Title: Hydroxychloroquine Use and Cardiovascular Events Among Patients with Systemic Lupus Erythematosus and Rheumatoid Arthritis

Running Head: Hydroxychloroquine and Cardiovascular Events

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None

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ABSTRACT

Objective: We evaluated the potential temporal association between Hydroxychloroquine (HCQ) use and cardiovascular (CV) events among patients with SLE or RA.

Methods: We conducted a nested case-control study within inception cohorts of SLE and RA patients using administrative health databases including the entire population of British Columbia, Canada. We identified cases with incident CV events, including myocardial infarction (MI), stroke, or venous thromboembolism (VTE). We matched each case with up to three controls on age, sex, and rheumatic disease. HCQ exposure was categorized by the time between the last HCQ prescription date covered and the index date as current use, recent use, remote use, or never used. We used conditional logistic regression to assess the association between HCQ exposure and CV events, using remote use as the reference group.

Results: We identified 10,268 cases and 29,969 controls. Adjusted conditional odd ratios (cORs) (95% CI) for current HCQ use relative to remote use were 0.86 (0.77-0.97) for combined CV events, 0.88 (0.74, 1.05) for MI, 0.87 (0.74, 1.03) for stroke, and 0.74 (0.59, 0.94) for VTE. Recent HCQ users and non-users had similar odds of combined CV events as remote users (cORs 0.93 ([95% CI, 0.77-1.13] and 0.96 [95% CI, 0.88-1.04], respectively).

Conclusion: In this nested case-control study of patents with SLE and RA, we found a reduced risk of overall CV events associated with current HCQ use including reductions in VTE and trends towards reductions in MI and stroke. These findings suggest a possible cardiovascular preventative benefit of HCQ use.

SIGNIFICANCE and INNOVATIONS

- To our knowledge, we provide the first report showing a lower risk of venous thromboembolism associated with current hydroxychloroquine use compared with remote use among patients with rheumatoid arthritis.
- We also found a possible association with current hydroxychloroquine use and lower risks of ischemic stroke and myocardial infarction among patients with systemic lupus erythematosus or rheumatoid arthritis in a general population context.
- These findings support possible protective effects of this medication against atherosclerotic and thrombotic events for patients with rheumatoid arthritis and lupus.

INTRODUCTION:

Systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) are chronic, systemic inflammatory diseases that are both associated with premature cardiovascular (CV) disease.[1,2] Hydroxychloroquine (HCQ) is near-universally recommended for patients with systemic lupus erythematosus (SLE) and is often used in the treatment of rheumatoid arthritis (RA). Use of HCQ has been associated with reductions in multiple established risk factors for cardiovascular-metabolic endpoints. Multiple observational studies have demonstrated a reduction in hyperglycemia and a lower risk of developing diabetes mellitus among patients with SLE and RA who are treated with HCQ.[3,4] Its use has also been associated with improved lipid profiles in SLE and RA patients.[5,6] Furthermore, HCQ use has been associated with a lower risk of venous thromboembolism among patients with SLE in several small studies.[7] However, it is not well established whether HCQ use can prevent other CV events. We aimed to determine the potential temporal association between HCQ use and cardiovascular (CV) events among patients with SLE or RA.

PATIENTS and METHODS:

Data Source, Study Population, and Study Design

We conducted a nested case-control study within a population-based cohort of patients with incident SLE and incident RA. This source population was the entire population of the province of British Columbia, Canada, over 5 million individuals, identified using linked administrative health databases from Population Data BC.[8] These databases capture demographics, vital statistics, and healthcare utilization data including all provincially-funded outpatient medical visits and hospitalizations since 1990.[9] Medications are captured through the comprehensive

PharmaNet prescription database, which includes information on the medication, dose dispensed, date dispensed, and quantity and days' supply dispensed for all outpatient medications since 1996.[9] These databases have been used previously to conduct population-based cohort studies of patients with SLE, RA, and other inflammatory and rheumatic diseases.[10,11]

