

COVID-19 Pneumonia during Hydroxychloroquine Treatment of Rheumatoid Arthritis

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ABSTRACT

The recently emerged and novel coronavirus, severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2), that caused the current global pandemic was detected for the first time in Turkey in March 2020. While it continues to spread rapidly worldwide, there are still many uncertainties in the prevention and treatment of new coronavirus disease. We report a case of coronavirus disease 2019 (COVID-19) pneumonia in a patient under hydroxychloroquine (HCQ) treatment for rheumatoid arthritis. A 38-year female patient developed severe respiratory distress with SARS-CoV-2 infection and was treated in Intensive Care Unit (ICU). With this report, we aim to discuss the place of HCQ in prophylaxis in the light of the literature with a case presentation of COVID-19 pneumonia under HCQ treatment.

Key Words: Coronavirus, Hydroxychloroquine, Prophylaxis, Rheumatoid arthritis, COVI-19.

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INTRODUCTION

The recently emerged novel coronavirus, severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2), causing the current global pandemic was first detected in Turkey in March 2020. While it continues to spread rapidly worldwide, there are still many uncertainties in the prevention and treatment of novel coronavirus disease 2019 (COVID-19). In addition to efforts about developing new drugs specific to SARS-CoV-2, *in vitro* studies are investigating the effects of existing drugs. Remdesivir, chloroquine (CQ) and hydroxychloroquine (HCQ) are the most popular drugs in this regard.¹

Healthcare workers infected during respiratory invasive procedures (i.e. intubation, endotracheal tube aspiration or bronchoscopy) obviously can be a source of infection in asymptomatic or pre-symptomatic periods for patients who have a medical care requirement not related to each other, their families and SARS-CoV-2.

Therefore, the use of prophylactic drugs has a crucial place among the strategies developed for the prevention of transmission. CQ/HCQ are known as anti-malarials for more than 70 years. Due to the fact that there is not enough evidence with regard to their mechanism of action against SARS-CoV-2, their use in prophylaxis has been questioned.¹

In this report, we aim to discuss the place of HCQ in prophylaxis in the light of the literature with a case presentation of COVID-19 pneumonia under HCQ treatment.

CASE REPORT

A 38-year female patient admitted to the hospital with the complaints of fever, cough, widespread muscle pain and dyspnoea; and was hospitalised after the computed tomography of the lung, which was compatible with COVID-19 and interstitial alveolar haemorrhage (IHA) (Figure 1). The patient developed severe respiratory distress within 24 hours and was intubated and taken to mechanical ventilation support, before transferring to ICU. In her medical history, she had rheumatoid arthritis and IHA disease and had been using 400mg/day HCQ as treatment for the last one year. Oseltamivir (150mg/day), and meropenem (3g/day) was started in ICU and HCQ (400 mg/day) was continued.

The patient, who developed moderate acute respiratory distress syndrome (ARDS) was followed up with 8 days' mechanical ventilation support. Clinical course and treatment of the patient are given in Table I and laboratory findings are given in Table II.

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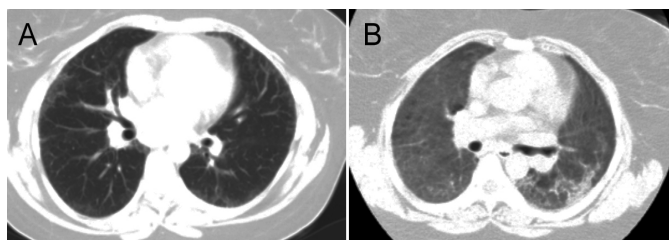
Table I: Clinical course, treatment and viral load of the patient.

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Day of illness	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Hospital day						1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
ICU day							1	2	3	4	5	6	7	8	9	10					
	Fever		Dyspnoea																		
	Muscle pain																				
			Dry cough																		
							ARDS														
							Invasive ventilation														
Hydroxychloroquine																					
							Oseltamivir														
							Meropenem														
Results of real time reverse transcription PCR							NEG			NEG			NEG								
Rapid antibody test of SARS-CoV-2																	IGM Positive				
																	IGG Positive				

Table II: Serial laboratory results of the patient.

