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CLINICAL INVESTIGATION

Development of SARS-CoV-2 infection in patients with rheumatic conditions on hydroxychloroquine monotherapy vs. patients without rheumatic conditions: A retrospective, propensity-matched cohort study

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ABSTRACT

Background: The primary purpose of the current study was to examine whether patients with rheumatologic conditions receiving only chronic hydroxychloroquine therapy for their disease are at less risk of developing SARS-CoV-2 infection than a comparative group of patients without rheumatologic conditions.

Methods: A retrospective, observational, nationwide stratified propensity analysis was conducted comparing patients only on chronic treatment with hydroxychloroquine for their rheumatologic condition to a random sample of patients without rheumatologic conditions and not receiving hydroxychloroquine, utilizing a Veterans Health Administration nationwide clinical administrative database.

Results: The 1-to-1 stratified propensity analysis was undertaken using a random sample of patients without rheumatoid conditions and not receiving hydroxychloroquine (n 33,081) and patients with rheumatoid conditions receiving hydroxychloroquine as the lone medication for their condition (n 6047). A total of 5,474 patients in each group were successfully matched. The incidence of documented SARS-CoV-2 infections during the study period did not differ between patients receiving hydroxychloroquine and patients not receiving hydroxychloroquine (41/5,474 [0.749%] vs. 36/5,474 [0.658%], respectively, p = 0.57; Odds ratio [OR] 1.14, 95% confidence interval [CI] 0.73-1.79). There were no statistically-significant differences in secondary outcomes between the two groups in patients who developed active SARS-CoV-2 infection. Multivariate logistic regression to determine independent variables associated with the development of active SARS-CoV-2 infection failed to include receipt of hydroxychloroquine (OR 0.99, 95% CI 0.62-1.56).

Conclusions: Hydroxychloroquine failed to demonstrate a preventative effect against SARS-CoV-2 infection in a large group of patients with rheumatologic conditions compared to patients without rheumatologic conditions.

Keywords: SARS-CoV-2 infection; Hydroxychloroquine; Rheumatologic conditions. **[Am J Med Sci 2022;■(■):1–7.]**

INTRODUCTION

Hydroxychloroquine was one of several drugs purported to have in vitro activity against the SARS-CoV-2 virus early in the global pandemic.[1-3] However, controlled evaluations into hydroxychloroquine's effects in the treatment of SARS-CoV-2 infection in humans have been not demonstrated favorable outcomes.[4,5] Hydroxychloroquine monotherapy or in combination with azithromycin may leave patient's at an increased risk of serious cardiovascular adverse events, including Torsades de Pointes and other ventricular arrhythmias when prescribed for the treatment or prophylaxis of COVID-19 disease.[6] Prevention of infection has also been evaluated in variable settings and

methods with consistent concerns of adequate statistical power.[7-11] This includes short-term (two weeks) prophylaxis in healthcare workers or household contacts with recent exposure to SARS-CoV-2 infected persons or longer term (8-12 weeks) pre-exposure prophylaxis in healthcare workers. Among the limitations of these approaches are the complicated pharmacokinetic and pharmacodynamic challenges that hydroxychloroquine poses, not the least of which includes an extremely long half-life (30-60 days) that delays reaching potentially-adequate steady-state serum and tissue concentrations.[12] To address some of these challenges and limitations, our group recently published a large (*n* 32,109) retrospective analysis of United States (US) Veterans Health Administration (VHA) to examine whether patients with rheumatologic conditions receiving chronic hydroxychloroquine therapy are at less risk of developing SARS-CoV-2 infection over a 4 month period compared to a propensity-matched group of patients with rheumatologic conditions not receiving hydroxychloroquine.[13] The incidence of documented SARS-CoV-2 infections did not differ between patients receiving hydroxychloroquine versus those not receiving hydroxychloroquine in our previous study.[13] In the prior publication multivariate logistic regression failed to include receipt of hydroxychloroquine as an independent variable associated with the development of SARS-CoV-2 infection. Limitations of this analysis included potential confounding variables related to the widespread use of immunomodulating agents in both groups. Thus, our group sought to follow this report with an analysis of Veterans only on hydroxychloroquine for their rheumatologic condition, comparing outcomes with a propensity-matched random sample of Veterans without rheumatologic conditions. Our hope is to add to the growing body of evidence to provide safe and evidence based treatment and prophylactic regimens to improve outcomes associated with the SARS-CoV-2 virus.

