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Impact of the Long-Term Hydroxychloroquine Use on COVID-19 Severity in Patients with Autoimmune Rheumatic Disease

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ABSTRACT

Aim: After the numerous studies, the clinical effectiveness of hydroxychloroquine (HCQ) against SARS-CoV-2 is now accepted limited. Besides this, HCQ has still been the first option in most rheumatology practices. To evaluate the frequency, severity and complication of COVID-19 in patients with autoimmune rheumatologic disease (ARD) receiving and not receiving long-term HCQ.

Methods: A total of 309 ARD patients were retrospectively evaluated for COVID-19 disease with a SARS-CoV-2 RT-PCR and IgM/IgG antibody.Patients were grouped as HCQ or non-HCQ groups. COVID-19 clinical symptoms development of viral pneumonia, rates of hospitalization, mortality due to COVID-19 and time from initial symptom to viral pneumonia, clinical recovery and RT-PCR negativity were evaluated.

Results: During the 13 month study period, 54 (17.4%) were diagnosed with COVID-19, the frequency of COVID-19 was similar between the HCQ (17.9%) and non-HCQ groups (16.7%), p=0.793. The frequency of the myalgia, arthralgia and sore throat were higher in the non-HCQ group, the frequency of other clinical signs and symptoms were higher in the HCQ group but none of them reached statistical significance. In all patients, viral pneumonia was diagnosed in 9 (16.7%), requiring hospitalization in 8 (14.8%), requiring oxygen therapy in 4 (7.4 %) patients and these severe COVID-19 clinical features were similar between groups. COVID-19 complications were seen in 2 patients, 1 of whom was mortality due to ARDS and one was supraventricular tachycardia but thromboembolism or rheumatologic disease activation were not observed.

Conclusions: As with the frequency of COVID-19, severity of COVID19 were similar between patients with and without long-term HCQ use in ARD. COVID 19 complications were found to be rare in our study.

Keywords: Autoimmune rheumatic disease, COVID-19, hydroxychloroquine, pneumonia, mortality.

ÖZET

Amaç: Güncel çalışmaların ışığında SARS- CoV- 2 enfeksiyonlarında hidroksiklorokin (HCQ) kullanımının klinik etkisi kısıtlı olarak kabul edilmektedir. Bununla birlikte HCQ halen romatoloji pratiğinde ilk tercih olarak kullanılmaktadır. Uzun dönem HCQ kullanımının otoimmün romatolojik hastalığı olan hastalarda COVID-19 sıklığı, ciddiyeti ve komplikasyonları üzerine etkisinin değerlendirilmesi amaçlandı.

Metod: Toplam 309 otoimmün romatizmal hastalığı olan hasta retrospektif olarak COVID-19 enfeksiyonu yönünden SARS-CoV-2 RT-PCR ve IgM/IgG antikoru ile değerlendirildi. Hastalar uzun süreli HCQ alıp almamasına göre sınıflandı. COVID-19 semptomları, viral pnömoni gelişmesi, hastane yatış oranları, COVID-19'a bağlı mortalite ve viral pnömoni başlangıç semptomlarının gelişmesinden klinik düzelme ve RT-PCR negatifliği geçen süre değerlendirildi.

Bulgular: On üç aylık çalışma periyodu boyunca 54 (17.4%) COVID-19 tanısı konuldu. COVID-19 sıklığı HCQ kullanan ve kullanmayan gruplarda benzer olarak saptandı p=0.793. Miyalji, artralji ve boğaz ağrısı HCQ kullanmayan grupta daha fazla saptandı. Diğer klinik bulgu ve semptomlar HCQ grubunda daha fazla saptandı ancak istatistiksel olarak anlamlı gösterilemedi. Toplam 9 (16.7%) hastada viral pnömoni gelişti, 8 (14.8%) hastada hastane yatışı, 4 (7.4 %) hastada oksijen tedavisi gerekti. Ciddi COVID-19 klinik bulguları her iki grupta benzerdi. COVID-19 komplikasyonları 2 hastada görüldü; 1'i ARDS' ye bağlı ex oldu ve birinde supraventriküler taşikardi gelişti ama tromboemboli veya romatolojik hastalık aktivasyonu gözlenmedi.

