 1 (3.1%), $p = 0.05$) and antibiotic administration (27 (90%) vs. 21 (65.6), $p = 0.02$), while more patients in the ADH group required corticosteroid administration (9 (28.1%) vs. 2 (6.7%), $p = 0.03$). However, the mortality rate (6 (20%) vs. 3 (9.4%) for KH and ADH groups respectively, $p = 0.20$), ICU admission rate (9 (30%) vs. 4 (12.5%), $p = 0.09$), and hospitalization period (7.1 ± 6.44 vs. 7.19 ± 4.63, $p = 0.95$) were not significantly different between the two treatment groups (Table 4).

4 | DISCUSSION

As the infection rate of COVID-19 shows no signs of slowing down and due to its substantial transmission potential, it is quickly becoming one of the deadliest pandemics in modern history with a death toll of more than two million globally.[2]

In the present study, we compared the efficacy of two treatment regimens, Lopinavir/Ritonavir (Kaletra) plus Hydroxychloroquine and Atazanavir/Ritonavir/Dolutegravir plus Hydroxychloroquine, in Covid-19 patients. Our results showed that Atazanavir/Dolutegravir treatment regimen may have a significant advantage over the more common Lopinavir/Ritonavir regimen in the treatment of COVID-19 as patients in the ADH group required less aggressive or supplementary treatments and had more favorable laboratory test results at discharge date.

From the beginning of the pandemic, several drugs have been in the center of attention as a possible cure for COVID-19 including, Hydroxychloroquine, Remdesivir, Lopinavir/Ritonavir, Ribavirin, Intravenous immunoglobulin (IVIG), Interferon, etc.[32] Unfortunately, despite the efforts, no definitive cure has been identified to date.

One of the more common treatment options is Lopinavir/Ritonavir (Kaletra), a well-known protease inhibitor that is primarily used in HIV treatment. Computerized models revealed that Lopinavir/Ritonavir is able to effectively inhibit the SARS-CoV-1 and SARS-CoV-2 protease (3CLpro).[33,34] Translating these computerized models into *in-vitro* and *in-vivo* studies showed that Lopinavir/Ritonavir is able to inhibit SARS-CoV-1 and MERS-CoV replication and cytopathic effects in fRhK4, Vero-E6, and Huh7 cells[21,35] and improved the

TABLE 4 Comparing outcome and supplementary treatment procedures between two groups

	KH	ADH	*p* value
Intravenous fluids	24 (82.8)	23 (74.2)	0.42
ACE inhibitors	1 (3.4)	6 (20.7)	0.10
IVIG	3 (10.3)	3 (10.3)	1
ICU admission	9 (30)	4 (12.5)	0.09
Oxygen therapy	23 (79.3)	27 (84.4)	0.61
Noninvasive ventilation	5 (17.2)	1 (3.1)	0.09
Invasive ventilation	6 (20)	1 (3.1)	0.05
Inotropes or vasopressors	24 (82.8)	23 (74.2)	0.42
ECMO	2 (6.7)	0 (0)	0.23
Prone position	1 (3.3)	0 (0)	0.48
Additional antiviral drugs	1 (3.3)	2(6.3)	1
Antibiotic	27 (90)	21 (65.6)	0.02
Corticosteroid	2 (6.7)	9 (28.1)	0.03
Plasma freeze	2 (6.7)	0 (0)	0.23
Actemra (Tocilizumab)	0 (0)	2 (6.3)	0.49
Hospitalization period (days)	7.10 ± 6.4-4	7.19 ± 4.6-3	0.95
Death	6 (20)	3 (9.4)	0.29

Abbreviations: ACE, angiotensin-converting enzyme; ECMO, extracorporeal membrane oxygenation; IVIG, intravenous Immunoglobulin.

