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ORIGINAL ARTICLE

Risk of COVID-19 infection in patients with rheumatic disease taking disease-modifying anti-rheumatic drugs

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Abstract

Background and objective Patients with rheumatic disease taking long-term disease-modifying anti-rheumatic drugs (DMARDs) are expected to have a higher risk of infection due to the alterations in cellular immunity associated with these medications. However, the potential risks associated with these drugs remain unclear. This study aimed to estimate the risk of COVID-19 infection in patients with rheumatic disease taking disease-modifying anti-rheumatic drugs.

Methods Patients with autoimmune rheumatic disease taking DMARDs with or without long-term (> 6 months) HCQ treatment prior to the COVID-19 outbreak were selected consecutively. The diagnosis of COVID-19 was made based on the history of symptoms suggestive of the disease and/or serum IgG positivity. During statistical analysis, the risk of COVID-19 infection was calculated in rheumatic patients taking DMARDs versus controls, as well as in patients taking HCQ versus those who are not. The ORs and 95% CIs were also calculated. The participants in the control group were selected from individuals without RD.

Results A total of 800 patients with RD and 449 controls were analyzed. COVID-19 infection was detected in 16.8% of rheumatic patients versus 17.6% of controls (OR 0.95; 95% CI 0.7–1.28). The proportions of COVID-19 infection in HCQ users versus non-users were 15.3% and 18.1%, respectively (OR 0.87; 95% CI 0.61–1.26). These results remained unchanged after adjusting for all covariates using logistic regression analysis.

Conclusion These findings indicate that rheumatic patients taking DMARDs are not at a higher risk of COVID-19 infection, and that HCQ therapy has no influence on the risk of COVID-19 infection.

Key points
- *The risk of COVID-19 infection is not higher in patients with RD on DMARD therapy.*
- *The prevalence of COVID-19 infection in HCQ users has not significant difference relative to non-users.*
- *Significant percent of RD patients taking DMARDs had asymptomatic infection.*
- *There was a positive association between leflunamide therapy and the risk of COVID-19 infection.*

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Keywords COVID-19 · Disease-modifying anti-rheumatic drugs · Hydroxychloroquine · Infection risk · Rheumatic patients

Introduction

Since the initial outbreak in China, the coronavirus disease (COVID-19) has continued to spread and remains an important cause of mortality across numerous geographic regions (1). Despite the development of several vaccines to prevent transmission, COVID-19 transmission remains a problem as it may still be possible for an individual to spread the virus after being vaccinated. Therefore, until these vaccines are able to prevent secondary infections, the use of masks, observation of quarantine practices, and social isolation are effective and important strategies for controlling the spread of the disease (2–4).

The first generation of COVID-19 vaccines is expected to reduce the transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). However, suppression of community transmission requires immunity in 20–50% of the population. Although these vaccines may confer protective effects against COVID-19 infection, their influence on infection rate, and thus transmission rate, remains to be seen (5).

Given the worldwide spread of COVID-19, observing quarantine practices, enforcing social distancing, identification of high-risk populations, and implementing pharmacologic interventions to stop the spread of infection in the general population should be considered (2–4).

Several factors have been associated with an increased risk of COVID-19 development, as well as increased transmission and fatality. A systematic review and meta-analysis found that hypertension, cardiovascular disease, history of smoking, and diabetes were present in 16.37%, 12.11%, 7.63%, and 7.87% of patients infected with COVID-19, respectively (6). Infection occurs more frequently in middle-aged and older individuals, particularly those with chronic comorbidities such as cardiovascular disease, hypertension, and diabetes, as well as chronic lung, renal, and liver diseases (7). Rheumatic patients, such as those with rheumatoid arthritis (RA) and systemic lupus erythematosus, who are taking disease-modifying anti-rheumatic drugs (DMARDs) are at a higher risk of infection and have greater morbidity and mortality than the general population. These effects may be due to the medications themselves or from alterations in cellular immunity (8–10).

However, this issue has not been adequately investigated, and the potential risks conferred by treatment with DMARDs remain unclear. While methotrexate therapy itself decreases disease activity, it may also increase the risk for infections (11).

