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BRIEF REPORT

Susceptibility to COVID-19 in Patients Treated With Antimalarials: A Population-Based Study in Emilia-Romagna, Northern Italy

Carlo Salvarani,[1] [iD] Pamela Mancuso,[2] Federica Gradellini,[2] Nilla Viani,[3] Paolo Pandolfi,[4] Massimo Reta,[4] Giuliano Carrozzi,[5] Gilda Sandri,[6] Gianluigi Bajocchi,[2] Elena Galli,[6] Francesco Muratore,[2] Luigi Boiardi,[2] Nicolò Pipitone,[2] Giulia Cassone,[6] Stefania Croci,[2] Anna Maria Marata,[7] Massimo Costantini,[2] and Paolo Giorgi Rossi[2]

Objective. To evaluate the susceptibility to coronavirus disease 2019 (COVID-19) in patients with autoimmune conditions treated with antimalarials in a population-based study.

Methods. All residents treated with chloroquine (CQ)/hydroxychloroquine (HCQ) from July through December 2019 and living in 3 provinces of Regione Emilia-Romagna were identified by drug prescription registries and matched with the registry containing all residents living in the same areas who have had swabs and tested positive for severe acute respiratory syndrome coronavirus 2 (SARS–CoV-2). Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated.

Results. A total of 4,408 patients were identified. The prevalence of patients receiving antimalarials was 0.85 per 1,000 men and 3.3 per 1,000 women. The cumulative incidence of testing during the study period was 2.7% in the general population and 3.8% among those receiving CQ or HCQ, while the cumulative incidence of testing positive was 0.55% in the general population and 0.70% among those receiving CQ/HCQ. Multivariate models showed that those receiving CQ/HCQ had a slightly higher probability of being tested compared to the general population (OR 1.09 [95% CI 0.94–1.28]), the same probability of being diagnosed as having COVID-19 (OR 0.94 [95% CI 0.66–1.34]), and a slightly lower probability of being positive once tested (OR 0.83 [95% CI 0.56–1.23]). None of the differences were significant.

Conclusion. Our findings do not support the use of antimalarials as a prophylactic treatment of COVID-19.

INTRODUCTION

Given the increasingly widespread use of the antimalarial drugs chloroquine (CQ) and hydroxychloroquine (HCQ), not only as therapy but also as prophylaxis for coronavirus disease 2019 (COVID-19) (1–4), there is an immediate unmet need to obtain insights into their efficacy, particularly because of their potential toxicity (5).

Antimalarial drugs are well-known, disease-modifying anti-rheumatic drugs (DMARDs) used in the treatment of several autoimmune conditions such as rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), systemic lupus erythematosus (SLE), discoid lupus erythematosus (DLE), and other off-label uses including antiphospholipid syndrome and primary Sjögren's syndrome. In addition to their immunomodulatory capacity, these drugs protect patients with inflammatory rheumatic diseases against infection. For example, in SLE, the duration of antimalarial treatment is a protective factor against infections (6). Antimalarials have also been reported to inhibit severe acute respiratory syndrome

[1]Carlo Salvarani, MD: Azienda USL-IRCCS di Reggio Emilia and Università di Modena e Reggio Emilia, Reggio Emilia, Italy; [2]Pamela Mancuso, BS, Federica Gradellini, MD, Gianluigi Bajocchi, MD, Francesco Muratore, MD, Luigi Boiardi, MD, Nicolò Pipitone, MD, Stefania Croci, MB, Massimo Costantini, MD, Paolo Giorgi Rossi, MD: Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy; [3]Nilla Viani, MD: Azienda USL di Modena and Azienda OU di Modena, Modena, Italy; [4]Paolo Pandolfi, MD, Massimo Reta, MD: Azienda USL di Bologna, Bologna, Italy; [5]Giuliano Carrozzi, MD: Azienda USL di Modena, Modena, Italy; [6]Gilda Sandri, MD, Elena Galli, MD, Giulia Cassone,

MD: Università di Modena e Reggio Emilia, Modena, Italy; [7]Anna Maria Marata, MD: Regione Emilia Romagna, Bologna, Italy.