Inception cohorts of patients with SLE and RA from Population Data BC have been previously reported.[9,10] The SLE cohort includes 6,241 patients at least 18 years of age with SLE diagnosed between 1997-2015. Subjects were classified as having SLE if they met the following criteria: ≥1 International Classification of Diseases, Ninth Revision (ICD-9) or Tenth Revision, Clinical Modification (ICD-10-CM) code for SLE by a rheumatologist or from a hospital encounter (ICD-9 710.0 or ICD-10-CM M32.1, M32.8, and M32.9) or at least two codes for SLE at least two months apart within two years by a non-rheumatologist physician. We excluded individuals with diagnoses of other inflammatory rheumatic diseases (i.e., RA, psoriatic arthritis, and ankylosing spondylitis) occurring in at least two physician visits at least two months apart after the first SLE diagnosis. To ensure incident cases, all individuals were required to have no SLE diagnosis recorded for at least seven years prior to the index date (i.e., from January 1990, the earliest data available). The RA cohort includes 64,012 patients at least 18 years of age with RA diagnosed between 1997-2015. These subjects were classified as having RA if they met the same criteria but with the relevant RA ICD-9 (714.X) or ICD-10-CM codes (M06.X, M05.X).

Case and Control Ascertainment

From this combined incident SLE/RA cohort, we identified patients with incident CV events (cases) and up to three matched controls selected from risk set samples. In the primary analysis, cases were defined by incident combined CV events, which included myocardial infarction (MI),

ischemic stroke or transient ischemic attack (TIA), and venous thromboembolism (VTE). Deep vein thrombosis (DVT) and pulmonary embolism (PE) comprised VTE. These events were identified by corresponding ICD-9 and ICD-10 CM codes. Cases and controls were matched by age, sex, and rheumatic disease (i.e., SLE vs RA) on the index dates of the defining CV events for cases, since these variables are considered to be the major confounders for the risk of CV events in this population.

We conducted secondary analyses using alternative case definitions of specific CV events. In these alternative case definitions, we defined cases by incident MI, incident stroke/TIA, and incident VTE, respectively. Cases and controls were matched by the same variables as in the primary analysis.

Assessment of Exposure

The exposure of interest was HCQ use status relative to the index date. Using the PharmaNet database, we determined the dates associated with the end of the medication supply according to the last prescription date covered by the final HCQ dispensation. We categorized HCQ use as current, recent, remote, or never. We classified patients as current HCQ users if they had an active supply of HCQ spanning the index date or if their HCQ supply ended within a 90-day grace prior to the index date to reduce exposure misclassification due to delayed prescription refills and due to the long half-life of the medication. We classified patients as recent users if their HCQ supply ended between 91-365 days prior to the index date, and we classified patients as remote users if their HCQ supply ended more than 365 days prior to the index date. We classified patients as never users if they had no dispensed HCQ prescriptions.

In a sensitivity analysis, we used alternative definitions of current and recent use, classifying patients as current users if their HCQ supply ended within 30-days prior to the index date or spanned the index date. We classified patients as recent users if their HCQ supply ended between 30-365 days prior to the index date. To assess the potential influence of the duration of HCQ use on the potential association between HCQ use and CV events, we additionally conducted a stratified analysis according to duration of HCQ use of less than one year or at least one year as of the index date.

Assessment of Covariates

Covariates were assessed during the year prior to the index date/matching and included variables associated with the risk of CV events or associated with illness severity of SLE or RA. These included the Charlson comorbidity index, chronic kidney disease (CKD), prior CV disease, CV medication use (i.e., statins, anti-hypertensives, cardiac glycosides, diuretics, anti-arrhythmics, and nitrates), anticoagulants, glucocorticoid use, immunosuppressive/disease modifying antirheumatic drug (DMARD) use (i.e., azathioprine, methotrexate, mycophenolate, leflunomide, cyclosporine, and cyclophosphamide), biologic immunosuppressant use (i.e., belimumab, adalimumab, infliximab, golimumab, certolizumab, etanercept, tocilizumab, and abatacept), and healthcare utilization (hospitalizations and outpatient visits).

Statistical Analysis

We generated descriptive statistics for cases and controls. We used conditional logistic regression to calculate the conditional odds ratios (cORs) and 95% confidence intervals (CI) for combined CV events associated with HCQ exposure status (i.e., current use, recent use, remote

use, or never used), using remote users as the reference group in order to minimize confounding by indication, as in previous studies.[11,12] We similarly calculated cORs for specific CV events including MI, stroke/TIA, and VTE in secondary analyses using the alternate case definitions according to these specific CV events. We additionally calculated cORs for CV events within disease categories of SLE and RA and stratified by duration of HCQ use. Finally, we repeated this analysis using the alternate exposure definitions. Adjusted analyses included the covariates described above. Statistical analyses were performed using SAS (version 9.3, SAS Institute Inc); all p-values were two-sided (α=0.05).

