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BRIEF REPORT

Antirheumatic Drug Intake Influence on Occurrence of COVID-19 Infection in Ambulatory Patients with Immune-Mediated Inflammatory Diseases: A Cohort Study

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ABSTRACT

Introduction: We aimed to study the prevalence of a history of COVID-19 infection among patients suffering from systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjögren's syndrome (SjS) or psoriatic arthritis (PsA), and the potential influence of long-term hydroxychloroquine (HCQ) intake.

Methods: We performed an observational monocentric cohort study at the Adolphe de Rothschild Foundation Hospital ophthalmology division (Paris, France). Electronic medical records (EMR) data were searched for keywords associated with SLE, RA, SjS, or PsA. Patients were contacted by phone and were interviewed using a standardized questionnaire. The primary outcome was the occurrence of a positive COVID-19 test result during the study period. We determined the adjusted association between various antirheumatic drugs intake, COVID-19 risk factors, and occurrence of COVID-19 using a logistic regression model. This study is registered on ClinicalTrials.gov (Identifier: NCT04345159).

Results: Patients were recruited between Apr 17, 2020, and Apr 30, 2020 and were recontacted between Oct 6, 2020, and Nov 2, 2020. A total of 569 patients were included, of whom 459 patients were eligible for data analysis. One hundred and eighty-one patients were treated with long-term HCQ and 18 patients had tested positive for COVID-19. No antirheumatic drug intake, including HCQ intake, was significantly associated with an increased or decreased risk of developing COVID-19 infection.

Conclusions: No antirheumatic drug intake was associated with an increased or decreased risk of developing COVID-19 infection in our cohort of patients suffering from immune-mediated inflammatory diseases.

Keywords: Systemic lupus erythematosus; Rheumatoid arthritis; Sjögren's syndrome; Psoriatic arthritis; Hydroxychloroquine; Antirheumatic drugs

Bertrand Kevin and Sené Thomas contributed equally to this work.

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Key Summary Points

Why carry out this study?

The role of antirheumatic drugs, including hydroxychloroquine, as a risk factor or protective factor in COVID-19 infection has been debated.

These drugs are predominantly used to treat patients with immune-mediated inflammatory diseases.

We wanted to determine the influence of antirheumatic drugs on the incidence of COVID-19 infection in a cohort of patients suffering from immune-mediated inflammatory diseases.

What was learned from this study?

No major prophylactic effect of long-term HCQ intake was observed in our cohort.

Patients with immune-mediated inflammatory diseases taking HCQ can be infected with SARS-CoV-2 and develop severe forms of COVID-19 infection.

INTRODUCTION

The potential role of hydroxychloroquine (HCQ) in the coronavirus disease 2019 (COVID-19) pandemic caused by the coronavirus strain SARS-CoV-2 has been debated. An in vitro effect of hydroxychloroquine against SARS-CoV-2 has been described [1, 2].

Early reports have suggested that hydroxychloroquine and azithromycin association allowed respiratory viral load reduction [3]. The same team reported a clinical benefit of this association in a retrospective study [4]. Lower incidences of SARS-CoV-2 infections were noted among patients suffering from rheumatic diseases under treatment with hydroxychloroquine [5]. Hydroxychloroquine oral chemoprophylaxis has been described as effective in young and healthy men in a randomized trial [6]. Conversely, hydroxychloroquine intake with or without azithromycin has been found to be ineffective against COVID-19 infection in multiple observational [7–14], intent-to-treat [15], and randomized controlled [16–24] studies. Recently published meta-analysis found that hydroxychloroquine had no efficacy as a prophylaxis for COVID-19 infections [25], and no clinical benefit in patients hospitalized for COVID-19 [26–30].

We aimed to study the potential influence of long-term HCQ intake on the prevalence of a history of COVID-19 infection among patients having an ophthalmological follow-up in our center and suffering from systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjögren's syndrome (SjS), or psoriatic arthritis (PsA).