Day of illness	Illness day 6	Illness day 10	Illness day 14	Illness day 18	Illness day 20
Hospital day	HD 1	HD 6	HD 11	HD 14	HD 16
ICU day	ICU day 2	ICU day 5	ICU day 10		
PaO ₂ /FIO ₂	135	250	>400	-	-
Lactate	2.5	1.9	0.4	-	-
White Blood Cell Count, x10 ³ /ml	15,69	14,9	15,8	14,95	16,0
Lymphocyte, %	5.4	1.4	7.9	15.3	17.3
Segment of Neutrophil, %	86,5	92,5	86,7	96,7	88,6
Hemoglobin, g/dl	9.5	8,9	9,3	10,1	11
Platelets, x10 ³ /ml	294	248	294	349	334
Glucose, mg/dl	201	120	126	141	138
Creatinine, mg/dl	1,09	0,98	0,45	0,52	0,48
BUN, mg/dl	48	43	43,5	49	58,9
AST, U/L	39	92	94	75	34
ALT, U/L	16	68	34	35	50
Albumine, g/dl	40	33	29	30	34
CK, U/L	131	2293	1951	592	296
LDH, U/L	1053	641	708	409	479
CRP, mg/dl	85	45	16	7,8	5,26
Procalcitonin, ng/ml	0.508	0,094	-	-	<0,05
PT, sec	14,3	13	12,5	14,1	12,8
PT, INR	1,29	1,14	1,1	1,24	1,13
aPTT, sec	65	17	17,7	17,4	18
Ferritin	88,8				119
D-dimer, mg/ml	735	4612	5364	3852	

HD = hospital Day, AST = aspartate aminotransferase, ALT = alanine aminotransferase, CK = creatine kinase, ALP = alkaline phosphatase, LDH dehydrogenase, ESR = erythrocyte sedimentation rate, CRP = C-reactive protein, PT = prothrombin time, INR = international normalized ratio, partial thromboplastin time.

**Figure 1: Radiologic findings of the patient; (A) CT scan of prior to COVID-19 pneumonia (date, 2019) (B) CT scan of illness day 6, hospital day.**

Other viral and bacterial pathogens were excluded for the moderate ARDS (PaO₂<100/FIO₂<200). Haemoptysis was not observed in ICU follow-up. The SARS-CoV-2 real time-polymerase chain reaction (RT-PCR) test results were negative. However, because clinical and CT findings were compatible with COVID-19, rapid antibody test of SARS-CoV-2 was studied and it has shown to be immunoglobulin (Ig)M-IgG positive.

The patient was discharged from ICU on 10th day of hospitalisation, and from the hospital on 16th day with recovery.

DISCUSSION

The rapid spread of SARS-CoV-2 in China has resulted in a search for an effective drug that can treat symptomatic patients. This drug should reduce the virus transmission time as well as side effects, be safe and with effective antiviral properties. As information about the replication of the virus becomes clear, *in vitro* studies gained speed and CQ/HCQ have been found to be effective against SARS-CoV-2.^{2,3}

It is known that CQ/HCQ are able to inhibit replication at early phase of viral infection, increasing endosomal pH, inhibiting autophagosome-lysosome fusion and inactivating enzymes at the time of coronavirus-human cell fusion.⁴ In the case of COVID-19, Wang *et al.* demonstrated with time-of-assay that CQ functioned at both entry and at post-entry stages of infection in the VERO E6 cells assay.² Other *in*

vitro studies have shown that the glycosylation process of the angiotensin converting enzyme 2 (ACE2) receptor gets affected, thus causing the VERO cells pre-treated with CQ to be refractory to SARS-CoV infection.²⁻⁵ The SARS-CoV-2 is known to bind to human cells *via* ACE 2 receptors.⁶ Due to the above-mentioned effects of CQ/HCQ against SARS-CoV-2, their use in pre-exposure and post-exposure prophylaxis has begun to be discussed.

Despite all these mechanisms, COVID-19 with moderate ARDS developed under HCQ treatment in this case. Despite the lung pathology, the patient's clinical condition improved rapidly. This may partly be explained by the fact that the patient was receiving HCQ both pre-exposure and post-exposure to virus infection. However, HCQ was not completely successful in preventing infection by SARS-CoV-2. This demonstration raises some scepticism regarding the effectiveness of HCQ in SARS-CoV-2 prophylaxis.

Currently, there are no randomised clinical trials (RCTs) to provide clinical guidance on the use, dose, and duration of CQ/HCQ. But many are planned or are underway to study CQ and HCQ for treating and preventing COVID-19 in different countries (examples: NCT04315896, NCT04318015, NCT04318444, NCT04321278, NCT04308668, NCT04304053, NCT0431637 and NCT04303299). In the light of all these studies, we will have a better understanding of the use of CQ/HCQ in prophylaxis in the future.

CONFLICT OF INTEREST:

The authors declared no conflict of interest.

PATIENT'S CONSENT:

Informed consent was obtained from the patient for publishing his details and data.

AUTHORS' CONTRIBUTION:

CG: Concept, design, definition and intellectual content, literature search, data acquisition, data analysis, and manuscript preparation and editing.

ÖOT, ED: Concept, design, data acquisition, data analysis.

TT: Design, definition and intellectual content.

SGD: Concept, design, definition and intellectual content, manuscript preparation and editing.

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