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SHORT COMMUNICATION

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Frequency and severity of COVID-19 in patients with various rheumatic diseases treated regularly with colchicine or hydroxychloroquine

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Abstract

This study aimed to investigate whether patients regularly using colchicine or hydroxychloroquine (HCQ) have an advantage of protection from coronavirus disease 2019 (COVID-19) or developing less severe disease. Patients who were taking colchicine or HCQ regularly for a rheumatic disease including Familial Mediterranean Fever, Behçet's syndrome, Systemic Lupus Erythematosus, Rheumatoid Arthritis, and Sjogren's syndrome, as well as their healthy household contacts as the control group, were included in the study. The clinical data regarding COVID-19 were collected using a standard form, and serum samples were analyzed for anti-severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) nucleocapsid immunoglobulin G (IgG). A total of 635 regular colchicine users with their 643 household contacts and 317 regular HCQ users with their 333 household contacts were analyzed. Anti-SARS-COV-2 IgG was positive in 43 (6.8%) regular colchicine users and 35 (5.4%) household contacts (odds ratio [OR] = 1.3; 95% confidence interval [CI]:0.8–2; $p = 0.3$). COVID-19-related symptoms were described by 29 (67.4%) of the patients and 17 (48.6%) household contacts (OR = 2.2; 95% CI :0.9–5.5; $p = 0.09$), and hospital admission was observed in five (11.6%) and one (2.9%) of these subjects (OR = 4.5; 95% CI: 0.5–40.2; $p = 0.1$), respectively. Seropositive subjects were observed in 22 (6.9%) regular HCQ users and 24 (7.2%) household contacts (OR = 1.1; 95% CI: 0.6–1.9; $p = 0.8$). COVID-19-related symptoms occurred in 16 (72.7%) of the 22 patients and 12 (50%) of 24 household contacts (OR = 2.7; 95% CI: 0.8–9.1; $p = 0.1$). Three patients (13.6%) were admitted to hospital, while one household contact (4.2%) was hospitalized (OR = 3.6; 95% CI: 0.3–37.8; $p = 0.2$). Being on a regular treatment of colchicine or HCQ did not result in the prevention of COVID-19 or amelioration of its manifestations.

KEYWORDS

colchicine, covid-19, Famial Mediterranean fever, hydroxychloroquine, rheumatic and musculoskeletal disease

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) has caused a pandemic of acute respiratory disease, named "coronavirus disease 2019" (COVID-19). A hyperinflammatory response which is also referred to as cytokine storm occurs in a subset of COVID-19 patients, leading to acute respiratory distress syndrome (ARDS) and multiorgan failure[1,2]

Several anti-inflammatory drugs which were targeted different mechanisms and were investigated for both mild and severe COVID-19.[3] Inflammasome activation was one of the previously defined pathways in ARDS pathogenesis leading to exaggerated caspase 1 activation and robust interleukin-1b (IL-1b) and IL-18 secretion.[4] Colchicine has been used to suppress caspase-1 activation by inhibiting inflammasome signaling,[5] and it has been the mainstay treatment in familial Mediterranean fever (FMF), gout, and mucocutaneous Behçet's Syndrome (BS).[6,7] After the identification of the crucial role of inflammasome activation in COVID-19-related acute lung injury, colchicine was considered among the potential therapeutic agents.

Hydroxychloroquine (HCQ), an antimalarial drug frequently used in the treatment of connective tissue diseases, was shown to be effective against SARS-CoV-2 in an in vitro model.[8,9] At the beginning of the pandemic several groups reported favorable results with HCQ in COVID-19 patients, but these initial results could not be confirmed by randomized controlled trials.[10] However, the impact of the regular HCQ use on COVID-19 has still been debated.

We aimed to investigate whether users of regular doses of colchicine or HCQ had an additional advantage in terms of prevention of COVID-19 or its severity. We, therefore, conducted a comparative study with patients regularly using colchicine or HCQ for several underlying disorders and their healthy household contacts by assessing their COVID-19 manifestations and anti-SARS-COV-2 antibody status.

