The effect of hydroxychloroquine against SARS-CoV-2 infection in rheumatoid arthritis patients

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Research Article

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Abstract

INTRODUCTION: The effectiveness of hydroxychloroquine in SARS-CoV-2 prophylaxis and treatment is still controversial. In this study, our aim is to investigate the potential effects of hydroxychloroquine therapy on patients with diagnosed with rheumatoid arthritis and a confirmed SARS-CoV-2 infection.

METHOD: We included patients who were followed up with a diagnosis of rheumatoid arthritis and whose SARS-CoV-2 infection was confirmed. The patients were divided into two groups as those who previously used hydroxychloroquine and those who did not, and were compared in terms of clinical and laboratory data.

RESULTS: Our study included 17 patients with adequate data (2 males, 15 females). The mean age of the patients was 57.2 ± 11.6 years. 7 (41.2%) patients were receiving hydroxychloroquine regularly for the last 6 months. When the effect of hydroxychloroquine on clinical and laboratory parameters of patients was examined, there was no significant difference between the groups of patients using and not using hydroxychloroquine. The patients using and not using hydroxychloroquine were compared for the presence of typical SARS-CoV-2 infection findings on computed tomography images, admission to the hospital and intensive care. No significant differences were observed between these two groups.

CONCLUSIONS: Many studies on the effectiveness of hydroxychloroquine use in SARS-CoV-2 infection are still ongoing. Due to its importance in rheumatology practice, it is very important to clarify the position of hydroxychloroquine in SARS-CoV-2 therapy. Our findings suggest that having previously used hydroxychloroquine does not have any negative or positive effect on the infection.

Introduction

Antimalarial drugs, which recently took an important place in the global agenda because of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, actually constitute one of the quite ordinary components of daily rheumatology practice. Hydroxychloroquine (HCQ) and chloroquine, which are 4-aminoquinoline derivatives, have been used as conventional synthetic disease-modifying anti-rheumatic drugs (csDMARD) for various rheumatic diseases, especially rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), for many years. Both drugs have a planar aromatic nucleus structure and a highly similar mechanism of action [1]. However, chloroquine has been replaced by HCQ in most countries owing to its faster gastrointestinal absorption, favorable renal elimination rate, and better safety profile [2]. HCQ was first approved for the prevention and treatment of malaria in the United States [3].

However, the efficacy of the molecule is not limited to the control of malaria and inflammatory processes as its broad-spectrum activity against many bacterial, fungal, and viral infections have been demonstrated [4-7]. Chloroquine is a versatile bioactive agent with in vitro antiviral activity against RNA viruses including rabies virus, poliovirus, HIV, influenza viruses, chikungunya virus, dengue virus, zika virus, lassa virus, Crimean Congo hemorrhagic fever virus, and Ebola virus, as well as against various

DNA viruses such as hepatitis B virus and herpes simplex virus. These in vitro antiviral properties have occasionally been confirmed during the treatment of patients; however, chloroquine therapy has not been successful at all times in clinical trials depending on the disease, the concentration of chloroquine used, the duration of treatment and the clinical team in charge of the trial [2].

HCQ has several immunomodulatory effects such as the inhibition of chemotaxis, phagocytosis, toll-like receptor (TLR) signaling, calcium signals in B and T cells, macrophage-mediated cytokine production, and metalloproteinases [8]. HCQ is a weak base and increases endosomal pH in host intracellular organelles, thereby preventing the virus from fusing with host cells and from replicating. Apart from that, it prevents antigen processing and MHC-2-mediated autoantigen presentation to T cells, thereby reducing the T cell activity and suppressing the expression of CD154 and other cytokines (IL-1, IL-6, and TNF-alpha). Moreover, it disrupts the interaction of cytosolic viral DNA / RNA with TLRs and the nucleic acid sensor. Thereby, it halts the transcription of proinflammatory genes and reduces the likelihood of a cytokine storm (type-I interferons, IL-1, and TNF-alpha) [9]. Furthermore, it can inhibit the glycolysis of angiotensin-converting enzyme-2 receptor (ACE2R), which is the receptor used by SARS-CoV-2 to enter cells [10,11].

The worldwide effects of the SARS-CoV-2 pandemic have prompted the world of science to consider all possible solutions. Several researchers have suggested using 4- aminoquinolines against the new virus because of its similarities with SARS-CoV [12-14]. Wang et al. found that chloroquine was effective in reducing the entry of the virus into the cell and in inactivating it after its entry. That study showed that chloroquine reached sufficient concentrations at standard doses, had easy access to tissue including the lungs, and was very effective in reducing the viral replication. Furthermore, this study suggested the potential prophylactic use of chloroquine against SARS-CoV-2 [15]. Yao et al. concluded that HCQ was more effective than chloroquine in vitro for both prophylaxis and treatment [16].