No potential conflicts of interest relevant to this article were reported.

Address correspondence to Carlo Salvarani, MD, Unità Operativa di Reumatologia, Azienda Ospedaliera-IRCCS di Reggio Emilia, Viale Risorgimento 80, 42100 Reggio Emilia, Italy. Email: salvarani.carlo@ausl.re.it.

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coronavirus 2 (SARS–CoV-2) in vitro (7,8). Therefore, because of their immunomodulatory and antiviral effects, these drugs have been proposed to be repurposed not only for the treatment of COVID-19, but also for the primary prophylaxis in healthy subjects living in highest risk areas.

Patients with autoimmune conditions who received long-term treatment with antimalarials before the onset of SARS–CoV-2 infection, potentially represent the best candidates to test the efficacy of these drugs in preventing symptomatic COVID-19 (9,10). In these patients, CQ and HCQ accumulate at the cell and tissue level, including in the lungs, where they may exert an antiviral effect, although it is unclear whether such antiviral action may be achieved using the standard therapeutic doses of antimalarials (7,8,11). We decided to evaluate, in a population-based study, the risk of COVID-19 in patients treated with antimalarials before the start of the infection in a large geographic area (3 provinces of Emilia-Romagna) with a high rate of spread of COVID-19.

PATIENTS AND METHODS

Study population. The 3 provinces included in the catchment areas (Bologna, Modena, and Reggio Emilia) have 2,251,903 residents. We identified all resident populations who had been prescribed CQ or HCQ during the period from July 1 through December 31, 2019, via the local drug prescription registries. The database is updated every 3 months. Those receiving CQ or HCQ were cross-referenced with the archive of residents who had oral nasopharyngeal swabs for SARS–CoV-2 reverse transcriptase–polymerase chain reaction (RT-PCR) testing and with the COVID-19 registry. All residents in the study areas who have had oral nasopharyngeal swabs since February 21, 2020, the date of diagnosis of the first COVID-19 case in Italy, are registered in a local registry. Those who tested positive were included in the COVID-19 registry, with data collected at the local level and gathered at the national level (12,13).

With a few exceptions, swabs were performed only in symptomatic subjects. Therefore, all patients included in the COVID-19 registry are considered to be COVID-19 patients. Initially, only patients who had contact with other SARS–Cov-2 patients were tested, but after the second week of the outbreak, all patients with symptoms compatible with COVID-19 were tested with RT-PCR on oral nasopharyngeal samples.

A fiscal code (a government-issued identification number used in Italy) was used to identify and match patients treated with antimalarial agents and those with COVID-19 infection. We used data updated on May 13, 2020. In Emilia-Romagna, the epidemic curve peaked in the last third of March and then decreased. At the end of the study period, the cumulative incidence of COVID-19 in the general population was 0.48%, 0.54%, and 0.9%, in Bologna, Modena, and Reggio Emilia, respectively.

The study was approved by the Reggio Emilia Provincial Ethics Committee, and all participants and their relatives provided informed consent. Approval was obtained on July 4, 2020 (no. 2020/0045199).

Statistical analysis. We identified age- and sex-specific cumulative rates of being tested and of testing positive in the general population and in patients who received CQ or HCQ during the second half of 2019, with odds ratios (ORs) and 95% confidence intervals (95% CIs) calculated. Multivariate logistic regression models were used to evaluate whether treatment, age classes, and sex increased the odds of being tested or having a positive test. We also identified the probability of being positive once tested.

RESULTS

The drug prescription databases indicated that 4,408 patients had at least 1 prescription for CQ or HCQ during the second half of 2019. Their mean ± SD age was 62.4 ± 18.2 years, and 80.2% were women. The median number of packs per patient (each pack containing 30 tablets) was 6 (interquartile range 4–9). Only 3.6% of the patients were prescribed only 1 pack of tablets during the period. CQ and HCQ were mainly prescribed for their approved indications, i.e., RA, JIA, SLE, and DLE.