2 | METHODS

2.1 | Patients and controls

This study was conducted between June 1 and September 1, 2020 in patients with FMF and BS who had been taking colchicine and in patients with systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and Sjogren's syndrome (SS) who had been taking HCQ for at least 3 months. We reviewed the electronic records of the patients who had a visit in rheumatology outpatient clinics of Istanbul University-Cerrahpasa and Istanbul University for the last 2 years. Patients treated with any biologic or anti-cytokine treatments were not included in the study. Patients and their household contacts who were not taking colchicine or HCQ were invited to participate in the study by phone calls. Figure S1 shows the volunteered individuals in the study flowchart. Demographic features of the participants were recorded, and all of them were questioned for COVID-19 diagnosis or its known symptoms (fever, cough, myalgia, headache, dyspnea, sore throat, diarrhea, loss of smell, and taste) before study entry. COVID-19-associated hospitalizations including intensive care unit (ICU) of the subjects were checked from the electronic health records. Patients and controls who were diagnosed as COVID-19 with a positive SARS-CoV-2 polymerase chain reaction (PCR) test before antibody assessment were also included in this study.

The ethics committee of Istanbul University-Cerrahpasa Medical Faculty approved the study protocol (Approval number:62050) and written informed consent was obtained from each subject before enrollment.

3 | ANTIBODY STATUS

Venous blood samples were collected from all participants, and serum samples were stored at −70 °C until anti-SARS-CoV-2 antibody analysis. Antibodies against SARS-CoV-2 were determined by the electrochemiluminescence method on Cobas e 601 (Roche Diagnostics). The sensitivity and specificity of the Elecsys Anti-SARS-CoV-2 immunoassay were 99.5% at ≥14 days post-PCR confirmation and 99.80%, respectively.[11] This assay detected total (predominantly IgG) antibodies against an epitope of the viral nucleocapsid protein. Results were evaluated according to a cut-off index (COI) and reported as negative (COI < 1.0) or positive (COI ≥ 1.0). Serum samples of previous COVID-19 cases were obtained at least 14 days after the COVID-19 diagnosis.

4 | STATISTICS

Statistical analysis was performed with SPSS 22.0 software. Mean ± standard deviation values and percentages were used for the analysis of continuous data. The χ^2 test was performed for categorical variables to compare parameters. An independent sample *t* test was conducted for parametric data. Age and gender were analyzed with a univariate logistic regression model.

5 | RESULTS

A total of 635 colchicine users (373 FMF and 262 BS) and their 643 contacts as well as 317 HCQ users (197 SLE, 79 RA, and 41 SS) and 333 contacts were included to study. Demographic features, daily colchicine, and HCQ doses of the patients are shown in Table 1.

5.1 | Effects of regular colchicine use on symptoms and severity of COVID-19

Anti-SARS-Cov-2 nucleocapsid IgG was positive in 43 (6.8%) colchicine users and 35 (5.4%) contacts (odds ratio [OR] = 1.3; 95% confidence interval [CI]: 0.8–2; $p = 0.3$). COVID-19-related symptoms were described

TABLE 1 Demographic features and anti-SARS-COV-2 Nucleocapsid IgG status of entire subjects

Characteristics	Colchicine			Hydroxychloroquine		
	Patients (*N* = 635)	Household contacts (*N* = 643)	*p* value	Patients (*N* = 317)	Household contacts (*N* = 333)	*p* value
Age, mean ± *SD* years	39.1 ± 12.9	37 ± 15.8	0.01	48.3 ± 12.9	40.5 ± 16.8	0.001
Gender, *n* (%)						
Male	226 (25.6)	352 (54.7)	0.001	19 (6.0)	228 (68.5%)	0.001
Female	409 (64.4)	291 (45.3)		298 (94.0)	105 (31.5%)	
Mean colchicine dose, mg/day ± SD	1.5 ± 0.4	N/A	N/A	N/A	N/A	N/A
Mean duration of colchicine usage, years ± *SD*	11.3 ± 8.3	N/A	N/A	N/A	N/A	N/A
Mean HCQ dose, mg/day ± *SD*	N/A	N/A	N/A	263.4 ± 99.4	N/A	N/A
Mean duration of HCQ usage, years ± *SD*	N/A	N/A	N/A	9 ± 6.3	N/A	N/A
Positive antibody to SARS-COV-2, *n* (%)	43 (6.8)	35 (5.4)	0.3	22 (6.9)	22 (7.2)	0.8
Symptomatic COVID-19 in seropositive cases, *n* (%)	29 (67.4)	17 (48.6)	0.09	16 (72.7)	12 (50.0)	0.1
Hospital admission in seropositive cases, *n* (%)	5 (11.6)	1 (2.9)	0.1	3 (13.6)	1 (4.2)	0.2
Prior confirmed COVID-19 cases, *n* (%)	20 (2.8)	6 (0.9)	0.005	16 (5)	5(1.5)	0.01
Positive antibody to SARS-COV-2 in prior confirmed cases, *n* (%)	17 (83.3)	5 (83.3)	0.9	13 (81.2)	4 (80)	0.9
Total hospital admission, *n* (%)	7[a] (1)	2[b] (0.003)	0.09	5[c] (2)	1 (0.003)	0.8