The promising results of in vitro trials have led to the conduct of several clinical studies to further investigate the effect of chloroquine on SARS-CoV-2 [17]. Gao et al. demonstrated the superiority of chloroquine over control therapy in more than 100 patients in terms of prevention of pneumonia exacerbations, improvement of pulmonary imaging findings, promotion of the virus-negative conversion, and shortening the duration of the disease course in more than 10 hospitals in China [18]. Gautret et al. treated 20 patients with HCQ and compared the results with those of 16 participants in the control group. They concluded that HCQ was effective in reducing the viral load. Also, they described the synergistic effects of azithromycin and HCQ against the reduction of the viral load when used in combination [19].

All these data created the need to study the effects of HCQ on the prophylaxis and treatment of SARS-CoV-2 infections. In particular, the examination of the post-SARS-CoV-2 infection clinical features of patients who are already on these drugs before the pandemic can provide important information in this regard. In this study, our aim is to investigate the potential prophylactic effects of HCQ therapy on patients with diagnosed with RA and a confirmed SARS-CoV-2 infection and its effect on the clinic.

Methods

The study included patients who were previously followed up with the diagnosis of RA and who were admitted to Bezmialem Vakıf University Hospital for SARS-CoV-2 infection. The patients were divided into two groups as those who were already on HCQ for the treatment of RA (at least for the last 6 months) and those who were not on HCQ. The patients' demographic data, other anti-rheumatic drugs used, and comorbidities were recorded. The following data including fever, peripheral oxygen saturation (SpO2) levels, typical pneumonia findings of SARS-CoV-2 on computed tomography (CT) images, and laboratory findings including sedimentation, C-reactive protein (CRP), ferritin, d-dimer, hemoglobin (HGB), platelet (PLT), and absolute lymphocyte levels, which were obtained during the follow-up of the patients for the treatment of SARS-CoV-2, were evaluated from the database retrospectively. The rates of the requirement for hospitalization and / or intensive care admissions and the mean length of hospital stay were calculated. All data obtained were compared between the two groups to analyze whether HCQ had a prophylactic effect on SARS-CoV-2 and its effects on clinic. The study included patients who were diagnosed with RA according to the 2010 ACR & EULAR RA classification criteria, who were positive for the real-time reverse transcription polymerase chain reaction (rRT-PCR) test that was performed using nasopharyngeal swab samples and sputum samples, and who had available relevant data in the hospital database. Patients with a non-confirmed RA diagnosis, patients with irregular use of HCQ in the last 6 months, patients with negative rRT-PCR test result, and patients with inadequate data were excluded from the study.

Results

Our study included 17 patients with adequate data (2 males, 15 females). The mean age of the patients was 57.2 ± 11.6 years. In order to better analyze the extent of clinical worsening in the patients, the poorest values of the vital signs and laboratory test results observed during the treatment of SARS-CoV-2 infection were noted. Because the levels of ferritin and d-dimer were not measured in 2 and 3 patients respectively, they could not be included in the analysis. The distribution of the patients' descriptive data is presented in detail in Table 1.

Table 1: The distribution of the descriptive data

	N	Minimum	Maximum	Mean	Std. Deviation
Age (year)	17	38.0	79.0	57.2	11.6
SpO2	17	80.0	99.0	92.7	5.3
Fever (C^o)	17	35.2	39.0	36.8	1.0
Sedimentation (mm/h)	17	6.0	140.1	54.3	38.9
CRP (mg/l)	17	0.6	315.0	96.4	98.6
Ferritin (ng/ml)	15	4.1	1220.0	256.4	349.8
D-Dimer (ng/ml)	14	107.0	3446.0	999.0	1106.7
HGB (gr/dl)	17	8.01	14.5	11.2	2.1
PLT ($10*^3$/ul)	17	77.0	325.0	204.1	67.2
Absolute lymphocyte count ($10*^3$/ul)	17	0.26	2.21	1.2	0.6
LDH (u/l)	17	181.0	774.0	339.6	169.8
Duration of hospitalization (day)	17	0.0	22.0	6.1	6.9
Duration of intensive care (day)	17	0.0	6.0	0.5	1.6
N:Sample size, C^o ; Celcius, Spo2; peripheral oxygen saturation, CRP; C-Reactive Protein, HGB; hemoglobin, PLT;platelet, LDH;Lactate Dehydrogenase					

In the frequency analyses, 7 (41.2%) patients were receiving HCQ regularly for the last 6 months. The most common comorbidity was diabetes, observed in 7 patients (41.2%). While 11 patients (64.7%) were followed up inpatiently, 2 patients (11.8%) required intensive care. The number of patients with pneumonia findings consistent with SARS-CoV-2 infection on thoracic CT was 11 (64.7%). Table 2 presents the medications used, comorbidities, and other clinical parameters in detail.