clinical, radiological and pathological findings in an animal (common marmoset) model of MERS-CoV infection.[22] Based on these results, Lopinavir/Ritonavir was considered as a treatment option in SARS and MERS disease outbreaks and a 400/100 mg dose for a period of 10–14 days proved to be effective in reducing the mortality, intubation, and ARDS development rates in SARS patients and showed a 40% decrease in the infection rates of healthcare workers exposed to patients with severe MERS-CoV infection.[3,4,36]

Reproducing these relatively successful results in the COVID-19 pandemic has proven to be much more challenging as contradicting results are being reported. A case–control study consisting of a treatment group receiving a dose of Lopinavir/Ritonavir (400/200 mg twice daily) and a control group receiving Arbidol and Interferon, reported that Lopinavir/Ritonavir use results in a much more rapid normalization of body temperature and can significantly reduce the number of days required to achieve a negative nCoV-RNA test result.[37]

Another study suggested that Lopinavir/Ritonavir may work better in a combination treatment regimen than monotherapy. The study, compared Lopinavir/Ritonavir monotherapy (400/200 mg twice daily) with Lopinavir/Ritonavir plus Arbidol (200 mg every 8 h) combination treatment and reported that the combination treatment resulted in a higher rate of improvements in chest CT scans after 7 days (69% vs. 29%) and also higher negative RT-PCR results at 7 and 14 days after treatment.[38]

Other studies reported better results from other drugs in comparison to Lopinavir/Ritonavir. Arbidol monotherapy for 7 days (200 mg three times a day) in comparison to Lopinavir/Ritonavir (400/100 mg twice daily) resulted in a much better viral load resolve (0% vs. 44.1%) and a shorter duration of positive RNA test.[39] Also, Favipiravir (1600 mg twice daily) plus interferon-α (5 million U twice daily) compared to Lopinavir/Ritonavir (400/100 mg twice daily) plus interferon-α (5 million U twice daily) showed a better viral clearance (4 (2.5–9) days vs. 11 (8–13) days) and higher resolution in chest abnormalities (91.43% vs. 64.22%).[40]

Another study comparing Lopinavir/Ritonavir (400/100 mg twice daily) with standard care (with no antiviral therapeutic agents) for a duration of 14 days reported that treatment with Lopinavir/Ritonavir had no significant advantages regarding the clinical improvement, mortality rate, and viral RNA clearance of patients.[23]

These results suggest that although Lopinavir/Ritonavir treatment may prove effective in some cases, it cannot be regarded as a reliable or definitive treatment option for COVID-19.

In the present study, although patients in the KH group had a high mortality rate (20%), this might be due to the fact that only moderate and severe COVID-19 patients were included in the study. The remaining patients were all discharged from the hospital and were clinically stable, had obvious signs of disease resolve, and showed improvement in their chest CT scan results. Due to the study design and in the absence of a control group with no antiviral treatment, we cannot confirm or deny the advantages of the Lopinavir/Ritonavir treatment regimen compared to standard care.

Dolutegravir is a relatively new INSTI drug that is also used in treating AIDS. Like the other treatment options, Dolutegravir has also been shown to be a potent inhibitor of SARS-CoV-2 3CLpro.[27] Further bioinformatic approaches revealed that Dolutegravir can also inhibit the SARS-CoV-2's 2′-O-ribose methyltransferase (2′-O-MTase) (nsp-16), an enzyme responsible for viral messenger RNA methylation that prevents the host immune system from recognizing and responding to these viral elements.[41] To the best of our knowledge, this is the first time that Dolutegravir has been used as a treatment option in COVID-19 patients.