METHODS

This investigation was a retrospective, observational, nationwide analysis across the US VHA of all patients with rheumatologic conditions on sole chronic treatment with hydroxychloroquine to patients without rheumatologic conditions and not on hydroxychloroquine drawn from a random sample of veterans whose birth month was March. All information was obtained in a de-identified format using a central clinical and administrative relational database described previously.[13]

The patient cohort receiving hydroxychloroquine consisted of all veterans $\geq$ 18 years of age with 1) evidence of receipt of hydroxychloroquine to the equivalent of at least four 90-day supplies since 4/1/2019 and medication possession ratio calculation of $\geq$ 80% from 7/1/2019 to 6/30/2020, with most recent receipt within a timeframe to include the date of 3/1/2020; 2) no evidence of receipt of any other agent (through outpatient dispensing records or infusion clinic orders as appliable) used for the treatment of rheumatologic conditions including methotrexate, leflunomide, sulfasalazine, tofacitinib, adalimumab, certolizumab, etanercept, golimumab, infliximab, abatacept, rituximab, belimumab, apremilast, or tocilizumab where last dose administered would remain active (based on frequency given) through the date of 3/1/2020, and 3) evidence of VHA clinic encounters with International Classification of Diseases, 10th edition (ICD-10) diagnostic code entries placed from 10/1/2016 to 3/1/2020 for rheumatoid arthritis, lupus erythematosus, and associated rheumatologic conditions (see supplementary table S1).

Data collection was also conducted to determine the following: 1) baseline demographic data as of 3/1/2020 to determine age, race, gender, and smoking status; 2) all ICD-10 codes from 10/1/2016 to present to determine presence of chronic comorbidities; 3) laboratory variables to assess organ dysfunction from 4/1/2019 to 6/30/2020, including white blood cell count, hemoglobin, platelet count, blood urea nitrogen, serum creatinine, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, and alkaline phosphatase; 5) Outpatient prescriptions containing angiotensin II converting enzyme inhibitors, angiotensin II receptor blockers, zinc, vitamin D or vitamin C where availability included the date of 3/1/2020.

Univariate variables were assessed for their association with the use of hydroxychloroquine. Those univariate variables with a standardized mean difference of $>$ 0.10 were entered into a nominal multivariate logistic regression model to determine independent variables associated with the use of hydroxychloroquine. This model computed a propensity formula and propensity score for each participant. Each patient receiving hydroxychloroquine was matched to one patient not receiving hydroxychloroquine (controls) with the next-nearest propensity score to the patient receiving hydroxychloroquine and stratified by age $\pm$ 10 years, gender, VAMC site, and rural or urban status, with a maximum propensity score caliper of 0.25.

The resultant propensity population was assessed with the following data collection for data points between 3/1/2020 and 9/30/2020: any polymerase chain reaction (PCR) test results for SARS-CoV-2 infections; Covid-19 positive status per corporate data warehouse designation (derived from a positive PCR test result outside of the VHA system); hospitalization admission and discharge dates; admission ward locations associated with any hospitalization; and date of death if applicable.

This study was conducted after obtaining approval of the University of Oklahoma Health Sciences Center Institutional Review Board and the Oklahoma City VA Healthcare System Research and Development Committee.

Endpoints and statistical analysis

The primary endpoint was the rate of SARS-CoV-2 infection in patients with rheumatologic conditions receiving sole therapy with chronic hydroxychloroquine

versus the propensity-matched patients without rheumatologic conditions nor chronic hydroxychloroquine between March 1, 2020 and September 30, 2020. Secondary endpoints comparing these two groups consisted of the following within the same time period: rate of hospitalization associated with SARS-CoV-2 infection; rate of intensive care requirement associated with SARS-CoV-2 infection; mortality rate associated with SARS-CoV-2 infection; and overall comparative rates of any hospitalization and mortality.

Univariate analysis was conducted to determine univariate variables associated with the development of SARS-CoV-2 infection, including receipt of chronic hydroxychloroquine. Those univariate variables with a standardized mean difference of >0.25 were entered into a multivariate logistic regression model to determine independent variables associated with the development of SARS-CoV-2 infection.

For all tests and analyses except where specified, the *a priori* level of significance was set at $p \leq 0.05$. Standardized mean difference measurements were considered well-balanced if ≤0.25. Categorical variables were assessed using Chi-square test and Fisher's exact test when appropriate. Wilcoxon rank sum test was utilized to assess continuous variables.