Sonuç: COVID-19 sıklığı ve ciddiyeti uzun dönem HCQ kullanımından bağımsız olarak her iki grupta benzer olarak saptandı. COVID-19 komplikasyonları çalışmamızda nadir olarak saptandı.

Anahtar Kelimeler: Otoimmün romatizmal hastalığı, COVID-19, hidroksiklorokin, pnömoni, mortalite.

After hydroxychloroquine (HCQ) had been demonstrated to interfere with the proliferation of diverse viruses, including the severe acute respiratory syndrome coronavirus (ARDS), by inhibiting virus/cell fusion in vitro studies, it has become a subject of research in prevention and treatment of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1, 2]. Despite there being some studies supporting the use of HCQ in COVID-19 patients, after recent studies HCQ is not recommended for prophylaxis and treatment of COVID-19 [3, 4]. However HCQ concentrates in the lung one hundred times higher than the blood and the function of the pulmonary compartment could be affected due to these high concentrations [5]. Therefore, some studies also suggest HCQ might reduce morbidity in COVID-19, shorten the time to clinical recovery and promote the resolution of pneumonia [6-7].

The COVID-19 clinical course is heterogeneous. Although most patients suffer mildly, a significant portion of the patients develop fatal complications such as ARDS, multiorgan failure and a hyperimmune state so-called "cytokine storm" which is characterized by the extreme release of various cytokines and chemokines, disequilibrium in distribution of T-cell subsets and related with a poor prognosis. The true cause of this state has not yet been fully clarified. However hypothetically the underlying reasons may be a overactive immun system, prolonged immun response due to delayed viral clearence or immun dysregulation. Cytokine storm has been observed in critically ill patients with SARS-CoV-2 infection [8, 9]. HCQ is considered as an immunomodulator and can reduce inflammation and organ damage by inhibiting antigen presentation to T cells and reducing the expression of cytokines such as interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF) α. Theoretically, although it could not prevent the emergence of disease, these findings support the notion that HCQ may have the ability to inhibit the production of cytokines and alleviate the clinical symptoms in patients with COVID-19 [10,11].

In rheumatology practice, HCQ has been used to treat autoimmune rheumatic diseases [12]. In the light of recent studies, the effect of HCQ on disease severity rather than protection from COVID-19 is intriguing and can be further investigated. In this study, we aimed to investigate the efficacy of long-term HCQ use in preventing viral pneumonia, admission to hospital, length of clinical-serological recovery, severity, complication and mortality in the COVID-19 patients with an autoimmune rheumatic disease.

Materials and methods

Study Design

This study was designed as a cross-sectional, retrospective cohort study with approval by Ankara Bilkent City Hospital Ethics Committee and was therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments (IRB no. E1-20-683). An official permission was also obtained from the Republic of Turkey Ministry of Health, to conduct this study dated 30 September 2020.

Patients

This cohort was formed from autoimmune rheumatic disease patients who have previously been followed in Ankara Bilkent City Hospital. To collect the cumulative incidence of confirmed COVID-19, patients of this cohort were retrospectively investigated for a SARS-CoV 2 real-time reverse transcription polymerase chain reaction (RT-PCR) test result from Public Health Management System (HSYS) between March 11th 2020 and April 23th 2021. All cases with a RT-PCR test were registered in HSYS during the pandemic in Turkey. SARS-CoV-2 IgM/IgG antibodies were screened to determine COVID-19 disease in RT-PCR negative cases. Patients with a positive nasopharyngeal swab RT-PCR test or SARS-CoV-2 IgM/IgG antibodies were enrolled in the study. Subjects with age under 18 years, pregnant, lactating, receiving immunosuppressive and immunomodulatory therapy for a reason other than rheumatological disease, patients whose HCQ treatment was initiated due to COVID-19 and incomplete medical record were excluded from the study. Patients were grouped as HCQ or non-HCQ groups according to whether they received HCQ as treatment for underlying autoimmune rheumatic disease or not. According to the Republic of Turkey Ministry of Health COVID-19 protocol, Favipiravir (with 3200 mg twice daily for 1 day, followed by 1200 mg twice daily for 4 days) and/or HCQ (400 mg twice daily for 5 days) was administered to patients [13].