Data from the COVID-19 Global Rheumatology Alliance physician-reported registry demonstrated that in patients with rheumatic disease, exposure to prednisolone at a dose of > 10 mg/day was associated with higher odds of hospitalization, while the use of anti-TNF was associated with reduced odds of hospitalization (12).

A review of 69 studies that summarized the advantages and disadvantages of current immunosuppressive drugs on COVID-19 infection found contradictory results (13). This may be partly attributed to the different mechanisms of action of these drugs on the immune system or to variations in the combinations of DMARDs used in the treatment of rheumatic disease. As a result, while a number of DMARDs may increase the probability of acquiring COVID-19 infection, antimalarial drugs that are widely used in rheumatic patients may provide potential benefits against COVID-19 infection (14).

Antimalarial drugs have demonstrated antiviral activity through their PH-dependent effects on several viruses, including coronaviruses. A systematic review of 6 studies and 23 ongoing clinical trials showed that chloroquine could effectively limit the replication of SARS-CoV-2 in vitro (6). Therefore, in patients with rheumatic disease, the administration of hydroxychloroquine (HCQ), irrespective of its immunomodulatory effects, might decrease the risk of COVID-19 infection. For these reasons, the safety of the use of immunosuppressive drugs during the COVID-19 pandemics remains questionable, and the prevalence of COVID-19 infection in rheumatic patients varies across different studies.

Nonetheless, current data do not provide overwhelming evidence that patients with rheumatic disease, when compared with other comorbidities, are at a higher risk of COVID-19 infection. In one study of Portuguese patients with autoimmune diseases, treatment with HCQ was associated with a lower prevalence of COVID-19 infection (15). However, data regarding the distribution of COVID-19 infection in rheumatic patients are scarce, and the risk of COVID-19 infection in patients taking certain immunosuppressive drugs is particularly unclear. Therefore, we conducted the present study to determine the risk of COVID-19 infection in rheumatic patients who are using DMARDs versus the general population, and to assess the risk of COVID-19 infection in rheumatic patients who use HCQ versus those who do not.

Patients and methods

This observational study was composed of 800 patients with inflammatory rheumatic disease aged 18 years and older who presented for follow-up clinical examination in a rheumatology clinic between May 1, 2020, and November 2020.

At the time of study, each patient was taking one or more DMARDs, such as methotrexate, HCQ, low-dose prednisolone, anti-TNF drugs, or other immunosuppressive medications, for more than 6 months (between 8 and 110 months). See Table 1.

The diagnosis of COVID-19 infection was made based on clinical symptoms in addition with combination of positive laboratory tests, such as PCR or antibodies, and/or CT findings. The participants of the control group were selected from asymptomatic individuals who presented to the same laboratory for COVID-19 testing prior to elective surgery during the study period. The subjects in the control group had no current or history of rheumatic diseases and were not taking anti-rheumatic drugs. Serum IgG was measured by ELISA according to the manufacturer's instructions using an IgG antibody kit against SARS-Cov-2 provided by Pishtaz Teb, Tehran, Iran.

The manufacturer-reported sensitivity and specificity of the ELISA kits were 94.1% and 98.3%, respectively (17). IgG antibody serum values > 1.1 AU/mL were considered positive. All tests were performed at the Razi Medical Diagnostic Laboratory in Babol, Iran.

Individuals who (1) had chronic allergic symptoms, (2) had irregular follow-up consults, and (3) were non-adherent to medications were excluded from the study.

Table 1 Characteristics of the study population with rheumatic diseases

Variables	*N* (%)
Age > 50 years	479 (59.5)
Obesity (BMI ≥ 30 kg/m^2)	206 (25.8)
Diabetes	94 (11.8)
Hypertension	56 (7)
History of cardiovascular disease	30 (3.8)
History of respiratory disease	58 (7.3)
Rheumatic diseases	
Rheumatoid arthritis	473 (59.1)
Systemic lupus erythematosus	110 (13.8)
Other diseases (PSA, SS, PM,DM, SCL)	217 (27.1)
Medications	
Hydroxychloroquine	430 (46.3)
Methotrexate	467 (58.4)
Prednisolone	716 (89.4)
Leflunomide	176 (22.4)
Anti-TNF drugs	81 (10.1)
Other medications	59 (7.4)
Duration of treatment with DMARDs, months, median (range)	24 (8–110)