METHODS

Study Design and Participants

In this transversal, monocenter, observational cohort study, we aimed to determine the association of ongoing long-term HCQ treatment with the incidence of confirmed COVID-19 infection in patients with SLE, RA, SjS, and/or PsA followed at the Adolphe de Rothschild Foundation Hospital, which is a center dedicated to the treatment of eye and brain diseases. Data were collected from Adolphe de Rothschild Foundation Hospital's data warehouse. EMR containing keywords relevant with a history of SLE, RA, SjS, PsA, or a history of HCQ intake were extracted. All potentially relevant patients were called by phone between April 17, 2020 and April 30, 2020. After having obtained informed consent of the patient, the interview was conducted using a standardized questionnaire about their medical history and their regimen. A second call was made 5 months later. Exclusion criteria were: patient's refusal to participate in the study; no history of corresponding pathology; poor compliance with hydroxychloroquine treatment reported by the patient; introduction, modification, or interruption of hydroxychloroquine treatment between Jan 1, 2020 and Nov 2, 2020. Primary outcome was a history of COVID-19 infection confirmed by serology, PCR, or antigen

test. Each patient was given detailed oral information and the rationale for the study was explained. Oral consent was then collected and consigned. This proceeding was followed by written information sent by e-mail or by post. The COVCALL protocol was approved by research ethics committees Nord-Ouest 1 in France. The "Centre d'investigation clinique" of Rothschild foundation gave approval to access the data. The study was performed in accordance with the declaration of Helsinki 1964 and its later amendments.

Procedures

A group of ophthalmologists was responsible for calling the patients between April 17, 2020 and April 30, 2020. The survey looked for a history of SLE, RA, SjS, PsA; other relevant medical conditions; posology, duration, and observance of a current or past HCQ treatment; other relevant treatments; stability of the pathology under treatment; blood type of the patient; non-steroidal anti-inflammatory (NSAID), corticosteroid, immunosuppressant, conventional or biological disease modifying antirheumatic drugs (cDMARDs, bDMARDs) drug intake; results of COVID-19 real-time reverse transcription polymerase chain reaction (rRT-PCR) testing if it had been performed; history of COVID-19 infection assessed by a doctor; occurrence and cause of a recent hospitalization; symptoms compatible with a COVID-19 infection. Low-dose aspirin prophylaxis was not considered as NSAID intake. The questionnaire used for the interview was standardized and clear instructions were given to the investigators. Patients were called back between Oct 6, 2020, and Nov 2, 2020: they were asked if a COVID-19 test had been realized in the meanwhile, its outcome if appropriate, initiation or termination of HCQ intake between the inclusion and the test, and occurrence of COVID-19-related hospitalization.

Outcomes

The primary endpoint was the occurrence of a biologically confirmed COVID-19 infection.

Statistical Analysis

Python 3.7.5, Scikit learn 0.21.3, Pandas 0.25.3, and Statsmodels 0.11.1 were used for data handling and statistical analysis. We used a logistic regression model to quantify the association between group characteristics and primary outcome. Confirmed COVID-19 infection was the dependent variable of the model. Age, as a continuous feature, was standardized by scaling the maximum value to unit size and the minimum value to 0 using Scikit learn MinMaxScaler function. Other categorical variables had only two possible values. Because of the low number of proven COVID-19 infections, COVID-19 comorbidities were analyzed as a whole. Because of missing data, blood type was not included in the analysis. In order to handle multicollinearity among features, variation inflation factors (VIF) were calculated using statsmodels variance_inflation_factor function. A maximum VIF value of 5 was considered acceptable. A logistic regression model (implemented in Python statsmodels 0.11.1 library using the logit function with L1 regularization) was trained to predict the dependent variable. Non-informative variables were then dropped and the model was refitted. Odds ratios associated with each feature were obtained by calculating the exponential function of each coefficient value and related p value was reported.