All procedures were conducted in compliance with British Columbia's Freedom of Information and Privacy Protection Act. Ethics approval was obtained from the University of British Columbia's Behavioral Research Ethics Board.

RESULTS:

From the combined RA and SLE inception cohorts (n=70,253), we identified 10,268 cases with CV events and 29,969 matched controls without CV events. This included 532 cases with SLE and 9,736 cases with RA as well as 1,249 and 28,720 controls with SLE and RA, respectively (**Table 1**). The majority of patients (64%) were female, and the mean age was 74 years at the index date. Cases had a higher mean Charlson comorbidity index score than controls, and a higher proportion of cases used cardiovascular medications.

Current HCQ use was associated with an unadjusted cOR of 0.88 (95% CI 0.81-0.97) for combined CV events compared with remote users (**Table 2**). The fully-adjusted cOR for current HCQ use was 0.86 (0.77-0.97). Recent HCQ use and never use were each associated with similar odds of CV events as remote HCQ use (fully-adjusted cORs 0.93 [95% CI 0.77-1.13] and 0.96

[95% CI 0.88-1.04], respectively). Current HCQ use was associated with fully-adjusted cORs of 0.88 (95% CI 0.74-1.05) for MI, 0.87 (95% CI 0.74-1.03) for stroke/TIA, and 0.74 (95% CI 0.59-0.94) for VTE compared with remote HCQ users (**Figure 1, Table 2**).

In stratified analyses according to rheumatic disease, patients with RA had similar findings as in the overall analysis (**Figure 1, Supplemental Table 1**). For the smaller subgroup with SLE, these findings did not reach significance.

With the alternative exposure definitions requiring current users to have a last prescription date covered within 30 days prior to the index date, overall findings were similar (**Supplemental Table 2**). When stratified by duration of HCQ use, the results were similar among patients with at least one year of current or prior HCQ use (adjusted cOR 0.83 [95% CI 0.73-0.94] among current users compared with remote users) but did not reach significance among patients with less than one year of HCQ use (adjusted cOR for CV events of 0.85 [95% CI 0.70-1.04] (**Supplemental Table 3**).

DISCUSSION:

In this nested case-control study within a population-based inception cohort of patients with SLE or RA, we found a lower risk of incident CV events associated with current HCQ use compared with remote HCQ use. We observed a lower risk of overall CV events as well as a lower risk of VTE and a trend towards lower risks for MI and ischemic stroke associated with current HCQ use. These associations were also observed in the larger RA subgroup, but we did not observe a significant difference in the odds of CV events according to HCQ use status within the smaller SLE subgroup.

Multiple prior observational studies have found a lower risk of thrombotic events in HCQ users with SLE than in non-users, including the outcome of VTE with or without stroke.[7] Our study adds to this literature by additionally demonstrating lower risks of thrombotic events, including both VTE and ischemic stroke, associated with HCQ use in patients with RA. Although our study did not reach significance in the smaller SLE subgroup, our overall findings are consistent with this prior work. Larger studies would be needed to assess the potential benefits of HCQ use in preventing ischemic stroke and myocardial infarction among patients with SLE.

Our findings also suggest that HCQ use may be associated with a lower risk of acute MI. Prior studies have linked HCQ use with improvement in several risk factors for coronary artery disease, including hyperlipidemia[5,6] and insulin resistance,[3,4] indicating potential mechanisms for prevention of MI. However, it has not been well-established whether HCQ use can prevent actual acute coronary events. A single center study from Israel[13] and a population-based study from Taiwan[14] each found a protective effect of lower risks of MI in HCQ users than non-users among RA patients. However, a recent study of multiple population-based cohorts did not find a difference in the risk of MI between HCQ users and sulfasalazine users with RA.[15] The use of different comparison groups may have contributed to this difference in findings. Our study utilized remote users as the comparison group to minimize confounding by indication, as both the current user and the remote user groups had to have had an indication for HCQ use. In contrast, prior studies that used non-users or sulfasalazine-only users as the reference group may have introduced bias by unmeasured confounders that influence both the use of HCQ and the outcome. Prospective studies are warranted to confirm the possible benefit of HCQ in preventing CAD and MI events in patients with rheumatic disease.