RESULTS

An ICD-10 code for rheumatologic-associated condition was found for 75,745 patients who were alive as of 3/1/2020. Prescriptions for hydroxychloroquine that included possession through 3/1/2020 were identified in 16,178 patients. Exclusion due to a medication possession ratio of less than 0.8 was documented in 5475 patients. A total of 6047 patients were found to be on monotherapy with hydroxychloroquine for their rheumatologic condition and were included in the study – these patients were a subset of the patients in our previous study.[13] Random sampling for veterans with no ICD-10 code for rheumatologic conditions (and no hydroxychloroquine prescriptions) included 33,081 patients.

Several univariate variables were found to be associated with the selection of hydroxychloroquine at a statistically-significant level (see supplementary table S2). A good fit was found for the resultant multivariate logistic regression (MLR) model derived from these variables. Odds ratios and 95% confidence intervals for variables found to be independently associated with hydroxychloroquine selection are found in Table 1.

Our propensity matching methodology with strict stratification resulted in 5474 patients solely receiving hydroxychloroquine successfully matched with 5474 patients not receiving hydroxychloroquine. Thus, 573 patients receiving hydroxychloroquine were excluded from further analysis due to the inability to match to an individual not receiving hydroxychloroquine given the combination of stratification and caliper restrictions. Table 2 presents the baseline demographic variables for the two propensity matched groups. The two groups were largely similar, although absolute standard mean differences in rates of certain concomitant prescriptions, dermatologic condition, hematologic condition, and elevated lactate dehydrogenase were above 0.25.

Table 3 presents the primary and secondary outcomes. The incidence of documented SARS-CoV-2 infection during the study period did not differ between the two groups (OR 1.14, 95% CI 0.73-1.79). There were no statistically-significant differences in any of the secondary outcomes between the two groups in patients. Fig. 1 displays overall mortality (OR 1.0, 95% CI 0.83-

Table 1. Baseline variables found to be independently associated with hydroxychloroquine selection by multivariate logistic regression.

Baseline variable	Odds Ratio	95% Confidence Interval	*p*
Age 65 years and older	1.59	1.47 to 1.70	<0.001
Race other than Caucasian	1.50	1.40 to 1.61	<0.001
Female gender	4.03	3.71 to 4.37	<0.001
Respiratory disease	1.42	1.31 to 1.53	<0.001
Renal/Genitourinary disease	1.23	1.14 to 1.32	<0.001
Cardiovascular disease	1.40	1.31 to 1.50	<0.001
Gastrointestinal disease	1.30	1.21 to 1.41	<0.001
Hepatobiliary disease	1.32	1.11 to 1.57	0.002
Neurological disease	1.36	1.27 to 1.46	<0.001
Hematological disease	1.55	1.40 to 1.71	<0.001
Neoplastic disease	1.14	1.03 to 1.25	0.010
Any tobacco use	1.60	1.45 to 1.78	<0.001
Elevated aspartate alanine	1.21	1.03 to 1.40	0.020
Elevated lactate dehydrogenase	9.51	7.10 to 12.9	<0.001
Low hemoglobin	2.72	2.54 to 2.92	<0.001
Thrombocytopenia	1.49	1.29 to 1.71	<0.001
Elevated urea nitrogen	1.27	1.13 to 1.43	<0.001
Elevated serum creatinine	0.647	0.563 to 0.741	<0.001

Table 2. Baseline demographic variables for the propensity-matched hydroxychloroquine-receiving patients compared to non-hydroxychloroquine-receiving patients.