PSA psoriatic arthritis, *SS* Sjogren syndrome, *PM* polymyositis, *DM* dermatomysitis, *SCL* scleroderma,

DMARDs disease-modifying anti-rheumatic drugs

All participants were evaluated for history of COVID-19 infection or contact with a known case. Data were provided through face-to-face interviews in accordance with a questionnaire made to assess pre-specified signs and symptoms suggestive of COVID-19 infection, such as the presence of cough, shortness of breath, difficulty breathing, fever, chills, rigors, myalgia, headache, sore throat, and new olfactory or taste disorders. In addition, data were collected with respect to household or occupational contacts, especially contact with confirmed cases of COVID-19 infection which were defined as either hospitalization or a positive PCR test for the virus. Symptomatic disease was defined as the presence of any above symptoms, in addition to positive PCR or IgG Ab or CT scan confirming COVID-19. However, asymptomatic disease was defined as positive PCR or IgG Ab against COVID-19 without any of the abovementioned symptoms.

In the statistical analysis, the proportions of COVID-19 infection between rheumatic patients and the controls were compared. Furthermore, the proportion of COVID-19 infection was compared between HCQ users and non-users, as well as between HCQ users and the control group. The χ^2 test, with calculation of the ORs and 95% CIs, was used to determine the risk of COVID-19 infection.

Multiple logistic regression analysis was applied to examine the independent association between COVID-19 infection and HCQ treatment; COVID-19 infection was treated as the dependent variable while other variables, such as medications and demographic features, were treated as covariates. All analyses were performed using SPSS software version 18. This study protocol was approved by the Ethics Committee of Babol University of Medical Sciences, Babol, Iran (code IR.MUBABOL.HRI.REC.1399.344).

Results

A total of 800 patients with rheumatic disease and 449 controls were analyzed. One hundred thirty-five out of the 800 rheumatic patients (16.8%) and 79 out of the 449 controls (17.6%) had COVID-19 infection (OR 0.95; 95% CI 0.7–1.28). The characteristics of study patients are shown in Tables 1 and 2.

Seventy-three (54%) of 135 rheumatic patients with COVID-19 infection were symptomatic and the rest (46%) had asymptomatic infection. All patients in the control group were asymptomatic. Thirty-one out of 135 COVID-19 infections in the patient group (23%) were hospitalized for a median duration of 6 (range 3–12) days and there was no mortality.

In the statistical analysis, the two groups of symptomatic and asymptomatic rheumatic patients did not show significant differences in age, disease duration, and distribution of DMARDs (data are not shown).

Table 2 Distribution of demographic features and self-reported symptoms in 73 patients with symptomatic COVID-19 infection

Demographic features or symptoms	*n* (%)
Age > 50 years	45 (61.6)
Fever and chills	57 (78.1)
Myalgia	15 (20.5)
Gastrointestinal symptoms	25 (34.2)
Headache	12 (16.4)
Olfactory or taste disorders	20 (27.4)
Respiratory symptoms	58 (79.2)
Obesity (BMI ≥ 30 kg/m^2)	30 (41.7)
PCR positivity	12 (16.4)
Serum IgG positivity	3 (4.1)
Increased C-reactive protein or ESR	3 (4.1)
Compatible findings in lung CT scan	41 (56)
Number of hospitalizations	31 (23)
Family contact with a known case	44 (60.2)
Diabetes	13 (18.1)
Hypertension	9(12.5)
Cardiovascular diseases	2(2.8)

The prevalence of COVID-19 infection in HCQ users and non-users were 15.3% and 18.1% (Table 3), respectively (OR 0.87, 95% CI 0.61–1.26). When compared with controls, the odds of COVID-19 infection in HCQ users was 0.9 (95% CI 0.63–1.28). The risk of COVID-19 infection in HCQ users versus non-users, after adjustment for all covariates such as DMARDs other than HCQ and demographic factors, are shown in Table 4. After adjustment for all covariates, multiple logistic regression analysis showed that the risk of COVID-19 infection in HCQ users remained non-significant, suggesting that there is no association between the risk of COVID-19 infection and use of other DMARDs including methotrexate, low-dose prednisolone, and anti-TNF drugs except leflunomide. There was a positive association between leflunomide therapy and the risk of COVID-19 infection (OR 1.95; 95% CI 1.08–3.5).