We additionally observed that patients who had recently discontinued HCQ at least 90 days prior to the index date as well as remote HCQ users who discontinued the medication at least one year prior to the index date had similar risks of CV events as patients who had never used HCQ. This may suggest a loss of benefits after HCQ discontinuation which is of relevance to weighing the risks and benefits of continuing long-term use of HCQ in patients with SLE or RA.

The main limitations of this study are that of administrative data. The diagnoses of SLE and RA were not clinically confirmed, but they were identified using an administrative algorithm as has been previously reported.[9,10] Further, we lack information on disease activity and severity, which may impact the use of HCQ. Although we used a large administrative database with an inception cohort of patients with SLE and RA, the number of cases with SLE was small which limited power for the SLE-only subgroup analysis. A major strength of our study is the use of a comprehensive prescription drug database, which captures all dispensed outpatient medications and the timing of refills. Our ascertainment of HCQ exposure status by actual prescription refills was less susceptible to misclassification of HCQ users than could occur with reliance on prescribing data alone. Furthermore, our population-based data source which includes all patients regardless of age or funding adds to the generalizability of our findings. Additionally, as mentioned, our use of a remote user comparison group was employed to limit potential confounding by indication that can occur when comparing users with non-users and has been employed in other pharmacoepidemiology studies.[11,12] However, there may be some variation between current users and remote users. To address this, we adjusted for potential differences in comorbidities, other medications including glucocorticoids and DMARD use, and healthcare utilization between the different HCQ exposure groups. We also conducted a sensitivity analysis

using a stricter definition of current HCQ users, and the results were unchanged, which contributes to the robustness of our findings.

Overall, we found lower risks of CV events associated with current HCQ use in a combined cohort of SLE and RA patients in a general population context. These findings support possible protective effects of this medication for patients with SLE and RA.

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TABLES and FIGURES:

Table 1. Characteristics of Systemic Lupus Erythematosus and Rheumatoid Arthritis Cases with Cardiovascular Events and Matched Controls

Characteristics*	Cases (n=10,268)	Controls (n=29,969)	SMD
Age (mean, SD)			
Overall	74 (13)	74 (13)	0.013
Systemic Lupus Erythematosus	59 (14)	57 (13)	0.133
Rheumatoid Arthritis	75 (13)	75 (12)	0.022
Sex (% female)			
Overall	63.6	63.7	0.003
Systemic Lupus Erythematosus	91.0	95.4	0.178
Rheumatoid Arthritis	62.1	62.3	0.005
Charlson comorbidity index, mean (SD)			
Overall	1.20 (1.21)	1.04 (1.03)	0.147
Systemic Lupus Erythematosus	1.52 (1.36)	1.19 (0.91)	0.285
Rheumatoid Arthritis	1.18 (1.20	1.03 (1.02)	0.138
Cardiovascular Disease (%)			
Overall	1.3	0.6	0.077
Systemic Lupus Erythematosus	2.3	0.6	0.136
Rheumatoid Arthritis	1.3	0.6	0.073
Chronic Kidney Disease (%)			
Overall	14.3	11.8	0.075
Systemic Lupus Erythematosus	27.3	18.1	0.220
Rheumatoid Arthritis	13.6	11.5	0.063
Medications (%)			
Glucocorticoids			
Overall	32.0	27.0	0.101
Systemic Lupus Erythematosus	49.4	36.0	0.275
Rheumatoid Arthritis	31.1	27.1	0.089
Cardiovascular medications			
Overall	53.6	42.9	0.215
Systemic Lupus Erythematosus	43.4	29.0	0.304
Rheumatoid Arthritis	54.2	43.5	0.214
Anticoagulants (%)			
Overall	5.4	3.0	0.120
Systemic Lupus Erythematosus	6.2	1.4	0.250
Rheumatoid Arthritis	5.3	3.1	0.115
Other DMARD use (%)			
Overall	15.9	14.6	0.036
Systemic Lupus Erythematosus	19.2	17.1	0.055
Rheumatoid Arthritis	15.8	14.5	0.034
Oral DMARDs (%)			
Overall	16.0	17.4	0.038
Systemic Lupus Erythematosus	22.4	20.0	0.060
Rheumatoid Arthritis	15.6	17.3	0.045
Biologic DMARDs (%)			
Overall	2.2	1.9	0.024
Systemic Lupus Erythematosus	1.1	1.4	0.028