Main Outcomes and Other Variables

Data regarding demographics, comorbidities, medical treatments and last disease activity of underlying rheumatic disease in the last follow-up before COVID-19 diagnosis was obtained from medical records and telephone interviews. COVID-19 clinical symptoms at presentation, laboratory results, rates of viral pneumonia, hospitalization, intensive care unit (ICU) admission, 28th day mortality due to COVID-19 and time from initial symptom to viral pneumonia, clinical recovery and RT-PCR negativity were evaluated. Disease activity of patients was classified as

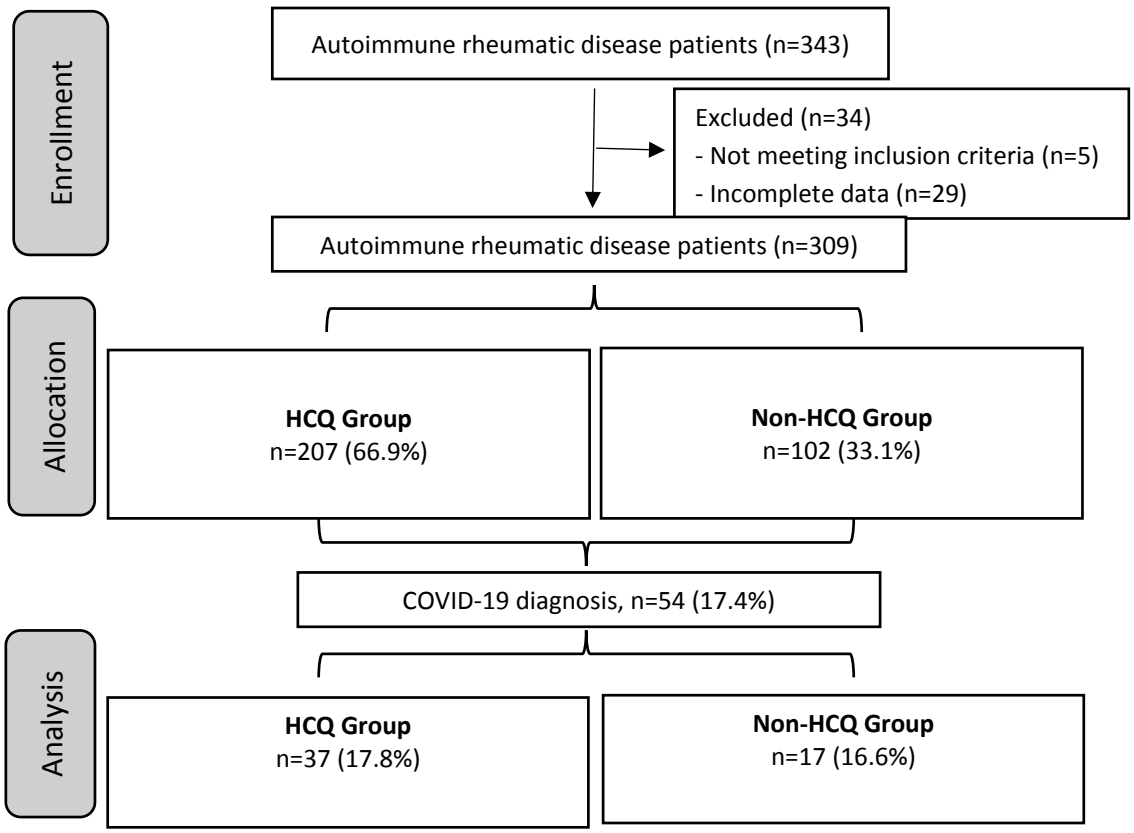
active or in remission by the rheumatologist according to clinical findings and laboratory results at the last control follow-up. COVID-19 pneumonia was diagnosed when the other causes of pneumonia ruled out with chest computed tomography scan. All demographic, laboratory, clinical data and primary outcome variables were compared between groups. The all glucocorticoid doses specified as prednisolone equivalent.