Furthermore, close contact with confirmed COVID-19 cases in the family was independently associated with an increased risk of COVID-19 infection (adjusted OR 38.6; 95% CI 14.39–103.8) (Table 4). Subgroup analyses of patients with RA and non-RA diseases did not change the risk of COVID-19 infection.

Table 3 Distribution of COVID-19 infection in rheumatic diseases treated with and without hydroxychloroquine

Variable	Hydroxychloroquine − (*n* = 370)	Hydroxychloroquine + (n = 430)	*P* value
COVID-19 infection (*n* = 135)	67 (18.1%)	68 (15.3)	0.27

Table 4 Association between pre-exposure[a] hydroxychloroquine (HCQ) treatment and acquisition of COVID-19 in rheumatic patients taking disease-modifying anti-rheumatic drugs

Predictors	OR (95% CI)	Adjusted OR (95% CI)
HCQ	0.89 (0.62–1.28)	0.76 (0.41–1.38)
Prednisolone	0.75 (0.43–1.31)	0.76 (0.23–2.5)
Methotrexate	1.01 (0.69–1.46)	1.16 (0.56–2.41)
Anti-TNF drugs	63 (32–1.27)	0.58 (0.18–1.84)
Leflunomide	1.93 (1.29–2.89)	1.95 (1.08–3.5)
Other drugs	72 (33–1.56)	0.64 (0.079–5.22)
Age > 50 years	1.30 (89–1.90)	0.86 (0.43–1.74)
Obesity (BMI ≥ 30 kg/m^2)	1.74 (1.17–2.57)	1.11 (0.60–2.05)
Diabetes	1.43 (0.84–2.41)	1.17 (0.54–2.54)
Hypertension	1.17 (59–2.33)	0.72 (0.24–2.14)
Cardiovascular disease	1.46 (0.61–3.49)	1.82 (0.57–5.87)
Household contact with a known COVID-19 case	41.6 (19.07–90.01)	38.6 (14.39–103.8)

The association was determined using multiple logistic regression analysis with calculation of OR and 95% CI after adjustment for all covariates including drugs, demographic and epidemiological factors

[a]Initiation of treatment several months prior to COVID-19 outbreak

Discussion

The findings of the present study indicate that patients with RD on long-term DMARD therapy were not at a higher risk of COVID-19 infection than the general population. Furthermore, HCQ therapy had no influence on the risk of COVID-19 infection. Although the prevalence of COVID-19 infection in HCQ users was lower than that in non-users (15.3% and 18.1%, respectively), the difference was not statistically significant. Individual analysis of patients with RA and non-RA diseases did not change the results.

The findings of this study regarding COVID-19 infection are consistent with the results of a recent large population-based cross-sectional study. In that study, SARS-COV-2 antibody positivity was detected in 17.1% (95% CI 14.6–19.5%) of randomly selected participants from the general population of Iran (17). In another study, the prevalence of COVID-19 infection in the general population of different countries varied from < 0.1 to > 20% (18).

The lack of association between DMARD therapy and the risk of COVID-19 infection has also been shown in a cross-sectional study of 10,260 rheumatic patients from Italy; treatment with DMARDs and other small molecules were shown to have no influence on the susceptibility to COVID-19 infection when compared with the general population (19).

Interestingly, 46% of COVID-19 infections in rheumatic patients of the present study were asymptomatic, indicating

that a significant proportion of patients taking DMARDs may acquire asymptomatic COVID-19 infection. This may be partly dependent on the overlap of symptoms of COVID-19 and those of rheumatic diseases. Thus, in a proportion of patients with COVID-19, the occurrence of mild symptoms may be attributed to the exacerbation of underlying rheumatic diseases.