Atazanavir, another drug that's used primarily in HIV patients also shows potential as a candidate for COVID-19 treatment. Studies revealed that Atazanavir may be able to inhibit different SARS-CoV-2 proteins such as 3CLpro,[27] Helicase,[28] and these results have since been confirmed in an *in-vitro* study showcasing the inhibition of SARS-CoV-2 replication and ameliorating the induced interleukin-6 and tumor necrosis factor-α production in both Vero cells and human pulmonary epithelial cell line.[42] An study evaluating the Atazanavir/Ritonavir (300/100 mg daily) plus Hydroxychloroquine (400 mg BD on the first day and then 200 mg BD) combination treatment for 7 days in moderate and severe COVID-19 patients concluded that although this treatment regimen may be effective in patients with moderate disease, it is not beneficial in patients with SpO_2 lower than

90% and the SpO_2 was the only predictor of outcome in the study population.[43]

Studies regarding the therapeutic effect of Atazanavir in COVID-19 are scarce, thus the exact efficacy of Atazanavir as a treatment option has not been confirmed. In the present study, patients in the ADH group showed significant improvements in oxygen saturation and clinical and paraclinical characteristics. However, this fact should be considered that these results might have been due to a synergetic effect with Dolutegravir or even Dolutegravir alone.

The following limitations were present in our study and should be taken into consideration before interpretation of our findings. In the current study, we could not determine the efficiency of either of the treatment regimens compared to standard care as we did not have a control group. Our study population was relatively small and our results showed an advantage in the Atazanavir/Dolutegravir group compared to Lopinavir/Ritonavir group, and to precisely determine the efficiency of the Atazanavir/Dolutegravir regimen a more comprehensive study with a larger study population is recommended. Some laboratory tests required for determining the efficiency of treatment regimens were not repeated at discharge date for a number of patients.

5 | CONCLUSION

Based on our results, Atazanavir/Ritonavir/Dolutegravir plus Hydroxychloroquine shows noticeable advantages compared to Lopinavir/Ritonavir plus Hydroxychloroquine in treating COVID-19 patients. Due to the small size of the study population and until a more comprehensive study reports a definitive advantage of the Atazanavir/Ritonavir/Dolutegravir regimen, we can only suggest this combination treatment as an alternative option to be used alongside the standard care procedures.

ACKNOWLEDGMENTS

This study was granted by the Research Deputy of Iran University of Medical Sciences (Registration number: 17671).

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Saeed Kalantari and Sara Minaeian designed the study and reviewed the manuscript. Soheil R. Fard was responsible for literature search, data interpretation, and manuscript writing. Donya Maleki and Saeed Kalantari were the principal physicians and supervised data collection. Saeed Kalantari was responsible for drug acquisition. Mahshid T. Taher and Zeynab Yassin helped with patient care and data collection. Yousef Alimohamadi was responsible for the statistical analysis of data. Sara Minaeian was the study coordinator and supervised the data analysis.

ORCID

Saeed Kalantari http://orcid.org/0000-0001-9896-4139
Soheil R. Fard http://orcid.org/0000-0002-9731-5345
Donya Maleki http://orcid.org/0000-0002-1252-8035
Mahshid T. Taher http://orcid.org/0000-0002-3133-7859
Zeynab Yassin https://orcid.org/0000-0002-1915-6596
Yousef Alimohamadi http://orcid.org/0000-0002-4480-9827
Sara Minaeian http://orcid.org/0000-0002-8787-5971