Statistical Analysis

Normality of continuous variables was evaluated with Shapiro–Wilk test and with plots and histograms visually. Continuous variables were presented as mean ± SD and median with interquartile range (IQR) (25–75%). Proportions are used as descriptive statistics for categorical variables. Comparisons between groups were done using the x^2 test or Fisher exact test in categorical and with independent sample t-test or Mann-Whitney test in continuous variables, as appropriate. $p<0.05$ was considered statistically significant. All reported p values were 2-sided. Data analysis was performed using SPSS V.24.0 software.

Results

During the study period (13 months), 17.4% (n=54/309) patients with autoimmune rheumatic diseases were diagnosed with COVID-19 which was similar between the HCQ (17.9%) and non-HCQ groups (16.7%), p=0.793. The patients' flow diagram is presented in Figure 1. Among these 54 COVID-19 patients, 22 (40.7%) were also treated with systemic prednisolone, at doses usually below 10 mg per day. Twenty-one (38.8%) patients were also taking non-HCQ disease modifying antirheumatic drugs (DMARDs); such as methotrexate in 11, leflunomide in 4, tofacitinib in 3, azathioprine in 2 and sulphasalazine, cyclophosphamide, rituximab and etanercept each in 1. Half of the patients with COVID-19 had at least one comorbidity, the most common comorbidity being hypertension.



Abbreviations: HCQ: hydroxychloroquine

Figure 1: Flow chart of the study

The demographics, baseline clinical characteristics, the frequency of comorbidity , on going treatments and disease activity of autoimmune rheumatic disease were similar between the HCQ and non-HCQ groups (Table 1).

In the HCQ group, 17 (46%) patients were receiving HCQ at a dose of 200 mg/day and 20 (54%) were receiving HCQ at a dose of 400 mg/day.

Table 1: Comparison of demographics, baseline clinical characteristics, organ involvements and current treatments of autoimmune rheumatic disease patients between hydroxychloroquine group and non-hydroxychloroquine group

	HCQ group (n=37)	Non-HCQ group (n=17)	p
Women, n (%)	35 (94.6)	13 (76.5)	0.071
Age, years, mean±SD	50.3±11.9	53.5±9.1	0.283
Duration of diagnosis, months, median (IQR)	48 (24-90)	12 (12-108)	0.072
Autoimmune rheumatic diseases			
Rheumatoid Arthritis, n (%)	11 (29.7)	8 (47.1)	0.216*
Connective Tissue Diseases except RA, n (%) -Sjögren's Syndrome, n (%) -Systemic Lupus Erythematosus, n (%) -Others, n (%)	26 (70.3) -17 (45.9) -4 (10.8) -5 (13.5)	9 (52.9) -5 (29.4) -1 (5.9) -3 (17.6)	
Comorbidity, n (%)	17 (45.9)	10 (58.8)	0.379
Multimorbidity, n (%)	4 (10.8)	4 (23.5)	0.222
Hypertension, n (%)	5 (13.5)	5 (29.4)	0.162
Diabetes Mellitus, n (%)	1 (2.7)	2 (11.8)	0.230
Chronic obstructive lung disease, n (%)	4 (10.8)	1 (5.9)	1
History of thrombosis, n (%)	2 (5.4)	2 (11.8)	0.582
Disease activity at last follow-up	6 (16.2)	0	0.161
Current or history of organ involvement			
Arthralgia/Arthritis, n (%)	27 (73.0)	13 (76.5)	0.735
Cutaneous involvement, n (%)	7 (18.9)	1 (5.9)	0.411
Any internal organ involvement, n (%)	9 (24.3)	3 (17.6)	0.584
Treatment regimens			
Prednisone use, n (%)	18 (48.6)	4 (23.5)	0.081
Prednisone ≥10 mg per day, n (%)	2 (5.4)	0	NS
Non-HCQ DMARDs, n (%)	16 (43.2)	5 (29.4)	0.333
ACE inhibitors and/or ARBs, n (%)	4 (10.8)	5 (29.4)	0.088
Non-steroidal anti-inflammatory drugs, n (%)	2 (5.4)	1 (5.9)	1
Oral anticoagulant, n (%)	1 (2.7)	1 (5.9)	0.535