Abbreviations: COVID-19, coronavirus disease 2019; IgG, immunoglobulin G; SARS-COV-2, severe acute respiratory syndrome coronavirus 2.

[a]Two Behcet' syndrome cases who did not seroconvert were hospitalized.

[b]One household contact of a Behcet' syndrome who did not seroconvert was hospitalized.

[c]One SS case who did not seroconvert was hospitalized.

by 29 (67.4%) of 43 patients and 17 (48.6%) of 35 contacts (OR = 2.2; 95% CI: 0.9–5.5; $p = 0.09$), and hospital admission was observed in five (11.6%) and one (2.9%) of these subjects (OR = 4.5; 95% CI: 0.5–40.2; $p = 0.1$), respectively (Table 1). Neither the patients nor their contacts were admitted to ICU. Before serum anti-SARS-CoV-2 nucleocapsid IgG assay, 20 colchicine users and 6 household contacts had a history of COVID-19 (OR:3.4; 95% CI:1.4–8.7; $p = 0.005$).

5.2 | Effects of regular HCQ use on symptoms and severity of COVID-19

Anti-SARS-CoV-2 was positive in 22 (6.9%) HCQ users and 24 (7.2%) contacts (OR = 1.1; 95% CI: 0.6–1.9; $p = 0.8$). COVID-19-related symptoms occurred in 16 (72.7%) of 24 patients, and 12 (50%) of 24 contacts (OR = 2.7; 95% CI:0.8–9.1; $p = 0.1$). Three (13.6%) of the patients and one (4.2%) of the household contacts were admitted to hospital (OR = 3.6; 95% CI: 0.3–37.8; $p = 0.2$) (Table 1). Similar to colchicine users and household contacts, none of them required ICU admission. Before serologic testing, COVID-19 was diagnosed in 16 (5%) HCQ users and 5 (1.5%) contacts (OR = 3.4; 95% CI:1.3–9.6; $p = 0.01$).

6 | DISEASE-SPECIFIC ANALYSES

6.1 | FMF

Anti-nucleocapsid IgG was positive in 25 (6.7%) FMF cases and 23 (6.0%) contacts (OR = 1.1; 95% CI: 0.6–2; $p = 0.7$). COVID-19-related symptoms were observed in 18 (72.0%) of the 25 patients whereas in 10 (43.5%) of the 23 contacts (OR = 3.3; 95% CI: 1–11.1; $p = 0.04$).

One patient was admitted to the hospital and recovered, while none of the household contacts was hospitalized (Table 2).

6.2 | BS

Seropositivity for SARS-CoV-2 was detected in 18 (6.9%) patients and 12 (4.7%) contacts (OR = 1.5; 95% CI:0.7–3.2; $p = 0.3$). Four (22.2%) of the patients and one (8.3%) of the household contacts was admitted to hospital (OR = 3.1; 95% CI:0.3–32.3; $p = 0.3$) (Table 2).

6.3 | SLE

Anti- SARS-CoV-2 was detected in 14 (7.1%) SLE patients and 19 (8.6%) contacts (OR = 0.8; 95% CI: 0.4–1.7; $p = 0.6$). Symptomatic COVID-19 was observed 11 (78.6%) of 14 SLE cases and 9 (47.3%) of 19 contacts (OR = 4.1; 95% CI: 0.8–19.4; $p = 0.07$). Two SLE patients were hospitalized while none of the household contact had hospital admission ($p = 0.2$) (Table 3).