The prevalence of individuals receiving CQ or HCQ was 0.85 per 1,000 men and 3.3 per 1,000 women, with no differences between provinces. Prevalence increased with age until 80–89 years, when it reached 2.7 per 1,000 men and 6.1 per 1,000 women. After age 90 years, the prevalence of receiving CQ or HCQ decreased, at least among women, to 3.8 per 1,000.

The cumulative incidence of being tested during the study period was 2.7% in the general population and 3.8% among those receiving CQ or HCQ. Age- and sex-specific rates did not differ between those who were receiving CQ or HCQ and those who were not (Table 1). The cumulative incidence of testing positive was 0.55% in the general population and 0.70% among those receiving CQ or HCQ.

Multivariate models confirmed that women were more frequently tested, while individuals younger than 40 years were less frequently tested. Among individuals ages 40–79 years, the probability of being tested was quite homogenous; it increased among older individuals (Table 2). Those receiving CQ or HCQ had a slightly higher probability (nonsignificant) of being tested compared to the general population (OR 1.09 [95% CI 0.94–1.28]).

The cumulative incidence of COVID-19 increased exponentially with age, with women showing a slightly higher incidence. Those receiving CQ or HCQ had almost the same probability of being diagnosed as having COVID-19 as the general population (OR 0.94 [95% CI 0.66–1.34]). The probability of being positive once tested was slightly, albeit nonsignificantly, lower among those receiving CQ or HCQ than in the general population (OR 0.83 [95% CI 0.56–1.23]).

Table 1. Cumulative incidence of testing for severe acute respiratory syndrome coronavirus 2 and of testing positive, by age, sex, and use of hydroxychloroquine or chloroquine

	Population, no.		Tested, no (%)		Tested positive, no. (%)	
	Men	Women	Men	Women	Men	Women
Individuals taking antimalarials						
Age, years						
<40	47	318	1 (2.1)	9 (2.8)	0 (0.0)	1 (0.3)
40–49	84	483	2 (2.4)	19 (3.9)	1 (1.2)	4 (0.8)
50–59	152	671	2 (1.3)	29 (4.3)	1 (0.7)	6 (0.9)
60–69	162	707	6 (3.7)	9 (1.3)	2 (1.2)	0 (0.0)
70–79	254	781	14 (5.5)	33 (4.2)	0 (0.0)	7 (0.9)
80–89	151	500	7 (4.6)	30 (6.0)	1 (0.7)	6 (1.2)
≥90	24	74	3 (12.5)	4 (5.4)	0 (0.0)	2 (2.7)
Overall	874	3,534	35 (4.0)	133 (3.8)	5 (0.6)	26 (0.7)
General population						
Age, years						
<40	413,462	395,505	5,620 (1.4)	7,448 (1.9)	912 (0.2)	1,036 (0.3)
40–49	164,156	164,407	3,513 (2.1)	6,051 (3.7)	738 (0.4)	992 (0.6)
50–59	162,369	167,056	3,959 (2.4)	6,030 (3.6)	937 (0.6)	1,198 (0.7)
60–69	119,176	132,315	3,286 (2.8)	3,142 (2.4)	852 (0.7)	698 (0.5)
70–79	96,687	113,531	3,200 (3.3)	2,909 (2.6)	787 (0.8)	667 (0.6)
80–89	56,948	82,140	3,072 (5.4)	4,541 (5.5)	722 (1.3)	1,081 (1.3)
≥90	10,332	26,235	1,015 (9.8)	3,278 (12.5)	235 (2.3)	708 (2.7)
Overall	1,023,130	1,081,189	23,665 (2.3)	33,399 (3.1)	5,183 (0.5)	6,380 (0.6)

DISCUSSION

In a recent observational study involving a large sample of consecutive patients who had been hospitalized in New York City with COVID-19, HCQ use was not associated with a significantly higher or lower risk of intubation or death (14). Although these results may be affected by prescription bias, with patients with severe disease receiving the drug, they do not support the use of HCQ at present, outside of randomized clinical trials testing its efficacy. Furthermore, a randomized trial did not demonstrate a significant benefit of HCQ as postexposure prophylaxis for COVID-19 (15). Accordingly, the Italian Medicines Agency (AIFA), in addition to other regulatory national agencies, has recently stopped the use of HCQ both for treatment of and prophylaxis for COVID-19, outside of clinical trials.