HCQ: Hydroxychloroquine, RA: Rheumatoid arthritis, DMARDs: Disease modifying antirheumatic drugs, ACE: Angiotensin converting enzyme, ARBs: Angiotensin receptor blockers
**Comparison between rheumatoid arthritis and connective tissue disease except RA*

The most common initial symptoms of the COVID-19 were arthralgia in 16 (29.6%) patients, fatigue in 11 (20.3%), cough in 7 (12.9%), fever in 6 (11.1%), headache in 6 (11.1%). Comparison of clinical features, treatments and outcomes of COVID-19 between the HCQ and non-HCQ groups were shown in the table 2. The frequency of the myalgia, arthralgia and sore throat were higher in the non-HCQ group, the frequency of other clinical signs and symptoms were higher in the HCQ group but none of them reached statistical significance. None of the patients showed clinical activation signs of rheumatological disease during COVID-19 disease. Laboratory results at the diagnosis of COVID-19 disease were also similar between the groups and were shown in the supplementary table 1. After the diagnosis of COVID-19, HCQ was maintained with the same dose in 27 (73.0%) patients, whereas all other immunosuppressant drugs were cessated. In COVID-19 treatment period, HCQ was well tolerated with no side effects. Total steroid dose was needed to be increased in 3/8 (37.5%) of hospitalized patients. All patients received treatment for COVID-19 as HCQ and/or favipiravir. Antiviral treatments such as favipiravir were used in 48 (88.8%) patients and antibiotics were administered in nine (16.6%) even though no bacterial infections were shown in the cultures. No patient received additional biologic or immunomodulatory therapy other than steroids. Viral pneumonia was diagnosed in 9 (16.7%), requiring hospitalization in 8 (14.8%), requiring oxygen therapy in 4 (7.4 %) patients and one patient needed intensive care. None of the patients with viral pneumonia had more than 25% involvement on computed tomography of the chest. The median hospitalization time was 9.5 (1-20) days. Comparison of the 2 groups according to median (IQR) time from the initial symptom to viral pneumonia and time to clinical recovery, RT-PCR negativity were shown in table 3.

Supplementary Table 1: Comparison of the baseline laboratory results of COVID-19 patients at the diagnosis between with hydroxychloroquine group or non-hydroxychloroquine group

Baseline laboratory results	HCQ group, n=37	Non-HCQ group, n=17	p
White blood cell(/mm^3), mean(±SD)	6631(±2101)	6895(±1318)	0.673
Lymphocytes count, /mm^3, mean(±SD)	1644(±616)	1697 (±730)	0.810
Lymphopenia, n (%)	5 (19.2)	4 (28.6)	0.694
Hemoglobin (g/L), mean(±SD)	12.7(±1.2)	13.3(±1.3)	0.151
Platelet (/mm^3), mean(±SD)	274(±75)	268(±67)	0.821
Aspartate aminotransferase (IU/L), median (IQR)	23 (14-32)	21 (17-28)	0.887
Alanine aminotransferase (IU/L), median (IQR)	21 (18-34)	24 (14-39)	0.670
Lactate dehydrogenase, mean(±SD)	247(±79)	246(±87)	0.987
Albumin (g/L) , mean(±SD)	40.4(±9.1)	42.6(±3.6)	0.410
Creatinine kinase, median (IQR)	50 (37-80)	64 (40-106)	0.262
Creatinine (µmol/dL), mean(±SD)	0.73(±0.16)	0.76(±0.10)	0.416
D-dimer, median (IQR)	0.40 (0.23-1.05)	0.45 (0.35-0.80)	0.509
Procalcitonin, ng/mL, mean(±SD)	0.046(±0.017)	0.03(±0.004)	0.056
CRP (mg/L), median (IQR)	4 (3-14)	5 (2-19)	0.938
Ferritin, median (IQR)	38 (10-85)	50 (19-91)	0.786