Table 2: Distribution of medication, comorbidity and other clinical parameters

	YES N (%)	NO N (%)
Hydroxychloroquine	7 (41.2)	10 (58.8)
Methotrexate	4 (23.5)	13 (76.5)
Sulfasalazine	1 (5.9)	16 (94.1)
Leflunomide	4 (23.5)	13 (76.5)
Corticosteroids	6 (35.3)	11 (64.7)
Hypertension	8 (47.1)	9 (52.9)
Heart disease	4 (23.5)	13 (76.5)
Diabetes	7 (41.2)	10 (58.8)
Kidney disease	1 (5.9)	16 (94.1)
Lung disease	3 (17.6)	14 (82.4)
Smoking	1 (5.9)	16 (94.1)
Hospitalized	11 (64.7)	6 (35.3)
Intensive care	2 (11.8)	15 (82.2)
Positive CT finding	11 (64.7)	6 (35.3)
CT; Computed Tomography		

When the effect of HCQ use on the clinical and laboratory parameters of the patients was analyzed, there was no significant difference between the patient groups using HCQ and not using HCQ in terms of the data. A detailed comparison of the clinical and laboratory data by the previous HCQ use is presented in Table 3.

Table 3: Comparison of clinical and laboratory data in terms of previous HCQ use

	N	The use of HCQ	Mean	p
Fever (C^o)	10	Yes	37.0±1.17	0.518
	7	No	36.7±0.8	
SpO2 (%)	10	Yes	93.08±4.8	0.377
	7	No	91.2±5.9	
CRP (mg/l)	10	Yes	82.1±97.0	0.501
	7	No	116.8±104.9	
Sedimentation (mm/h)	10	Yes	46.9±28.5	0.418
	7	No	65.0±50.9	
Ferritin (ng/ml)	10	Yes	151.6±165.6	0.261
	5	No	466.2±533.0	
D-Dimer (ng/ml)	10	Yes	997.5±1237.2	0.993
	4	No	1003.0±846.1	
HGB (gr/dl)	10	Yes	11.7±1.8	0.269
	7	No	10.5±2.4	
PLT ($10*^3$/ul)	10	Yes	202.2±59.1	0.900
	7	No	206.8±82.3	
Absolute lymphocyte count ($10*^3$/ul)	10	Yes	1.3±0.5	0.714
	7	No	1.1±0.7	
LDH (u/l)	10	Yes	332.6±190.4	0.839
	7	No	349.7±149.3	
N:Sample size, HCQ; hydroxychloroquine, C^o ; Celcius, Spo2; peripheral oxygen saturation, CRP; C-Reactive Protein, HGB; hemoglobin, PLT;platelet, LDH;Lactate Dehydrogenase				

The patients using and not using HCQ were compared for the presence of typical SARS-CoV-2 infection findings on CT images, admission to the hospital and intensive care. No significant differences were observed between these two groups (Table 4).

Table 4: Comparison of CT findings, hospitalization and need for intensive care in terms of previous use of HCQ

		The use of HCQ		p
		No	Yes	
Positive CT finding	No	4	2	
	Yes	6	5	0,506
Hospitalized	No	4	2	
	Yes	6	5	0,627
Intensive care	No	9	6	
	Yes	1	1	0.787
HCQ; hydroxychloroquine, CT; Computed Tomography				

When the effect of other anti-rheumatic drugs on the clinic was analyzed, no effects of methotrexate, leflunomide, sulfasalazine, and low dose corticosteroid (<7.5 mg / day) use were observed on the laboratory and clinical parameters, CT findings, hospitalizations, and the requirement for intensive care.

When the effect of comorbid diseases was analyzed, it was observed that especially diabetes unfavorably affected several parameters such as SpO2, sedimentation, CRP, ferritin, and HGB levels. Furthermore, the presence of HT was found to be associated with low SpO2 levels and the presence of heart disease was found to be associated with high sedimentation and CRP levels and low HGB levels. No significant relationship was observed between comorbid diseases and hospitalization, need for intensive care or positive CT findings. Because only one patient was a smoker in the study population, no significant analysis could be made for this variable. Again, because only 2 of the study patients were males, no gender-specific comparisons could be made.

In the SARS- CoV-2 guideline of Republic of Turkey, Ministry of Health, the description of a complicated patient is given [21]. According to this classification, patients are considered complicated when the SpO2 is lower than 93% or poor prognostic criteria are present in blood laboratory tests (an absolute lymphocyte count of <800 / µl or CRP levels increased more than 10 times of the normal limit or ferritin levels of > 500 ng / ml or D-Dimer levels of > 1000 ng / ml). When the patients were grouped according to these criteria, 10 patients were included in the complicated patient group. When the complicated and uncomplicated patient groups were compared, no significant effects of previous rheumatic drug use, including HCQ, were observed in terms of the progression to complicated disease.