6.4 | RA

Among RA cases and household contacts, four patients (5.1%) and two contacts (2.7%) were seropositive (OR = 1.8; 95% CI: 0.3–10.6; $p = 0.5$). Three of four antibody-positive RA had symptomatic COVID-19 and one was hospitalized, while none of the household contacts described symptoms (Table 3).

6.5 | SS

Four SS cases (9.8%) and three (7.7%) household contacts were seropositive for anti-SARS-CoV-2 (OR = 0.97; 95% CI: 0.2–5.1; $p = 0.9$). Neither symptomatic COVID-19 nor hospitalization was not significantly different between the groups (Table 3).

TABLE 2 Demographic features and anti-SARS-COV-2 Nucleocapsid IgG status of regular colchicine users and household contacts.

	FMF			Behçet's Syndrome		
Characteristics	Patients ($N = 373$)	Household contacts ($N = 386$)	p value	Patients ($N = 262$)	Household contacts ($N = 257$)	p value
Age, mean ± *SD* years	36.4 ± 13.2	36.3 ± 16.1	0.9	42.9 ± 11.4	38.1 ± 15.2	0.001
Gender, *n* (%)						
Male	124 (33.2)	213 (55.2)	0.001	102 (38.9)	139 (54.1)	0.001
Female	249 (66.8)	173 (44.8)		160 (61.1)	118 (45.9)	
Mean colchicine dose, mg/day ± *SD*	1.5 ± 0.4	N/A	N/A	1.4 ± 0.4	N/A	N/A
Mean duration of colchicine usage, years ± *SD*	11.3 ± 8.3	N/A	N/A	10.4 ± 7.7	N/A	N/A
Positive antibody to SARS-COV-2, *n* (%)	25 (6.7)	23 (5.9)	0.6	18 (6.9)	12 (4.7)	0.3
Symptomatic COVID-19 in seropositive cases, *n* (%)	18 (72)	10 (43.4)	0.04	11 (61.1)	7 (58.3)	0.6
Hospital admission in seropositive cases, *n* (%)	1 (3.8)	0 (0)	-	4 (22.2)	1 (8.3)	0.3

Abbreviations: COVID-19, coronavirus disease 2019; FMF, familial Mediterranean fever; SARS-COV-2, severe acute respiratory syndrome coronavirus 2.

TABLE 3 Demographic features and anti-SARS-COV-2 Nucleocapsid IgG status of regular HCQ users and household contacts

Characteristic	SLE			RA			SS		
	Patients (N = 197)	Household contacts (N = 221)	p value	Patients (N = 79)	Household contacts (N = 73)	p value	Patients (N = 41)	Household contacts (N = 39)	p value
Age, mean ± *SD* years	44.2 ± 12.6	39.4 ± 17	0.002	53.9 ± 10.3	40.3 ± 16.6	0.001	57.1 ± 11.2	46.2 ± 16.1	0.001
Gender, *n* (%)									
Male	13 (6.6)	146 (66.1)		16 (38.9)	53 (72.6)		0 (0)	29 (74.4)	
Female	184 (93.4)	75 (33.9)	0.001	73 (61.1)	20 (27.4)	0.001	41 (100)	10 (25.1)	0.001
Mean HCQ dose, mg/day ± *SD*	263.6 ± 95.1	N/A	N/A	255 ± 90.8	N/A	N/A	273.7 ± 132.5	N/A	N/A
Mean duration of HCQ usage, years ± *SD*	10.1 ± 6.6	N/A	N/A	7.3 ± 5.2	N/A	N/A	9 ± 6.3	N/A	N/A
Positive antibody to SARS-CoV-2, *n* (%)	14 (7.1)	19 (8.6)	0.6	4 (5.1)	2 (2.7)	0.5	4 (9.8)	3 (7.7)	0.9
Symptomatic COVID-19 in seropositive cases, *n* (%)	11 (78.6)	9 (47.3)	0.07	3 (75)	0 (0)	0.4	2 (50)	3 (100)	0.4
Hospital admission in seropositive cases, *n* (%)	2 (14.3)	0 (0)	0.2	1 (25)	0 (0)	-	1 (25)	1 (33.3)	0.3

Abbreviations: COVID-19, coronavirus disease 2019; HCQ, hydroxychloroquine; RA, rheumatoid arthritis; SARS-COV-2, severe acute respiratory syndrome coronavirus 2; SLE, systemic lupus erythematosus; SS, Sjogren's syndrome.