Baseline variable*	Patients receiving hydroxychloroquine (*n* 5,474)	Patients not receiving hydroxychloroquine (*n* 5,474)	Standardized mean difference (OR, 95%CI)	*p*
Demographics				
Age, mean (SD)	64.5 (13.6)	64.5 (14.0)	−0.004 (−0.0379, 0.037)	0.43
Gender (male)	4151 (75.8)	4151 (75.8)	–	1.0
Rural residence	3449 (63.0)	3449 (63.0)	–	1.0
Race				
White	3654 (66.8)	3734 (68.2)	0.037 (−0.0071, 0.0811)	0.10
Black	1142 (20.9)	1180 (21.6)		
Hispanic	281 (5.13)	307 (5.61)		
Native	64 (1.17)	86 (1.57)		
American				
Asian/	105 (1.91)	166 (2.03)		
Pacific				
Islander				
Unknown	228 (4.17)	1 (0.02)		
Body mass index (m^2), mean (SD)	29.7 (6.17)	30.0 (6.39)	−0.049 (−0.087, −0.0104)	0.005
Any Tobacco Use	566 (10.3)	519 (9.48)	−0.053 (−0.122, 0.0161)	0.13
Prescriptions of interest				
Angiotensin-II receptor blocker	446 (8.15)	186 (3.40)	−0.51 (−0.606, −0.413)	<0.001
Angiotensin-II converting enzyme inhibitor	745 (13.6)	372 (6.80)	−0.425 (−0.497, −0.353)	<0.001
Vitamin D	1194 (21.8)	381 (6.96)	−0.73 (−0.79, −0.66)	<0.001
Vitamin C	83 (1.52)	35 (0.64)	−0.481 (−0.70, −0.77)	<0.001
Zinc	6 (0.11)	4 (0.07)	−0.22 (−0.922, −1.01)	0.82
Comorbidities				
Respiratory	1145 (20.9)	1054 (19.2)	−0.057 (−1.09, −0.055)	0.030
Renal/Urinary	1354 (24.7)	1314 (24.0)	−0.022 (−0.070, 0.026)	0.37
Cardiovascular	2233 (40.8)	2165 (39.6)	−0.028 (−0.071, −0.078)	0.18
Gastrointestinal	1242 (22.7)	1150 (21.0)	−0.054 (−0.10, −0.0043)	0.033
Hepatobiliary	187 (3.42)	197 (3.60)	0.030 (−0.082, 0.14)	0.60
Neurological	1604 (29.3)	1542 (28.2)	−0.031 (−0.076, 0.015)	0.19
Dermatological	984 (18.0)	491 (8.97)	−0.441 (−0.50, −0.38)	<0.001
Metabolic/Endocrine	2325 (42.5)	2328 (42.5)	0.0012 (−0.040, 0.043)	0.95
Hematological	713 (13.0)	544 (9.94)	−0.27 (−0.34, −0.20)	<0.001
Psychiatric	1583 (28.9)	1675 (30.6)	0.044 (−0.009, 0.090)	0.054
Neoplastic	660 (12.1)	623 (11.4)	−0.036 (−0.10, 0.028)	0.27
Laboratory abnormalities				
Elevated alkaline phosphatase	72 (1.32)	65 (1.19)	−0.057 (−0.24, 0.129)	0.55
Elevated alanine aminotransferase	111 (2.03)	138 (2.52)	0.12 (−0.016, 0.26)	0.083
Elevated aspartate aminotransferase	239 (4.37)	244 (4.46)	0.012 (−0.089, 0.11)	0.82
Elevated lactate dehydrogenase	95 (1.74)	24 (0.44)	−0.77 (−1.0, −0.52)	<0.001
Low hemoglobin	2257 (41.2)	1889 (34.5)	−0.16 (−0.20, −0.12)	<0.001
Thrombocytopenia	310 (5.66)	276 (5.04)	−0.068 (−0.16, 0.024)	0.15
Leukocytosis	227 (4.15)	215 (3.93)	−0.031 (−0.14, 0.74)	0.56
Leukopenia	110 (2.01)	151 (2.76)	0.18 (0.042, 0.32)	0.01
Elevated urea nitrogen	593 (10.8)	528 (9.65)	−0.071 (−0.14, −0.0031)	0.040
Elevated creatinine	427 (7.80)	410 (7.49)	−0.024 (−0.10, 0.054)	0.54

*Data presented are number (percent), unless otherwise noted.

1.19) between the two groups, as well as mortality associated with SARS-CoV-2 infection in the subgroup that developed active infection (0.87, 95% CI 0.17-4.60). The mean length of stay for the 6 inpatients with rheumatological conditions admitted with SARS-CoV-2 infection was 4.84 days (±3.35, range from 2 to 11 days) while the mean length of stay for the 6 inpatients without rheumatologic conditions was 30.3 days (±26.7), characterized by 3 patients with lengths of stay of 45, 53, and 63 days. None of the six inpatients with rheumatologic conditions

Table 3. Primary and secondary outcomes of the propensity-matched comparison of patients treated with hydroxychloroquine versus patients not receiving hydroxychloroquine.