REFERENCES

1. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med*. 2020;382(8):727-733.
2. World Health Organization. 2021. https://www.who.int/publications/m/item/weekly-epidemiological-update--9-february-2021. Accessed February 9, 2020.
3. Chan KS, Lai ST, Chu CM, et al. Treatment of severe acute respiratory syndrome with lopinavir/ritonavir: a multicentre retrospective matched cohort study. *Hong Kong Med J*. 2003;9(6):399-406.
4. Chu CM, Cheng VC, Hung IF, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax*. 2004;59(3):252-256.
5. Kiselev OI, Maleev VV, Deeva EG, et al. Clinical efficacy of Arbidol (umifenovir) in the therapy of influenza in adults: preliminary results of the multicenter double-blind randomized placebo-controlled study ARBITR. *Ter Arkh*. 2015;87(1):88-96.
6. Loutfy MR, Blatt LM, Siminovitch KA, et al. Interferon alfacon-1 plus corticosteroids in severe acute respiratory syndrome: a preliminary study. *JAMA*. 2003;290(24):3222-3228.
7. Omrani AS, Saad MM, Baig K, et al. Ribavirin and interferon alfa-2a for severe Middle East respiratory syndrome coronavirus infection: a retrospective cohort study. *Lancet Infect Dis*. 2014;14(11):1090-1095.
8. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet*. 2020;395(10224):565-574.
9. Abdul-Rasool S, Fielding BC. Understanding human coronavirus HCoV-NL63. *Open Virol J*. 2010;4:76-84. https://doi.org/10.2174/1874357901004010076
10. Graham RL, Donaldson EF, Baric RS. A decade after SARS: strategies for controlling emerging coronaviruses. *Nat Rev Microbiol*. 2013;11(12):836-848.
11. Ksiazek TG, Erdman D, Goldsmith CS, et al. A novel coronavirus associated with severe acute respiratory syndrome. *N Engl J Med*. 2003;348(20):1953-1966. https://doi.org/10.1056/NEJMoa030781
12. Vabret A, Mouthon F, Mourez T, Gouarin S, Petitjean J, Freymuth F. Direct diagnosis of human respiratory coronaviruses 229E and OC43 by the polymerase chain reaction. *J Virol Methods*. 2001;97(1-2):59-66.
13. Zaki AM, Van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med*. 2012;367(19):1814-1820.
14. Shang J, Ye G, Shi K, et al. Structural basis of receptor recognition by SARS-CoV-2. *Nature*. 2020;581(7807):221-224.
15. Brian D, Baric R. Coronavirus genome structure and replication. *Curr Top Microbiol Immunol*. 2005;287:1-30.
16. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*. 2020;181(2):271-280. https://doi.org/10.1016/j.cell.2020.02.052
17. Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. *Coronaviruses*. 2015:1-23.