Conclusions

There are adequate preclinical justification and evidence for the efficacy of 4-aminoquinolines in the treatment of SARS-CoV-2 infection and they are important to encourage new clinical studies on this subject. Except that, these drugs are inexpensive and have considerable quantities of adequate safety evidence as they have been in clinical use for other indications, especially for the treatment of rheumatic diseases, for a long time [20].

The report from a multicenter collaboration group in China particularly supported the use of chloroquine phosphate [22]. The Centre of Infectious Disease Control of the Netherlands also recommended chloroquine therapy for patients with severe infections requiring hospitalization, oxygen therapy, or intensive care. The guideline of the Italian Society of Infectious and Tropical Diseases, Lombardy recommended the use of 4-aminoquinolines at variable doses depending on the disease severity. The recommended target population ranged from patients with mild respiratory symptoms and comorbidities to patients with severe respiratory distress [20]. Also, many clinical studies on this subject still continue in China. The Turkish Ministry of Health positioned the use of HCQ as the first-line treatment for SARS-CoV-2 infections in the recently updated guideline on June 19, 2020 [21].

RA is a risk factor for serious infections that contribute to high overall morbidity and mortality compared to the general population. The high susceptibility of RA patients to infections can be explained by several

various endogenous and exogenous risk factors including (1) immune system imbalance caused by the disease itself, (2) the presence of comorbidities with immune deficiencies, and/or (3) the use of immune-suppressants such as the DMARDs [23,24]. Previous studies have reported that RA is associated with the risk of respiratory infections and respective complications, including viral diseases such as influenza [25,26].

However, it is unclear whether the presence of RA or receiving immunosuppressive therapy is associated with serious SARS-CoV-2 infections. Because of these above-mentioned factors, RA patients may be considered at high risk for a more severe course of SARS-CoV-2 infection, including hospital admissions, complications, and death. However, one of the confounding factors is the potential anti-SARS-CoV-2 efficacy of HCQ, which is regularly used by some of these patients. Therefore, the studies to be conducted on this patient group will also provide important information about the prophylactic effects of this medicine. Apart from our study, there is only one large-scale study, which evaluated those patients in this regard. This study evaluating 600 patients with rheumatic diseases from 40 countries found that advanced age, comorbidities (hypertension, cardiovascular disease, and diabetes), and the use of high prednisone doses (≥10 mg / day) were associated with increased hospitalization rates due to SARS-CoV-2 infections. However, this relationship did not exist with the use of antimalarials [8]. Although we found that the presence of Hypertension and heart disease, especially diabetes, were associated with deterioration of some laboratory and clinical parameters, we did not observe any significant relationships of these comorbidities with the length of hospital stay, the requirement for intensive care, and CT findings. Again, we did not find any significant effects of the use of HCQ, other csDMARDs, and low dose corticosteroids on any of the parameters. Because none of the patients included in the study were using high-dose corticosteroids or biological DMARDs, no comparisons could be made regarding the effects of these medications. Also, we did not observe a statistically significant effect of HCQ on the parameters associated with complicated SARS-CoV-2 infection, which was described earlier. This is a result that needs to be questioned about the prophylactic use of this drug.

The high mortality rate of the SARS-CoV-2 pandemic and its destructive effects on healthcare systems and the devastating impact on the economy alarmed all healthcare professionals to find a rapid solution. Discovering a prophylactic medication and developing a vaccine may be the leading milestones in any pandemic. However, the novelty of the SARS-CoV-2 virus, the uncertainty of the respective immune reactions, and the rapid spread of the infection make it uncertain whether a successful vaccine can be developed against this virus in the short term. Perhaps, this is the reason why HCQ was the first molecule to be introduced globally as a prophylactic drug [17].

The first reports recommending HCQ as an effective treatment for SARS-CoV-2 infection have been under increased scrutiny due to questionable methodologies and outcomes [13,19,27,28]. Our results support the negative studies on the prophylaxis and efficacy of HCQ therapy. Intensive use of HCQ as a treatment option for the treatment of SARS-CoV-2 infection is an important issue for rheumatology [29,31]. Because many rheumatology patients, especially patients with RA and SLE, have begun to state that they experience difficulties in their access to HCQ that they have been using for many years without any

problems. Further studies should definitely examine the effects of this on the course of these diseases and drug regimens. It should be kept in mind that HCQ is not yet a proven treatment or prophylactic therapy to be used for SARS-CoV-2 and that it is a critical drug for many patients with rheumatic diseases and it reduces mortality and exacerbations in these patients.

Declarations

Compliance with ethical standards

Disclosures: None.

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