RESULTS

A total of 2027 patients with relevant keywords in their EMR were found in the Rothschild Foundation Hospital data warehouse. A first screening aimed at removing the EMR mentioning a disease in another context than mentioning it as a diagnosis was performed; 1889 EMR were assessed for eligibility in this study and called between Apr 17, 2020 and Apr 30, 2020. Nine hundred and sixty-three patients (51.0%) could not be reached by phone. Among the 926 patients reached by phone, 155 (16.7%) declined to participate or were not able to answer, and 202 patients (21.8%) did not meet the inclusion criteria (none of the four

Table 1 Demographic data of study participants

	No HCQ intake (n = 278)	HCQ intake (n = 181)
Patient age (years)	61.5 (14.1; 21.0–97.0)	56.1 (15.0; 22.0–93.0)
Female	n = 245 (88.1%)	n = 171 (94.5%)
Duration of HCQ treatment	–	10.9 (8.8; 0.5–40.0)
SLE	n = 83 (29.9%)	n = 110 (60.8%)
SjS	n = 114 (41.0%)	n = 50 (27.6%)
RA	n = 94 (33.8%)	n = 55 (30.4%)
PsA	n = 40 (14.4%)	n = 3 (1.7%)
Chronic bronchitis	n = 23 (8.3%)	n = 10 (5.5%)
Cancer	n = 22 (7.9%)	n = 17 (9.4%)
CVD	n = 101 (36.3%)	n = 66 (36.5%)
Diabetes	n = 20 (7.2%)	n = 13 (7.2%)
Comorbidities (all)	n = 130 (46.8%)	n = 87 (48.1%)
NSAIDs	n = 43 (15.5%)	n = 19 (10.5%)
Corticosteroids	n = 163 (58.6%)	n = 105 (58.0%)
IS	n = 6 (2.2%)	n = 6 (3.3%)
cDMARDS	n = 51 (18.3%)	n = 17 (9.4%)
bDMARDS	n = 17 (6.1%)	n = 3 (1.7%)
JAKi	n = 7 (2.5%)	n = 1 (0.6%)
Tested	n = 130 (46.8%)	n = 95 (52.5%)
Tested positive	n = 12 (4.3%)	n = 6 (3.3%)
Hospitalization related to COVID-19 infection	n = 3 (1.1%)	n = 2 (1.1%)

CVD cardiovascular diseases, *DVT-PE* deep vein embolism/pulmonary embolism

pathologies necessary to be included, modification of hydroxychloroquine treatment between Jan 1, 2020 and time of survey and/or bad hydroxychloroquine treatment compliance), leaving 569 patients. After the second call, 16 patients were excluded from the analysis for the same reasons, 13 declined to answer, and 81 were lost to follow-up, leaving 459 patients suitable for analysis. Among those 459 patients, 225 had benefited from a COVID-19 test, of which 18 were positive.

Demographics of the population is presented in Table 1. The main pathology leading to inclusion was SLE (n = 193), followed by SjS (n = 164). Some patients (n = 84) cumulated different pathologies. The most represented comorbidity was a history of cardiovascular disease (n = 167); 120 patients (26.1%) did not know their blood type: therefore, this variable was excluded from the analysis; 181 patients were on long-term HCQ treatment. Among them, six (3.3%) described COVID-19-compatible symptoms during the epidemic period. This proportion was similar among the non-HCQ group (n = 12, 4.3%). Among the patients who tested positive for COVID-19 infection, five were hospitalized: two of them were under long-term HCQ treatment.