Outcome	Patients receiving hydroxychloroquine	Patients not receiving hydroxychloroquine	Odds ratio (95% Confidence Interval)	p
Primary outcome				
Developed active SARS-CoV-2 infection	41/5474 (0.749%)	36/5474 (0.658%)	1.14 (0.73, 1.79)	0.57
Secondary outcomes				
Hospitalization associated with SARS-CoV-2 infection	6/41 (14.6%)	6/36 (16.7%)	0.86 (0.25, 2.94)	0.81
Intensive care requirement associated with SARS-CoV-2 infection	2/6 (33.3%)	1/6 (16.7%)	0.50 (0.022, 5.03)	0.56
Mortality associated with SARS-CoV-2 infection	3/41 (7.32%)	3/36 (8.33%)	0.87 (0.17, 4.60)	0.99
Overall hospitalization	247/5474 (4.51%)	248/5474 (4.53%)	0.93 (0.82, 1.06)	0.96
Overall mortality	127/5474 (2.32%)	132/5474 (2.41%)	1.0 (0.83, 1.19)	0.75

died, and 3 of 6 inpatients with no rheumatologic conditions died. Of those patients that developed active infection but did not require hospitalization, 3 of the 35 outpatients with rheumatologic conditions died, and zero of the outpatients without rheumatologic conditions died. Daily dose of hydroxychloroquine of over 400 mg was not associated with less risk of developing SARS-CoV-2 infection (13/1390 [0.94%] for >400 mg daily versus 64/9558 [0.67%] for ≤400 mg daily, OR 1.40, 95% CI 0.77 - 2.55, $p = 0.29$).

Univariate variables associated with the development of SARS-CoV-2 infection are presented in supplementary table S3. The resultant multivariate logistic regression model consisted of two independent variables (see supplementary table S4): Race other than Caucasian (OR 1.61, 95% CI 1.01-2.57) and body mass index ≥ 30 m^2 (OR 2.03, 95% CI 1.28-3.27). Receipt of hydroxychloroquine failed to be included in the final model as an independent variable (OR 0.99, 95% CI 0.62-1.56).

No patients received outpatient COVID-19 treatments (no monoclonal antibody therapy; outpatient intravenous remdesivir and oral medications were not approved via emergency use authorization (EUA) during the study period). For patients requiring hospital admission, 1 of 6 patients with a rheumatologic condition and 4 of 6 patients without a rheumatologic condition received systemic intravenous glucocorticoid therapy. Intravenous remdesivir was not administered to any of the 12 inpatients.

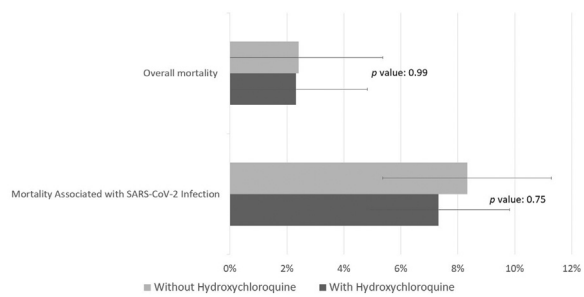

FIG. 1. Overall mortality and mortality in the subset of patients that developed active infection SARS-CoV-2 infection, stratified by receipt of chronic hydroxychloroquine.

DISCUSSION

Despite reports of hydroxychloroquine's in vitro activity against the SARS-CoV-2 virus early in the SARS-CoV-2 pandemic, in addition to a few favorable reports in small, non-controlled studies, the drug failed to improve clinical outcomes against SARS-CoV-2 active infection in multiple well-controlled studies.[14-18] A few prospective studies evaluating hydroxychloroquine's potential for preventing SARS-CoV-2 infection have been conducted, each with notable limitations. Three post-exposure trials have been conducted; each had 14-day follow-up after varying definitions of exposure for either healthcare workers and/or close contacts. The first published account by Boulware and colleagues was a trial that allowed symptoms consistent with SARS-CoV-2 infection to be counted as a primary endpoint, which drove the statistical power of the study; the symptomatic endpoint was reached for 11.6% (48) of those receiving hydroxychloroquine vs 13.5% (55) of those receiving placebo.[7] Only 2.4% (20) persons had confirmed SARS-CoV-2 infection by PCR testing. A second smaller study using ascorbic acid as placebo was limited by a delay in offering drug and found a higher overall incidence of confirmed SARS-CoV-2 infection in the two groups (98 events accounting for a 14.3% rate of reaching the primary endpoint).[8] Mitja and colleagues enrolled 2314 individuals in a non-placebo-controlled cluster-randomized study.[9] Asymptomatic testing only occurred at baseline and on day 14; PCR-positive participants at baseline (13% of the study population and numerically higher in the hydroxychloroquine group) were continued in the final analysis for the primary endpoint. However, for those at baseline that were PCR-negative, 3.0% (29/958) reached a primary endpoint event versus 4.3% (45/1042) in the usual-care group (OR 0.68, 95% CI 0.34-1.34). Two pre-exposure prospective trials consisting of 1483 and 132 participants followed for 12 and 8 weeks, respectively, were limited by power to reach the primary endpoint; only 17 events and 8 events occurred in the two trials, respectively [9,10]. The timeframe of these 5 trials occurred early in the pandemic when testing equipment was in short supply, providing uncertainty over the accuracy of the primary endpoints.