HCQ: Hydroxychloroquine, CRP: C-reactive protein

Table 2. Comparison of clinical features, treatments and outcomes of COVID-19 in patient between the hydroxychloroquine and non-hydroxychloroquine groups

Signs and symptoms at baseline	HCQ group, n (%)	Non-HCQ group, n(%)	p
Fever	18 (48.6)	4 (23.5)	0.081
Cough	23 (62.2)	9 (52.9)	0.522
Sputum	4 (10.8)	2 (11.2)	1
Shortness of breath	14 (37.8)	5 (29.4)	0.547
Chest pain	15 (40.5)	3 (17.6)	0.097
Myalgia	28 (75.7)	16 (94.1)	0.105
Back pain	28 (75.7)	9 (52.9)	0.095
Arthralgia	27 (73.0)	15 (88.2)	0.210
Confusion	1 (2.7)	0	1
Headache	27 (73.0)	11 (64.7)	0.537
Sore throat	21 (56.8)	11 (64.7)	0.581
Rhinorrhea	13 (35.1)	6 (35.3)	0.991
Dysgeusia	27 (73.0)	9 (52.9)	0.147
Anosmia	25 (67.6)	9 (52.9)	0.301
Nausea and/or vomiting	12 (32.4)	2 (11.8)	0.107
Stomach ache	7 (18.9)	0	0.084
Diarrhea	6 (16.2)	2 (11.8)	0.669
Treatment			
Hydroxychloroquine	27 (73.0)	10 (58.8)	0.298
Antiviral therapy	32 (86.5)	16 (94.1)	0.652
Increase steroid dose in hospitalized patients	2/6 (33.4)	1/2 (50)	0.587
Anticoagulant therapy	10 (27.0)	4 (23.5)	0.735
Antiaggregant therapy	11 (29.7)	6 (35.3)	0.683
Antibiotic therapy	8 (21.6)	1 (5.9)	0.149
Outcomes			
Viral pneumonia	5 (13.5)	4 (23.5)	1
Hospitalization	6 (16.2)	2 (11.8)	0.669
Oxygen support	3 (8.1)	1 (5.9)	1
Mortality	1 (2.7)	0	

HCQ: Hydroxychloroquine

Table 3. Comparison of the groups according to time from the initial symptom to viral pneumonia, time from initial symptom to clinical recovery and RT-PCR negativity

	HCQ group	Non-HCQ group	p
Initial symptom to viral pneumonia, days, median (IQR)	10 (5-10)	8.5 (7-10)	1
Initial symptom to clinical recovery, days, median (IQR)	14 (10.0-15.0)	10 (7.0-12.5)	0.065
Initial symptom to RT-PCR negativity, days, median (IQR)	14 (10-14)	14 (10-16)	0.293

RT-PCR: Real-time reverse transcription polymerase chain reaction, HCQ: Hydroxychloroquine

During the follow-up, 2 patients in the HCQ group had complications due to COVID-19, 1 of which resulted in death. Supraventricular tachycardia was developed in one patient (70 years old, female, with hypertension and diabetes mellitus) in the HCQ group whose initial symptom was also palpitations. The radiofrequency ablation had to be planned for not responding to medical treatment. Another patient (74 years old, male, with hypertension and chronic obstructive pulmonary disease) whose initial symptom was unconsciousness, progressed to ARDS and died in ICU. In evaluation for acute clinical symptoms, no neurological or thromboembolic complications were detected in either patient. Except for these patients, no acute renal failure was seen and no haemodialysis or extracorporeal membrane oxygenation was required and all patients had full recovery.