Our study is the first population-based study in a geographic area with a high level of spread of COVID-19 to evaluate if antimalarials might be effective in preventing symptomatic COVID-19 in a large number of patients (n = 4,408) treated with long-term CQ or HCQ for autoimmune conditions. These drugs have been reported to have antiviral activity in vitro against SARS–CoV-2; in particular, they seem able to block or decrease viral replication in a time- and concentration-dependent manner, as well as to inhibit the fusion of the virus to the cell membrane (7,8). Taken together, these effects have prompted suggestions for the use of antimalarials as prophylactic treatment of COVID-19. However, in our study, those individuals receiving antimalarials had the same probability of being diagnosed as having COVID-19 as the general population; therefore, our study does not support a role for CQ or

Table 2. Adjusted odds ratios of being tested for severe acute respiratory syndrome coronavirus 2, testing positive, and testing positive if tested in Emilia-Romagna, Italy between March 2020 and May 2020*

	Cumulative incidence of being tested	Cumulative incidence of testing positive	Probability of being positive, if tested
Individuals taking antimalarials	1.09 (0.94–1.28)	0.94 (0.66–1.34)	0.83 (0.56–1.23)
Men	1 (referent)	1 (referent)	1 (referent)
Women	1.24 (1.22–1.26)	1.05 (1.01–1.09)	0.85 (0.81–0.89)
Age, years			
<40	1 (referent)	1 (referent)	1 (referent)
40–49	1.82 (1.77–1.87)	2.19 (2.05–2.34)	1.27 (1.19–1.37)
50–59	1.90 (1.85–1.95)	2.70 (2.54–2.87)	1.56 (1.46–1.67)
60–69	1.58 (1.54–1.63)	2.56 (2.4–2.74)	1.79 (1.66–1.93)
70–79	1.80 (1.75–1.86)	2.88 (2.69–3.08)	1.76 (1.63–1.90)
80–89	3.45 (3.35–3.55)	5.42 (5.08–5.78)	1.78 (1.66–1.91)
≥90	7.72 (7.45–8.01)	10.84 (10.02–11.74)	1.66 (1.52–1.81)

* Values are the adjusted odds ratio (95% confidence interval).

HCQ in preventing symptomatic COVID-19 at the dosage used to treat autoimmune conditions. The maximum prescribed dosage of HCQ, the most commonly used antimalarial, is 400 mg daily. Safety is a major concern at higher doses.

The probability of those receiving CQ or HCQ being tested for SARS–CoV-2 was slightly increased, while the probability of those who were taking CQ or HCQ receiving a positive swab once tested was slightly lower. These differences are compatible with an increased propensity to test patients with autoimmune conditions who are considered at higher risk of infection, including patients with less typical symptoms or at lower risk of COVID-19. However, the differences were minimal and not significant and cannot have impeded the observation of an important prophylactic effect of antimalarials. In particular, the 95% CI suggests that a reduction larger than one-third is extremely unlikely.

Among patients who were followed up for at least 4 weeks, we observed a high rate of fatality (18%) in the Emilia Romagna COVID-19 population, which outlined the severity of the disease among our patients (16). We cannot rule out the possibility that a group of patients with asymptomatic or mildly symptomatic COVID-19 may have been tested; however, such a high case fatality rate suggests that patients with asymptomatic disease did not represent a substantial part of our COVID-19 registry.