Table 2 Odds ratio, confidence intervals, and associated *p* values of studied parameters

	Odds ratio	2.5%	97.5%	*p* value
Female	0.77	0.16	3.66	0.747
Patient age	0.72	0.03	14.94	0.829
SLE	0.62	0.15	2.63	0.521
SjS	1.2	0.34	4.27	0.775
RA	1.34	0.35	5.16	0.671
PsA	0.52	0.05	5.58	0.592
Disease stability	0.46	0.15	1.46	0.188
NSAIDs	0.73	0.15	3.53	0.695
Corticosteroids	1.41	0.5	3.95	0.516
cDMARDS	1.48	0.42	5.29	0.544
bDMARDS	1.17	0.13	10.79	0.889
Comorbidities (all)	1.39	0.47	4.07	0.554
Active HCQ treatment	1.03	0.33	3.2	0.955

The maximum VIF value was 2.21 and therefore no variables were dropped because of multicollinearity. L1 regularization led to drop the "Immunosuppressant intake" and "JAKi intake" features. Mean value or percentages, odds ratio, and *p* value of each selected feature are presented in Table 2. No feature, including HCQ intake, was significantly associated with a lower risk of COVID-19 infection. The lowest *p* value (0.188) was associated with the "Disease stability" feature, which had an OR of 0.46, suggesting a possible greater risk of COVID-19 infection in patients with a non-stabilized disease.

DISCUSSION

Because of their exposure to HCQ before the outbreak, the population of patients under long-term HCQ medication is of particular interest. A study evaluating a cohort of 165 patients with SLE using telemedicine found no evidence of protective action of HCQ and confirmed the occurrence of COVID-19 infection in patients taking HCQ. No COVID-19 infection risk reduction was found in an observational study analyzing 800 patients under long-term HCQ treatment and 449 controls [31]. Long-term HCQ intake was not associated with less severe presentations of COVID-19 among 14 hospitalized patients suffering from rheumatic conditions, matched with 28 control subjects [8]. In an observational study including 47 patients with rheumatic diseases who tested positive on a COVID-19 PCR, 25.5% of the patients were under long-term HCQ treatment and HCQ intake had no significant influence on the occurrence of severe COVID-19 pneumonia [32]. No reduction in COVID-19 mortality was found in a cohort of 194,637 patients with RA or SLE, of which 30,569 were taking HCQ and 547 died from COVID-19 infection [12], and no significant hospitalization rate reduction was found in a cohort of 58,052 patients with inflammatory rheumatic disease, of which 2722 were treated with HCQ [33].

A series of 17 patients with SLE treated with long-term HCQ and having developed severe forms of COVID-19 has been published [8].

Our study has some inherent limitations. Firstly, only 18 patients tested positive, and no variable reached statistical significance. Patients were interviewed by phone without physical examination and may consequently have given incomplete or wrong answers. Notably, 26% of the patients were unaware of their blood type. Another limitation of this study is the possibility that some patients did not answer the phone because of a more severe COVID-19 presentation leading to hospitalization or death, or on the contrary were infected but asymptomatic. In addition, our cohort was constituted of patients having an ophthalmologic follow-up, and may not be representative of patients with immune-mediated inflammatory diseases as a whole. The patient's ethnicity and social characteristics data were not collected in our study for regulatory reasons. This may also act as a confounding factor, as suggested by recent reports [34–38].

Despite its inherent shortcomings, this study brings interesting data. No major prophylactic effect of long-term HCQ intake was observed in

our cohort. Our study provides information confirming the fact that patients with immune-mediated inflammatory diseases taking HCQ can be infected with SARS-CoV-2 and develop severe forms of COVID-19 infection.

CONCLUSIONS

Our work does not support any prophylactic effect of long-term HCQ intake in COVID-19 infection in our population of patients suffering from immune-mediated inflammatory diseases and having an ophthalmological follow-up.

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Compliance with Ethics Guidelines. The COVCALL protocol was approved by research ethics committees Nord-Ouest 1 in France. The "Centre d'investigation clinique" of Rothschild Foundation gave approval to access the data. Each patient was given detailed oral information and the rationale for the study was explained. Oral consent was then collected and consigned. This proceeding was followed by written information sent by e-mail or by post. The study was conducted in accordance with the Declaration of Helsinki 1964 and its later amendments.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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