Comparison of the main outcomes in 22 COVID-19 patients who received prednisone was shown in the supplementary table 2. The main outcomes were also similar between HCQ group and non-HCQ group in these subgroups of patients.

Supplementary table 2: Comparison of the main outcomes of 22 COVID-19 patients received prednisolone between with hydroxychloroquine group or non-hydroxychloroquine group

	HCQ group, (n=18)	Non-HCQ group, (n=4)	p
Viral pneumonia, n (%)	3 (16.7)	2 (50.0)	0.210
Hospitalization, n (%)	3 (16.7)	1 (25.0)	1
Oxygen support, n (%)	1 (5.6)	1 (25.0)	0.338
Mortality, n (%)	None	None	
Clinical recovery, days, median (IQR)	14.5 (10-19.3)	13.5 (6.5-23.7)	0.962
Time to RT-PCR negativity, days, median (IQR)	14 (11.5-14)	13 (10.0-16.0)	0.554

HCQ: Hydroxychloroquine, RT-PCR: Real-time reverse transcription polymerase chain reaction.

Discussion

The frequency of COVID-19 was approximately 17% in the entire cohort and was similar between HCQ and non-HCQ groups and all mortality was just 0.3%. The primary outcomes of our study, such as viral pneumonia development, hospitalization, and length of clinical and serological recovery, were similar in patients with autoimmune rheumatic diseases regardless of long-term HCQ use.

Antimalarial medications interfere with the proliferation of various viruses, including SARS-CoV-2, by inhibiting virus/cell fusion in vitro studies [1, 2]. In a study, postexposure HCQ use in COVID-19 resulted in a significant increase in SARS-CoV-2 IgG/IgM seroconversion [14]. With the current knowledge, SARS-CoV-2 could enter the cell through two different mechanisms, one endocytosis and other membrane fusion. HCQ has been shown to suppress endocytosis mediated entry into the cell [14-16]. High viral load of SARS-CoV-2, primarily by suppressing type I interferon (IFN) response, leads to progression of disease to cytokine storm and ultimately death [17]. Another point that suggests HCQ can be effective in COVID-19 disease is that it prevents suppression of the IFN pathway by blocking endocytosis. But SARS-CoV-2 also enters the cell through transmembrane serine protease 2 mediated membrane fusion and the angiotensin converting enzyme 2 receptor. Unfortunately, HCQ could only block the endosomal entry into the host cell and not membrane fusion. This probably limits the effectiveness of HCQ in treating COVID-19 [15]. But in patients currently taking HCQ it is intriguing that early activation of the innate and adaptive immune response could prevent progression of disease with reduced viral load, decreased tissue damage and blocked cytokine storm. Many studies have evaluated disease severity and mortality in COVID-19 autoimmune rheumatic diseases and found no significant association between antimalarial treatment for COVID-19 infection and hospitalisation, disease severity; after adjustment for demographic and medical characteristics [18-20]. Supporting the previous studies, we found that the long-term HCQ use in autoimmune rheumatic diseases had no effect on severity of COVID-19.

In our study, while the frequency of COVID-19 in autoimmune rheumatic diseases with HCQ indication was 17.4%, its frequency in the general population in Turkey is reported to be 5.2%. And in this study period, mortality due to COVID-19 in all patients in our country was 0.8% [21]. We had just one (1.8%) mortality among the patients with COVID-19 in our cohort. Although the number of patients and total mortality were low in our study, HCQ use had no effect on mortality. In a study with 194,637 RA or

SLE patients, COVID-19 mortality was similar in HCQ and non-HCQ groups [22]. In a recent study with rheumatic diseases, the COVID-19-related mortality rate was found 10.5% which was higher than the general population [23]. A lower mortality rate of our cohort than the above study may be related with a low inflammatory load of our patients which suggests mild illness. In addition to increased inflammatory load, increased mortality associated with disease activity [23]. In our study, 11% of the patients had active disease, all in the HCQ group. After all, in accordance with the literature, both the frequency and mortality of COVID-19 in our cohort were higher in autoimmune rheumatic diseases than the normal population. In a study from Turkey (similar ethnicity and geography with our cohort), after evaluating 167 inflammatory rheumatic patients with COVID-19 infection, the mortality rate was found 10% between April-June 2020 [24]. Although the patient populations are different, our mortality rate is lower than this study, it may be related to the fact that the studies were carried out in different time periods and, as in the whole world, the increasing knowledge about COVID-19 disease and treatment options.