Only 3.6% of the patients were treated with a single pack of antimalarials, possibly prescribed as antimalarial prophylaxis in travelers, suggesting that most patients were treated long-term for autoimmune conditions and therefore, with regard to the accumulation of the drugs in the cells and tissues related to long-term treatment, our patients represented an ideal population for evaluating the prophylactic effectiveness of antimalarials.

This study has many limitations, but also some strengths. First, the number of patients with COVID-19 was too small to provide definitive conclusions; however, our study is the first population-based study on this topic, the case ascertainment was accurate using 2 reliable sources, and we examined a large population of patients (>4,000 patients) who received long-term antimalarials. However, we compared the incidence of COVID-19 in patients with autoimmune conditions with that of the general population, and we could adjust only for sex and age. The 2 populations are not comparable with regard to health conditions and possibly also for their probability of being infected by SARS–CoV-2 and developing COVID-19. In fact, the underlying autoimmune condition and immunosuppressive treatment could have influenced the susceptibility or the course of the infection. It is worth noting that, at least for susceptibility, we did not observe any impact of prolonged use of biologic DMARDs or targeted synthetic DMARDs (17). Finally, we cannot exclude the possibility that higher dosages of CQ or HCQ than those used in autoimmune diseases could be effective in treating COVID-19. Balevic et al showed that patients receiving HCQ treatment for rheumatic diseases are unlikely to

achieve total serum or plasma concentrations shown to inhibit SARS–CoV-2 in vitro; however, patients receiving HCQ long term may have tissue concentrations far exceeding serum/plasma levels (18).

In conclusion, our study did not show a prophylactic effect of antimalarial for symptomatic COVID-19 in a large population of patients with autoimmune conditions. If confirmed in larger observational studies, these results do not support the rationale for conducting large trials.

ACKNOWLEDGMENTS

AUTHOR CONTRIBUTIONS

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Errata

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In the article by Xu et al in the August 2020 issue of *Arthritis & Rheumatology* (Interleukin-17A Is Produced by CD4+ but Not CD8+ T Cells in Synovial Fluid Following T Cell Receptor Activation and Regulates Different Inflammatory Mediators Compared to Tumor Necrosis Factor in a Model of Psoriatic Arthritis Synovitis [pages 1303–1313]), a second institutional affiliation of one of the authors was inadvertently omitted from the title page footnotes. Dr. Dominique Baeten's information should have read "Academic Medical Center and UCB Pharma, Amsterdam, The Netherlands." Dr. Baeten was not, however, employed by UCB Pharma at the time of his work on the study reported in the August 2020 issue.

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In the letter by Bertin et al in the November 2020 issue of *Arthritis & Rheumatology* (Anticardiolipin IgG Autoantibody Level Is an Independent Risk Factor for COVID-19 Severity [pages 1953–1955]), two errors were inadvertently introduced in copyediting. The sentence "To this end, levels of IgG and IgM anticardiolipin antibodies (aCLs) and anti–β_2-glycoprotein I (anti-β_2GPI) autoantibodies were measured using real-time polymerase chain reaction in serum samples from 56 COVID-19 patients with severe acute respiratory syndrome coronavirus 2 (SARS–CoV-2)" (page 1953, right column) should have read "To this end, levels of IgG and IgM anti–β_2-glycoprotein I (anti-β_2GPI) and anticardiolipin (aCL) autoantibodies were measured by enzyme-linked immunosorbent assay in serum samples from 56 COVID-19 patients who were positive for severe acute respiratory syndrome coronavirus 2 (SARS–CoV-2) by reverse transcriptase–polymerase chain reaction." The sentence "Except for 1 patient who presented with a history of stroke, no other IgG aCL–positive patient with a severe manifestation of COVID-19 presented with a history of thrombosis, which suggests that positivity for aCL could be attributed to infection with SARS–CoV-2" (page 1954, right column) should have read "Except for 1 patient who presented with a history of stroke, no other IgG aCL–positive patient with a severe manifestation of COVID-19 presented with a history of thrombosis, which suggests that positivity for aCL could be attributed to severe infection with SARS–CoV-2."

We regret the errors.