Prevalence of COVID-19 in patients with rheumatoid arthritis (RA) already treated with hydroxychloroquine (HCQ) compared with HCQ-naive patients with RA: a multicentre cross-sectional study

COVID-19 is becoming the most serious problem of human society after World War II. The general recommendations of WHO, which include wearing mask, social distancing, washing hands and so on, are a widely accepted approach to preventing the spread of the virus. With lack of effective treatment, prophylactic strategies have attracted the attention of healthcare providers. Chemoprophylaxis is one of these strategies. Several in vitro studies showed that antimalarial agents interfere with the proliferation of various viruses, including the severe acute respiratory syndrome coronavirus, by inhibiting virus/cell fusion.[1] However, the main challenge is translating the impact of in vitro models to clinics. Given the higher mortality of patients with COVID-19 with autoimmune diseases,[2] we decided to investigate the efficacy of these medications by evaluating the incidence of COVID-19 in patients with rheumatoid arthritis (RA) already treated with hydroxychloroquine (HCQ) compared with HCQ-naive patients with RA.

In a multicentre cross-sectional study, patients with RA treated in the rheumatology clinics of the Tabriz University of Medical Sciences, Kashan University of Medical Sciences and Army Hospital of Tehran were recruited. For a period of 4 weeks from 19 August to 19 September 2020, data about symptoms suggestive of COVID-19 were obtained by telephone interview. Inclusion criteria were fulfilment of the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for RA, disease onset at age ≥16 and disease onset before the COVID-19 outbreak. Exclusion criteria were change or addition of new disease-modifying antirheumatic drugs during the last 8 months, non-adherence to medication, refusal to answer the questions and non-response to three phone calls. Patients with symptoms suggestive of or a diagnosis of COVID-19 or with any change in RA disease activity were invited to visit a multidisciplinary clinic. Disease activity was assessed by a rheumatologist, and diagnosis of COVID-19 was evaluated by a pulmonologist. Remission was defined according to the ACR/EULAR definition. Diagnosis of COVID-19 was made in patients with clinical manifestations consistent with COVID-19 and meeting one of the following criteria: (1) positive PCR or (2) chest CT scan findings of COVID-19 pneumonia, with other causes of pneumonia ruled out.

The normal distribution of data was assessed using the Kolmogorov-Smirnov test. Continuous and categorical variables were presented as mean±SD and frequency (percentage), respectively. Comparisons between groups were done using the χ^2 test, independent sample t-test and Mann-Whitney test, as appropriate. $P<0.05$ was considered statistically significant. Data analysis was performed using SPSS V.16.0 software.

After a telephone interview with 2341 patients with RA, 1858 patients were enrolled in this study. Forty-six patients had a diagnosis of COVID-19. Diagnosis was based on positive PCR in 35 (76.1%) and clinical criteria in 11 (23.9%) patients. Demographic and clinical characteristics and medications of patients with RA were compared between patients on HCQ and those not on HCQ (table 1). The dose of HCQ in all patients in the first group was 200–400 mg/day. No significant differences were observed in the demographic and clinical characteristics of the studied groups. Except for more patients treated with sulfasalazine in the HCQ-naive group, no significant differences were observed in the medications between the two groups. Since the start of the COVID-19 pandemic 8 months ago, 2.2% of patients with RA treated with HCQ and 2.8% of those HCQ-naive had developed COVID-19, which was not statistically significant (0.344) (table 1).

Our study showed that the prevalence of COVID-19 in patients with RA treated with HCQ is not lower than HCQ-naive patients with RA. Previous experiences have also shown that the effect of a drug on the virus in in vitro models does not necessarily lead to a clinical effect. Although antimalarial medications reduced the replication of viruses such as Zika, Ebola, chikungunya, dengue and influenza in cell culture media, they had no therapeutic effect in human or in animal models of these diseases.[1] In accordance with the

Table 1 Demographic and clinical characteristics and medications of patients with RA enrolled in the study

Characteristics and medications	HCQ (n=1436)	HCQ-naive (n=422)	P value
Female (%)	1035 (72.1)	301 (71.3)	0.404
Age, mean±SD	51.1±12.3	50.6±13.1	0.123
RA disease duration, median (IQR)	54 (30–109)	66 (38–120)	0.193
Risk factors for COVID-19 (%)			
Obesity (BMI >30)	253 (17.6)	63 (14.9)	0.252
Smoking	112 (7.8)	27 (6.4)	0.339
Diabetes	153 (10.7)	51 (12.1)	0.116
Hypertension	183 (12.7)	46 (10.9)	0.186
Pulmonary disease	33 (2.3)	13 (3.1)	0.127
Heart disease	36 (2.5)	10 (2.4)	0.592
Chronic kidney disease	13 (0.9)	5 (1.2)	0.271
Malignancies	19 (1.3)	3 (0.7)	0.419
Active RA disease	235 (16.4)	73 (17.3)	0.382
Medications (%)			
NSAIDs	159 (11.1)	51 (12.1)	0.326
Prednisolone	1057 (73.6)	326 (77.3)	0.059
Prednisolone dose, median (IQR)	5 (2.5–7.5)	5 (2.5–7.5)	0.106
Methotrexate	1106 (77.0)	318 (75.3)	0.328
Sulfasalazine	136 (9.5)	81 (19.2)	**0.001**
Leflunomide	219 (15.3)	55 (13.0)	0.222
Azathioprine	12 (0.9)	7 (1.7)	0.166
Calcineurin inhibitors	72 (0.5)	6 (1.4)	0.122
Biologics	40 (2.8)	15 (3.6)	0.314
COVID-19 (%)	34 (2.2)	12 (2.8)	0.344

*p<0.05 considered significant.
BMI, body mass index; HCQ, hydroxychloroquine; NSAIDs, non-steroidal anti-inflammatory drugs; RA, rheumatoid arthritis.

results of our study, several other studies did not report pre-exposure and post-exposure prophylactic effects of HCQ. Boulware *et al*[3] in a randomised clinical trial (RCT) on 821 participants with moderate-risk to high-risk exposure to a confirmed COVID-19 case at home or at their workplace prescribed HCQ 3800 mg or placebo for a total course of 5 days. No significant difference was observed in the occurrence of COVID-19 in HCQ and placebo groups.[3] Mitjà *et al*[4] in an RCT performed pre-exposure prophylaxis with HCQ in asymptomatic contacts of patients with PCR-proven COVID-19.[4] The incidence of COVID-19 in the HCQ and the control group was 5.7% and 6.2%, respectively. The difference was not significant. In an observational cross-sectional study, Revollo *et al*[5] assessed the occurrence of COVID-19 among hospital healthcare workers (HCWs) working in COVID-19 wards. There was no significant difference in the incidence of COVID-19 in HCWs receiving HCQ as pre-exposure prophylaxis compared with HCWs who did not receive HCQ.[5] In conclusion, the results of our cross-sectional study showed that HCQ may not be effective in the doses used to treat rheumatic diseases to prevent COVID-19 in patients with RA.

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