18. Knoops K, Kikkert M, Worm SH, et al. SARS-coronavirus replication is supported by a reticulovesicular network of modified endoplasmic reticulum. *PLOS Biol*. 2008;6(9):e226.
19. Masters PS. The molecular biology of coronaviruses. *Adv Virus Res*. 2006;66:193-292.
20. Cvetkovic RS, Goa KL. Lopinavir/ritonavir: a review of its use in the management of HIV infection. *Drugs*. 2003;63(8):769-802. https://doi.org/10.2165/00003495-200363080-00004
21. De Wilde AH, Jochmans D, Posthuma CC, et al. Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East respiratory syndrome coronavirus replication in cell culture. *Antimicrob Agents Chemother*. 2014;58(8):4875-4884.
22. Chan JF, Yao Y, Yeung M-L, et al. Treatment with lopinavir/ritonavir or interferon-β1b improves outcome of MERS-CoV infection in a nonhuman primate model of common marmoset. *J Infect Dis*. 2015;212(12):1904-1913.
23. Cao B, Wang Y, Wen D, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. *N Engl J Med*. 2020;382(19):1787-1799.
24. Mo P, Xing Y, Xiao Y, et al. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China [published online ahead of print March 16, 2020]. *Clin Infect Dis*. 2020:ciaa270. https://doi.org/10.1093/cid/ciaa270
25. Wang Z, Chen X, Lu Y, Chen F, Zhang W. Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine treatment. *Biosci Trends*. 2020;14(1):64-68.
26. Choi J, Horner KA, Carnevale K. Atazanavir. StatPearls [Internet]: StatPearls Publishing; 2019.
27. Beck BR, Shin B, Choi Y, Park S, Kang K. Predicting commercially available antiviral drugs that may act on the novel coronavirus (SARS-CoV-2) through a drug-target interaction deep learning model. *Comput Struct Biotechnol J*. 2020;18:784-790.
28. Borgio JF, Alsuwat HS, Al Otaibi WM, et al. State-of-the-art tools unveil potent drug targets amongst clinically approved drugs to inhibit helicase in SARS-CoV-2. *Arch Med Sci*. 2020;16(3):508-518.
29. Kandel CE, Walmsley SL. Dolutegravir—a review of the pharmacology, efficacy, and safety in the treatment of HIV. *Drug Des Devel Ther*. 2015;9:3547-353.
30. Gervasoni C, Meraviglia P, Riva A, et al. Clinical features and outcomes of HIV patients with coronavirus disease 2019. *Clin Infect Dis*. 2020;71(16):2276-2278.
31. Stoeckle K, Johnston CD, Jannat-Khah DP, et al. COVID-19 in hospitalized adults with HIV. *Open Forum Infect Dis*. 2020;7(8):ofaa327.
32. Ali MJ, Hanif M, Haider MA, et al. Treatment options for COVID-19: a review. *Front Med (Lausanne)*. 2020;7:480.
33. Nukoolkarn V, Lee VS, Malaisree M, Aruksakulwong O, Hannongbua S. Molecular dynamic simulations analysis of ritronavir and lopinavir as SARS-CoV 3CLpro inhibitors. *J Theor Biol*. 2008;254(4):861-867.
34. Nutho B, Mahalapbutr P, Hengphasatporn K, et al. Why are lopinavir and ritonavir effective against the newly emerged Coronavirus 2019? Atomistic insights into the inhibitory mechanisms. *Biochemistry*. 2020;59(18):1769-1779.
35. Chen F, Chan KH, Jiang Y, et al. *In vitro* susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. *J Clin Virol*. 2004;31(1):69-75.
36. Park SY, Lee JS, Son JS, et al. Post-exposure prophylaxis for Middle East respiratory syndrome in healthcare workers. *J Hosp Infect*. 2019;101(1):42-46.
37. Ye XT, Luo YL, Xia SC, et al. Clinical efficacy of lopinavir/ritonavir in the treatment of coronavirus disease 2019. *Eur Rev Med Pharmacol Sci*. 2020;24(6):3390-3396.
38. Deng L, Li C, Zeng Q, et al. Arbidol combined with LPV/r versus LPV/r alone against corona virus disease 2019: a retrospective cohort study. *J Infect*. 2020;81(1):e1-e5.
39. Zhu Z, Lu Z, Xu T, et al. Arbidol monotherapy is superior to lopinavir/ritonavir in treating COVID-19. *J Infect*. 2020;81(1):e21-e23. https://doi.org/10.1016/j.jinf.2020.03.060
40. Cai Q, Yang M, Liu D, et al. Experimental treatment with favipiravir for COVID-19: an open-label control study. *Engineering (Beijing)*. 2020;6(10):1192-1198.
41. Khan RJ, Jha RK, Amera GM, et al. Targeting SARS-CoV-2: a systematic drug repurposing approach to identify promising inhibitors against 3C-like proteinase and 2′-O-ribose methyltransferase. *J Biomol Struct Dyn*. 2020;39:1-14.
42. Rodrigues NF, Sacramento CQ, Lima CR, et al. Atazanavir, alone or in combination with ritonavir, inhibits SARS-CoV-2 replication and pro-inflammatory cytokine production. *Antimicrob Agents Chemother*. 2020;64(10):e00825.
43. Rahmani H, Davoudi-Monfared E, Nourian A, et al. Comparing outcomes of hospitalized patients with moderate and severe COVID-19 following treatment with hydroxychloroquine plus atazanavir/ritonavir. *DARU*. 2020;28(2):625-634.

How to cite this article: Kalantari S, Fard SR, Maleki D, et al. Comparing the effectiveness of Atazanavir/Ritonavir/Dolutegravir/Hydroxychloroquine and Lopinavir/Ritonavir/Hydroxychloroquine treatment regimens in COVID-19 patients. *J Med Virol*. 2021;93:6557-6565. https://doi.org/10.1002/jmv.27195