An additional concerning limitation for each of these trials is the unique pharmacokinetic and pharmacodynamic properties of hydroxychloroquine which may prevent adequate exposure in short-term durations. Hydroxychloroquine has an extremely long terminal half-life between 30 and 60 days, which prevents steady state serum and tissue concentrations to be achieved for months.[12] Variable dosing methods were used in these trials, most based on previous pharmacokinetic modelling analyses. The 12-week duration pre-exposure trial conducted by Rajasingham and colleagues was one of these. However, these investigators took the additional steps of obtaining serum concentrations of hydroxychloroquine and found that most individuals had serum concentrations much lower than anticipated and much lower than the concentrations (EC_{50}) necessary to have appreciable activity against the SARS-CoV-2 virus.[11]

To account for the limitations of the above trials, our investigator group initially reported a large, nationwide, multicenter propensity-matched retrospective study comparing a group of patients (*n* 10,703) with various rheumatologic conditions with documented high adherence to a chronic regimen of hydroxychloroquine to a group of patients (*n* 21,406) with rheumatologic conditions not receiving hydroxychloroquine in the first few months of the pandemic in the United States.[13] The primary endpoint - incidence of documented SARS-CoV-2 infections - during the study period was not different between patients receiving hydroxychloroquine and those not receiving hydroxychloroquine (31/10,703 [0.29%] vs. 78/21,406 [0.36%], respectively, $p = 0.27$; Odds ratio [OR] 0.79, 95% confidence interval [CI] 0.52-1.2). The study endpoints were gathered during the initial 4-month period of the pandemic in the US and may have had some of the same testing limitations of the trials noted above. Additionally, many of the concomitant rheumatologic medications that patients in both arms were receiving are highly immunomodulatory, potentially confounding variables that may have either increased or decreased a person's risk of developing active infection with the SARS-CoV-2 virus. Thus, our current project took the strengths of the previous project (chronic hydroxychloroquine use, documented high adherence, nationwide analysis, propensity matching methodology with strict stratification including age, gender, VA facility, rural/urban residence) and resulted in 5474 patients with rheumatologic conditions solely receiving hydroxychloroquine successfully matched with 5474 patients without rheumatologic conditions and not receiving hydroxychloroquine. This removed the immunomodulatory medication confounding issue, and also extended several months into the pandemic when testing became more uniform, providing a higher proportion of events than previous trials to improve the statistical power of the study.

The current study did have some of the limitations of the previous study; methodology of a non-randomized, observational retrospective study utilizing a clinical administrative database. Females comprised only 24.2% of the propensity-matched population, however a much higher proportion than the general VHA population of approximately 5-10%. The medication possession ratio method does not provide an exact accurate measure of patient medication adherence, but a high threshold of an MPR of 0.8 infers that our population was highly adherent. Another limitation with the secondary endpoints, is due to the nature of the study, the true causes of increased length of stay and mortality are unknown. Finally, it is possible that some veterans in this study sought medical assistance for active SARS-CoV-2 infection outside of the VHA.

In conclusion, hydroxychloroquine failed to prevent active SARS-CoV-2 infection in a large group of patients with rheumatologic conditions compared to patients without rheumatologic conditions. The incidence of documented SARS-CoV-2 infection during the study period did not differ between the two groups (OR 1.14, 95% CI 0.73-1.79). There were no statistically-significant differences in any of the secondary outcomes between the two groups. The resultant multivariate logistic regression model variables associated with the development of SARS-CoV-2 infection consisted of two independent variables, neither being receipt of hydroxychloroquine (OR 0.99, 95% CI 0.62-1.56). . This adds to the growing body of evidence recommending against the use of hydroxychloroquine for the prophylaxis of COVID-19 disease, and future efforts evaluating pharmacologic prevention strategies should focus on agents that have demonstrated clinical benefit in treatment (such as the new oral anti-covid agents nirmatrelvir/ritonavir and molnupiravir).

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