

Brief Communication

Lopinavir/ritonavir as a third agent in the antiviral regimen for SARS-CoV-2 infection

Periklis Panagopoulos, Vasilis Petrakis, Maria Panopoulou, Grigorios Trypsianis, Theano Penlioglou, Ioannis Pnevmatikos, Dimitrios Papazoglou

Department of Infectious Diseases, 2ND University Department of Internal Medicine, University General Hospital of Alexandroupolis, Democritus University of Thrace, Alexandroupolis, Greece

ABSTRACT

Corona Virus Disease (CoVID-19) is an emerging public health problem rapidly spread globally. New treatment options for patients with severe symptoms and ways of reducing transmission in the community are taken into consideration. A retrospective study was conducted in the Department of Infectious Diseases of Alexandroupolis (Greece) including 16 patients with CoVID-19. They were classified into two groups, A and B. Group A received lopinavir/ritonavir as a third agent in the antiviral regimen, while group B did not. Lymphocytes were more significantly increased in patients of group A. Ferritin serum levels were also decreased significantly in these patients. Number of days needed for a first negative result of Real Time-Polymerase Chain Reaction (RT-PCR) was lower for Group A. The present study suggests that lopinavir/ritonavir may reduce the viral carriage in a shorter period of time compared with other antiviral regimens. Further studies are needed in order to evaluate the effectiveness of lopinavir/ritonavir in the treatment of patients with SARS-CoV-2 infection.

Keywords: Lopinavir; ritonavir; CoVID-19; SARS-COV-2

Introduction

Corona Virus Disease (CoVID-19) is an emerging public health problem caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).¹ The SARS-CoV-2 belongs to β -coronaviruses and is an enveloped non-segmented positive-sense RNA virus.² It was firstly described in China in December 2019, but rapidly has been spread to other countries worldwide.¹ CoVID-19 was declared by WHO as pandemic on 12th March.³ Globally on 8th Apr 2020, there have been 1,317,130 confirmed cases of CoVID-19, including 74,304 deaths, reported to WHO.⁴ It is vital to find effective therapeutic options in order to treat patients, especially with severe symptoms and ways to reduce the transmission in the community.

Chloroquine, used for years as treatment of malaria, seems to be effective against SARS-CoV-2 infection.⁵⁻⁷ Chloroquine inhibits the viral replication of several viruses, has an immunomodulatory role and may work as an autophagy inhibitor⁵ Synergy between hydroxychloroquine and azithromycin has been documented preventing severe respiratory tract infections.^{6,7} Other antiviral agents

have been also used such as Remdesivir, a promising antiviral drug against a wide array of RNA viruses.⁸

Protease inhibitors lopinavir and ritonavir, used for human immunodeficiency virus (HIV) infection could be useful for SARS-CoV-2 infected patients.⁶ There is a significant long-term experience with this drug in Greek population.⁹ The aim of the present study was to assess the impact of lopinavir/ritonavir as a third agent for the treatment of SARS COV 2 infection especially for patients with severe pneumonia emphasizing in the number of days needed for reduction of viral load.

Methods

This was a retrospective study conducted in the Department of Infectious Diseases of the University General Hospital of Alexandroupolis (Greece). Data from routine care patient charts during the period 1st to 31st of March 2020 were retrospectively analysed. The study was carried out in accordance with the Helsinki Declaration of Human Rights and patients gave their informed consent.

Correspondence to: Petrakis Vasilis, Department of Infectious Diseases, 2ND University Department of Internal Medicine, University General Hospital of Alexandroupolis, Democritus University of Thrace, Alexandroupolis, Greece. Email: vasilispetrakis1994@gmail.com

Table 1. Results.