Rheumatoid Arthritis	2.3	1.9	0.027
Healthcare Utilization			
Number of hospitalizations, mean (SD)			
Overall	0.6 (1.1)	0.4 (0.8)	0.202
Systemic Lupus Erythematosus	1.0 (1.8)	0.5 (0.9)	0.376
Rheumatoid Arthritis	0.6 (1.1)	0.4 (0.8)	0.189
Number of outpatient visits, mean (SD)			
Overall	27.2 (19.7)	22.4 (15.5)	0.280
Systemic Lupus Erythematosus	36.2 (26.9)	26.0 (18.9)	0.457
Rheumatoid Arthritis	26.8 (19.1)	22.3 (15.3)	0.266

*Assessed within one year prior to matching/index date.
SMD, standardized mean difference; DMARDs, disease-modifying anti-rheumatic drugs.
Includes azathioprine, methotrexate, mycophenolate, leflunomide, cyclosporine, cyclophosphamide, or biologic DMARDs including belimumab, adalimumab, infliximab, golimumab, certolizumab, etanercept, tocilizumab, abatacept, .
Cardiovascular medications include anti-hypertensives, cardiac glycosides, diuretics, anti-arrhythmics, and nitrates.

Table 2. Hydroxychloroquine Use and Cardiovascular Events According to Hydroxychloroquine Exposure Status Among Patients with Systemic Lupus Erythematosus and Rheumatoid Arthritis

	Cases, N	Controls, N	Conditional Odds Ratio (95% CI)	Adjusted Conditional Odds Ratio* (95% CI)
All Combined CV Events				
Remote HCQ Users	1305	3385	1.0 (reference)	1.0 (reference)
Recent HCQ users	244	635	1.00 (0.85, 1.18)	0.93 (0.77, 1.13)
Current HCQ users	1182	3449	0.88 (0.81, 0.97)	0.86 (0.77, 0.97)
HCQ non-users	7537	22500	0.87 (0.81, 0.93)	0.96 (0.88, 1.04)
All Myocardial Infarction				
Remote HCQ Users	566	1411	1.0 (reference)	1.0 (reference)
Recent HCQ users	98	242	1.00 (0.78, 1.29)	1.12 (0.82, 1.53)
Current HCQ users	517	1495	0.85 (0.74, 0.98)	0.88 (0.74, 1.05)
HCQ non-users	3208	9753	0.81 (0.73, 0.91)	0.98 (0.85, 1.12)
All Stroke/TIA				
Remote HCQ Users	536	1474	1.0 (reference)	1.0 (reference)
Recent HCQ users	91	249	0.99 (0.76, 1.29)	0.83 (0.61, 1.12)
Current HCQ users	435	1401	0.86 (0.74, 0.99)	0.87 (0.74, 1.03)
HCQ non-users	3178	9340	0.95 (0.85, 1.05)	1.00 (0.88, 1.13)
All Venous Thromboembolism				
Remote HCQ Users	321	785	1.0 (reference)	1.0 (reference)
Recent HCQ users	60	155	0.94 (0.68, 1.31)	0.65 (0.44, 0.98)
Current HCQ users	266	820	0.78 (0.64, 0.95)	0.74 (0.59, 0.94)
HCQ non-users	1475	4475	0.80 (0.69, 0.93)	0.90 (0.75, 1.08)

*Additionally adjusted for Charlson comorbidity index, prior CV disease, chronic kidney disease, glucocorticoid use, DMARD use, cardiovascular medication use, anticoagulant use, and healthcare utilization including number of hospitalizations and number of outpatient visits all assessed one year prior to the index date.

CV, cardiovascular; HCQ, hydroxychloroquine; TIA, transient ischemic attack

Exposure classifications: current use- last prescription date covered <90 days before index date; recent use- last prescription date covered 90-365 days before index date; remote use- >365 days before index date

Figure 1. Forest Plots of Adjusted Odds Ratios for Cardiovascular Events Associated with Current Hydroxychloroquine Use Versus Remote Use Among Patients with Systemic Lupus Erythematosus and Rheumatoid Arthritis

Abbreviations: CV, cardiovascular; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; TIA, transient ischemic attack