In addition, it was shown that concentration of HCQ in the lung is higher than that in the blood. So it was supposed, apart from being unable to prevent disease, HCQ favorable effects could still be observed on the course and complications of COVID-19 [5]. Without statistical significance, despite the HCQ group having lower respiratory tract symptoms, the rate of viral pneumonia was lower than the non-HCQ group. In our cohort, only one patient had supraventricular tachycardia associated with COVID-19 and one had ARDS lead to death . Apart from these complications, in a median 5.7 months (4.4-6.8) of follow-up, no patients had acute or post-COVID complications such as thromboembolic and neurologic. In accordance with the severity of the disease, the frequency of COVID-19-associated thromboembolism had seen between 10-40% in the studies [25,26]. Perhaps this issue still needs to be explored in larger patient groups.

Another subject under investigation about HCQ is whether it can achieve clinical improvement by accelerating viral clearance. There were studies that both support and oppose this hypothesis. In a study, there was found that HCQ could improve the clinical outcome of patients by reducing SARS-CoV-2 viral load [27]. In a recent study evaluating a total of 393 COVID-19 patients, the addition of HCQ to the standard treatment was associated with less ICU admission, early discharge and higher CRP responses compared to the standard treatment group, but no difference was found in the 28th day mortality rate [28]. Despite these, in a randomized controlled trial, 150 patients were evaluated, and administration of HCQ did not result in better viral clearance than standard of care alone in hospitalized patients [29]. So, in our study, we could not find any positive effects of long-term HCQ use on viral clearance or outcomes in patients with autoimmune rheumatic disease.

Our study includes the first analysis of about COVID-19 patients with autoimmune rheumatic diseases with long-term HCQ use in the Turkish population. All cases were from a single center with follow-up duration longer than a year. The screening of RT-PCR negative cases with SARS-CoV-2 IgM/IgG antibodies had increased the strength of this study. On the other hand, there are important limitations. First of all, this study was conducted as a retrospective and sample size was limited. Secondly, although patients with RT-PCR and antibody positivity were included in the study, an asymptomatic group of patients may have been ignored. Thirdly, not all patients had control evaluation for RT-PCR negativity which may have caused some data to be underestimated. Lastly, activation of rheumatological disease during COVID-19 was just evaluated as clinical, without activity scores.

Conclusion

This study showed us that long-term use of HCQ in autoimmune rheumatic diseases had no effect on the development of pneumonia, clinical recovery and RT-PCR negativity on patients with COVID-19. The severity of COVID-19 was found similar between patients regardless of long term HCQ use. Although HCQ treatment in COVID-19 was seen ineffective, the absence of complications supports the continuation of the drug in patients with HCQ indication due to the underlying disease. Our study is informative, but not built to inform on potential efficacy of HCQ in terms of antiviral and/or immunomodulating in COVID-19 management. Lastly, we think that it could still be needed to evaluate the classical treatments, already in use for other reasons, for the COVID-19 disease which has novel mutations day by day and does not have a definitive treatment yet.

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Conflict of Interest

The authors have no conflicts of interest to declare.

Ethics Approval

All protocols for this study were approved by the Ankara Bilkent City Hospital Clinical Research Ethics Committee (Decree Date:30.09.2020 and No: E1-20-683)

Patient Consent for Publication

This was a retrospective study and all patients were deidentified. So, there was no need for written informed consent.

Availability of Data and Materials

All analyzed data obtained in this study are included in Table 1, Table 2, Table 3, Supplementary table 1 and Supplementary table 2.

Authors' Contributions

All authors contributed to data collection, writing the manuscript. BA has also done the statistical analysis.

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