	Group A-Treatment with Lopinavir/Ritonavir (n = 8)			Group B-Treatment without Lopinavir/Ritonavir (n = 8)				
Gender	6(75%)			4(50%)				
• Male, n (%)	55.75 ± 19.71 7(87.5%)			59.75 ± 10.51 5(71.4%)				
Age (years)	8(100%)			3(37.5%)				
Comorbidity, n (%)	8(100%)			3(37.5%)				
Severe radiological findings, n (%)	8(100%)			3(37.5%)				
	Day 0	Day 7	Day 14	P value	Day 0	Day 7	Day 14	P value
Lymphocyte (/ml)	968.57 ± 301.3	751.43 ± 187.12	1075.71 ± 223.3	0.011	1125 ± 376.12	866.67 ± 391.9	996.67 ± 312.84	0.451
Fibrinogen (mg/dl)	398.14 ± 35.82	490.86 ± 99.26	436.86 ± 93.96	0.048	409.83 ± 75.55	426.5 ± 169.83	373.67 ± 151.84	0.604
D-dimers (mg/dl)	606 (270–985)	866 (401–1261)	604 (149–1368)	0.086	736.5 (173–1291)	897 (235–6415)	1014 (222–2500)	0.107
Ferritin (mg/dl)	850 (102–1682)	532 (103–2137)	311 (90–2321)	0.345	252 (53–1293)	332 (72–1441)	339 (77–2163)	0.291
Procalcitonin (mg/dl)	0.1 (0–0.6)	0.1 (0–16.7)	0.0 (0–1.3)	0.431	0.0 (0–1.5)	0.0 (0–2.2)	0.1 (0–1.1)	0.913
C-reactive protein (mg/dl)	6.14 ± 2.8	10.86 ± 5.18	4.18 ± 3.62	0.001	4.6 ± 6.47	8.46 ± 5.67	1.58 ± 1.69	0.014
Partial pressure of oxygen (mm Hg)	70.57 ± 6.42	66.71 ± 14.64	73.43 ± 3.95	0.401	65.83 ± 10.76	72.67 ± 3.50	72 ± 2.97	0.236
Oxygen saturation (%)	94.71 ± 1.89	94.43 ± 2.07	96.14 ± 0.69	0.171	92.83 ± 3.43	95.83 ± 1.17	96.33 ± 1.8	0.082
Days of hospitalization								
Days for clinical improvement (no fever)		14.71 ± 0.76				11.40 ± 2.07		0.003
Days for negative result of RT-PCR for SARS-COV-2		6.00 ± 1.16				4.4 ± 1.52		0.064
Intubation		8.86 ± 1.68				13.8 ± 2.68		0.003
		1 (12.5%)				3 (37.5%)		

Bold values signifies parameters statically significant.

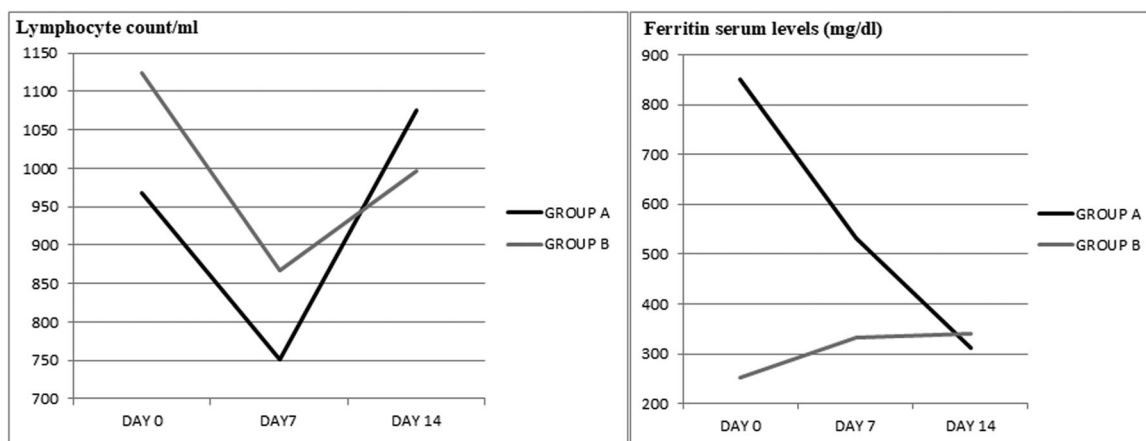


Figure 1. Lymphocyte count/ml and ferritin serum levels at days 0, 7 and 14 for Groups A and B.

Inclusion criteria were confirmed cases of SARS COV2 infection, complete laboratory analysis 7 and 14 days after hospital admission.

Patients were classified into 2 categories based on the usage of lopinavir/ritonavir in the antiviral regimen. Lymphocytes cell count, serum levels of fibrinogen, D-dimers, ferritin, C-reactive protein (CRP) and procalcitonin were estimated at the day of hospital administration and at days 7 and 14. Saturation oxygen levels and partial pressure of oxygen were also estimated. Number of days needed for clinical improvement and first negative result of Polymerase Chain Reaction (PCR) for SARS COV2 was evaluated.

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS), version 19.0 (SPSS Inc., Chicago, IL). Levels of all biochemical markers were expressed as mean \pm standard deviation (SD). Differences of biochemical markers between the three consecutive measurements were examined by one-way repeated measures ANOVA (rmANOVA) and paired-samples t test. Multiple comparisons were performed using Sidak's test. All tests were two-tailed and significance was defined at the 5% level ($p < 0.05$).

Results

The number of patients included in the present study was sixteen. Only closed cases were analyzed. The patients were classified into two groups. All patients received hydroxychloroquine and azithromycin. Eight patients received lopinavir/ritonavir as a third agent in the antiviral regimen (group A). The other eight patients did not receive lopinavir/ritonavir (group B). Lopinavir/ritonavir was added in patients with persistent fever, lymphocytopenia and severe radiological findings (bilateral, diffuse ground glass opacities and pleural effusions). The results are shown in the Table 1.

Patients in group A were mainly men (75%) with comorbidities and severe radiological findings. Seven patients were recovered and one needed intubation and mechanical ventilation. Four of them had hypertension and one chronic myeloid leukimia. In group B the majority of patients were older, with comorbidities but without severe radiological findings. Three patients had hypertension and one chronic renal failure. Four patients needed intubation. Three of them died and one was recovered.