Univariate logistic regression analysis showed no effect of age and gender on the SARS-CoV-2 seroprevalence rate among regular colchicine or HCQ users and household contacts ($p = 0.2$ and $p = 0.7$, respectively, for colchicine users vs. contacts, $p = 0.7$ and $p = 0.3$, respectively, for HCQ users vs. contacts).

7 | DISCUSSION

This study documented SARS-CoV-2 seroprevalence among regular colchicine and HCQ users first time, and similar rates of antibody positivity between colchicine or HCQ users and their household contacts suggested that colchicine and HCQ had no protective effects for COVID-19; also, more symptomatic COVID-19 cases and hospital admissions indicated that these drugs had no ameliorating effects on manifestations either.

We observed higher rates of symptomatic COVID-19 and more hospitalization among colchicine users compared with household contacts despite similar seropositivity for SARS-CoV-2, however, these findings were not significant. Bourguipa et al. disclosed similar rates of COVID-19 among FMF patients who were regular colchicine users, however, they reported higher rates of hospitalization (2% vs. 1%), and two of them died.[12] Recently, the COLCORONA trial showed a lower rate of hospitalization and death among PCR confirmed COVID-19 cases, nevertheless, this effect was disappeared in the analysis of whole study subjects.[13] Additionally, a recent study disclosed that there was no additional benefit of colchicine in terms of COVID-19-related death.[14] Although our results indicated no beneficial effects of colchicine on disease susceptibility or severity, there was no deleterious effect of colchicine either on the COVID-19 prognosis.

Likewise, daily use of HCQ at standard doses did not show any additional benefit for symptoms and hospitalizations due to COVID-19. Disease-specific analysis disclosed that SLE patients had fewer COVID-19 rates, however, this finding was not significant. Both seropositivity and symptomatic cases were more common in the RA and SS, and hospitalizations were more common among SLE, RA, and SS cases than their household contacts. Our findings were in the same line with the previous reports which compared continuous HCQ user patients with nonusers.[15]

This study has strengths and limitations. The major strength of the study is that it compared regular long-term users of colchicine and HCQ with their close household contacts, and also assessment of antibody status provided an advantage of distinguishing symptomatic and asymptomatic cases. A recent meta-analysis revealed an increased prevalence of COVID-19 infection in rheumatic patients compared with the general population which was a limitation to assess the preventive role of these medications in patients with rheumatic diseases.[16] The current study reflects the higher frequency of hospitalizations during the first wave of COVID-19, which was different from the current status, and some patients were hospitalized mainly because of their underlying rheumatic diseases with the aim of isolation and close follow-up. Additionally, we did not

determine the time of the hospital stay of the COVID-19 patients. Finally, we did not assess seropositivity for anti-spike IgG, which was found more durable in the late phase of COVID-19.[17]

In conclusion, being on the treatment of regular doses of colchicine or HCQ was not effective in the prevention of COVID-19 and ameliorating its manifestations. Nevertheless, these medications did not cause worse outcomes during the course of the COVID-19 either. However, further studies are needed to assess the preventive role of colchicine or HCQ.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it, and all authors approved the final version to be published. Dr. Ugurlu had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study conception and design*: Mert Oztas, Murat Bektas, Ilker Karacan, Numune Aliyeva, Ayten Dag, Sarvan Aghamuradov, Selim Berke Cevirgen, Selma Sari, Murat Bolayirli, Gunay Can, Huri Ozdogan, Ahmet Gul, Serdal Ugurlu. *Acquisition of data*: Mert Oztas, Murat Bektas, Numune Aliyeva, Ayten Dag, Sarvan Aghamuradov, Selim Berke Cevirgen, Selma Sari, Murat Bolayirli. *Analysis and interpretation of data*: Mert Oztas, Murat Bektas, Gunay Can, Huri Ozdogan, Ahmet Gul, Serdal Ugurlu.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

This study was approved by Istanbul University-Cerrahpasa Ethics Committee (14.05.2020-62050). We hereby confirm that this article has not been published and is not under consideration for publication elsewhere. All authors have contributed to, seen, and approved the final, submitted version of the manuscript. Written informed consent was obtained from the patients.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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