In contrast, two studies found a higher rate of COVID-19 infection in rheumatic patients than in those without rheumatic diseases (8, 9). In a multicenter retrospective study of 42 families with a documented history of COVID-19 exposure, rheumatic patients had a higher susceptibility to COVID-19 infection compared to those without RD. In this study, COVID-19 infection developed in 27 of 43 (63%) patients with RD versus 28 out of 83 (34%) patients without RD (OR 2.68; 95% CI 1.14–6.27). However, these findings are limited as the data were collected via telephone calls and not through direct interviews, as was done in our study (8). Similarly, Bozzella et al. (9) found a higher rate of COVID-19 infection in SLE patients who were on long-term HCQ for more than 6 months than in the general population (2.5% vs. 0.76%, respectively). However, the course of COVID-19 in SLE patients was mild and self-limiting (9), which is consistent with the high prevalence of asymptomatic patients in our study. In this study, the reason for the increased risk of COVID-infection with leflunomide therapy is unclear, and data in this context are scarce. In a separate smaller study, leflunomide therapy resulted in shorter viral shedding time in 5 out of 10 patients (20). However, in another study with a larger sample size, treatment with leflunomide had no influence on viral clearance or duration of hospital stay (21).

The impact of pre- or post-exposure prophylaxis using HCQ on the risk of COVID-19 infection, which has been addressed in several studies, yielded conflicting results in patients without rheumatic disease (22–28). The results of three randomized clinical trials and two observational studies were similar to those of our study. In these studies, pre-exposure prophylaxis with HCQ did not affect the risk of COVID-19 infection (22–26). Similarly, two RCTs that examined the effect of post-exposure prophylaxis with HCQ found no significant decrease in the risk of COVID-19 infection (27,28). Nonetheless, a few studies have shown that HCQ has a preventive effect against SARS-CoV-2 infection (15, 30–32). Contradictory findings can be explained by several factors, including study design, diagnostic method for COVID-19 detection, method of data collection, and the time of HCQ administration before or after exposure. Administration of HCQ after or prior to exposure may not provide the required serum concentrations of the drug to inhibit SARS-Cov-2. As a result, the effect of HCQ is delayed until the serum concentration reaches therapeutic levels. In contrast, rheumatic patients receiving long-term HCQ therapy achieve a steady state over time and are more likely to attain adequate serum levels at the time of exposure. However, a previous study found that the mean serum and plasma levels of HCQ in rheumatic patients taking long-term HCQ were almost one tenth of the concentration required for in vitro viral inhibition (33). Therefore, the lack of a significant difference between HCQ users and non-users in this study may be attributed to the insufficient serum concentrations of HCQ. Another limitation of our study is the small sample size; it may be possible to detect a significant difference if a larger sample size is used.

One of the strengths of our study is the consecutive selection of rheumatic patients who were taking long-term DMARDs with or without HCQ. The diagnosis of patients and controls was confirmed by serum IgG positivity. In areas with a high prevalence of infection, elevated levels of serum IgG are suggestive of previous exposure to or current infection with SARS-Cov-2 (34). Thus, this test is helpful for identifying people who were previously infected with COVID-19. A meta-analysis revealed that IgG antibodies have a sensitivity and specificity of 97% and 98%, respectively, for diagnosing COVID-19 (35). Because the patients and the control group were selected simultaneously, the risk of exposure to COVID-19 infection was similar between the two.

Conclusion

In conclusion, the results of this study indicate that rheumatic patients taking long-term immunosuppressive medications are not at a higher risk of COVID-19 infection. Furthermore, chronic exposure to HCQ in rheumatic patients does not significantly reduce the risk of COVID-19 infection. This study adds new information to the existing data and suggests that further studies with larger sample sizes are needed to clarify the impacts of DMARDs, particularly HCQ, on the risk of COVID-19 infection. There is still a long way to go before demonstrating the long-term protective effects of vaccination.

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

Declarations

Ethics approval and consent to participate Ethics Committee of Babol University of Medical Sciences, Babol, Iran (code IR.MUBABOL.HRI.REC.1399.344).

Consent for publication Yes.

Disclosures None.

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