Lymphocyte count at admission day was lower for patients in group A compared with group B. A reduction was observed at day 7 but at day 14 the number of lymphocytes was significantly increased. In patients of group B the alteration was less significant (Figure 1). Fibrinogen levels were similar in both groups. D-dimers were increasing in group B at day 7 and 14 while patients in group A had lower levels at day 14. Ferritin levels were significantly elevated at admission day for group A but they were dramatically reduced at day 14. No significant alteration was observed in group B (Figure 1). Procalcitonin and C-reactive protein were altered similarly for both groups.

Patients of group A were hospitalized for more days. The number of days needed for clinical improvement (no fever) was higher as well. However, the number of days needed for the first negative result of RT-PCR for SARS-CoV-2 was significantly lower for patients of group A.

Conclusion

The present study suggests that lopinavir/ritonavir could be a potential effective choice in treatment of patients with CoVID-19. The parameters significantly affected positively in our study were the count of lymphocytes and the ferritin serum levels. The number of days needed for negative result of RT-PCR was significant lower for patients

receiving lopinavir/ritonavir. These results indicate its possible role in reduction of viral carriage and improvement of clinical condition in patients with severe symptoms and radiological findings.

There are indications of a favourable outcome in MERS among patients treated with lopinavir/ritonavir that need to be confirmed by randomised clinical trials.^{10,11} Studies conducted in China showed a potential positive effect in the treatment of CoVID-19 as well.^{12–14} One of these studies included four patients with COVID-19 who received lopinavir/ritonavir. The three patients showed significant improvement in their clinical condition and were discharged negative for SARS-CoV-2.¹² However, a retrospective study conducted in China including 134 patients with CoVID-19 showed no effect on accelerating the clearance of SARS-CoV-2.¹⁵ A randomized, controlled, open-label trial including 199 patients with laboratory-confirmed SARS-CoV-2 infection showed no benefit with lopinavir–ritonavir treatment compared with standard care.¹⁶ Thirteen patients stopped treatment due to gastrointestinal adverse events.¹⁶ In our study, no patient stopped treatment due to adverse events.

Limitations of the study are the retrospective nature and the small number of patients. In conclusion, the results of the study suggest that lopinavir/ritonavir may reduce the viral carriage in a shorter period of time compared with other antiviral regimens. Further studies are needed with larger patient series in order to evaluate the effectiveness of lopinavir/ritonavir in the treatment of patients with SARS-CoV-2 infection and confirm the findings of the present study.

Conflicts of interest

PP has been an advisory board member of GS, MSD, JANSSEN; received honoraria as a speaker for GS, JANSSEN, MSD.

Notes on contributors

Periklis Panagopoulos is Assistant Professor of Internal Medicine and Infectious Diseases in Democritus University of Thrace. He is responsible of HIV Unit-Department of Infectious Diseases of University General Hospital of Alexandroupolis and currently of COVID-19 Department. His research interests are HIV infection, bacterial infections, virology and zoonotic diseases.

Vasilis Petrakis is Resident of Internal Medicine in 2nd Department of Internal Medicine of University General Hospital of Alexandroupolis. He is student in Msc “Infectious Diseases – International Medicine: From Bench to Bedside” and PhD

candidate of Democritus University of Thrace. He currently works in COVID-19 Department.

Maria Panopoulou is Associate Professor of Microbiology and Director of Microbiology Department of University General Hospital of Alexandroupolis. The Microbiology Laboratory consists of departments of Cultures, Molecular Diagnosis and Immunology, where diagnostic tests are performed for detection of bacteria, viruses, fungi and parasites by classical methods but also with methods of Molecular Biology. Diagnostic tests are performed with molecular methods for hepatitis B and C viruses, Brucella and Mycobacterium tuberculosis.

Grigorios Trypsianis is Professor of Medical Statistics and Director of the Laboratory of Medical Statistics in Medicine Department of Democritus University of Thrace. His research interests and teaching duties include subjects such as Infectious Diseases, Bio-Medical and Molecular Sciences in Diagnosis and Treatment of Diseases, Social Psychiatry and Hygiene and Safety at work.

Theano Penlioglou is Resident of Internal Medicine in 2nd Department of Internal Medicine of University General Hospital of Alexandroupolis. She has worked for the COVID-19 Department during the pandemic. She is Msc student of Clinical Microbiology in Democritus University of Thrace

Ioannis Pnevmatikos is Professor of Critical Care Medicine in Democritus University of Thrace and Head of Critical Care Department at University General Hospital of Alexandroupolis. His research interest include: Clinical Pharmacology, Medical Sleep, Bioethics, Contemporary OMN methodology and Infectious Diseases.

Dimitrios Papazoglou is Professor of Internal Medicine in Democritus University of Thrace. He is Director of 2ND Department of Internal Medicine and Department of Infectious Diseases at University General Hospital of Alexandroupolis. His research interests include: diabetes mellitus, obesity and endocrine system.

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