Use of Hydroxychloroquine And Risk of Heart Failure in Patients With Rheumatoid Arthritis

Ahmed A. Sorour
Reto D. Kurmann
Youssef E. Shahin
Cynthia S. Crowson
Sara J. Achenbach
Rekha Mankad
Elena Myasoedova

Key Indexing terms: Rheumatoid Arthritis, Hydroxychloroquine, Heart Failure, Drug toxicity

Departments: Department of Cardiovascular Medicine (Drs Sorour, Kurmann, and Mankad; Mr. Shahin), Division of Biomedical Statistics and Informatics (Dr Crowson and Miss Achenbach), Department of Rheumatology (Drs Crowson and Myasoedova), Mayo Clinic, Rochester, Minnesota.

Grants: National Institutes of Health/NIAMS R01 grants: AR046849, AG034676

Conflict of Interest: none

AS, Sorour, MD
RK, Kurmann, MD
YS, Shahin
CC, Crowson, Ph.D.
SA, Achenbach, MS
RM, Mankad, MD
EM, Myasoedova, MD, Ph.D.

Correspondence: Elena Myasoedova, MD, Ph.D , Department of Rheumatology, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (myasoedova.elena@mayo.edu)

Running title: Hydroxychloroquine and Heart Failure

Abstract

Objectives. To examine the relationship between the use of Hydroxychloroquine (HCQ) and risk of developing Heart Failure (HF) in Rheumatoid Arthritis (RA).

Methods. In this nested case-control study, cases were Olmsted county, Minnesota residents with incident RA (based on 1987 ACR criteria) from 1980-2013 who developed HF after RA incidence. Each case was matched on year of birth, sex and year of RA incidence with an RA control who did not develop HF. Data on HCQ use including start and stop dates and dose changes was reviewed, and used to calculate HCQ duration and cumulative dose. Age-adjusted logistic regression models were used to examine the association between HCQ and HF.

Results. The study identified 143 RA cases diagnosed with HF (mean age 65.8, 62% females) and 143 non-HF RA controls (mean age 64.5, 62% female). HCQ cumulative dose was not associated with HF (Odds Ratio [OR]: 0.96 per 100g increase in cumulative dose, 95% confidence interval [95% CI]: 0.90-1.03). Likewise, no association was found for patients with a cumulative dose ≥300g (OR 0.92, 95% CI 0.41-2.08). The HCQ duration of intake in years prior to index was not associated with HF (OR 0.98, 95% CI 0.91-1.05).

Conclusions. Use of HCQ was not associated with development of HF in patients with RA in this study. Further studies are needed to understand the impact of higher doses of HCQ on development of HF in RA.

Introduction

Rheumatoid Arthritis (RA) is a chronic systemic inflammatory disease characterized by joint damage and associated functional disability.[1] Increased risk of cardiovascular (CV) disease in RA as compared with the general population has been shown in multiple studies.[2] Furthermore, RA patients have been shown to have a 2-fold increased risk of developing congestive heart failure (HF) compared to subjects without RA.[3]

Hydroxychloroquine (HCQ) is a disease modifying anti rheumatic drug (DMARD) that has been widely used for the treatment of RA.[4] HCQ cardiotoxicity has been implicated as a rare, yet potentially life threatening, side effect of the drug, primarily causing cardiomyopathy resulting in HF.[5] The evidence of cardiotoxicity associated with the use of HCQ relies mainly on case reports and case series, while large cohort studies on the subject are lacking. In this population-based study, we aim to examine the association between exposure to HCQ and development of HF in patients with RA.

Materials and Methods

Study design and population. This nested case-control study was conducted using the resources of the Rochester Epidemiology Project (REP). The REP system ensures a ready access to all inpatient and outpatient records of Olmsted County, MN residents from all community medical providers including the Mayo Clinic, its affiliated hospitals, and the Olmsted Medical Center.[6] The study included adult patients with incident RA from the pre-identified cohort of all incident cases with RA in Olmsted County, Minnesota from 1980-2013. All patients included in the study

were ≥ 18 years of age and fulfilled the 1987 American College of Rheumatology (ACR) classification criteria.[7] Cases were defined as RA patients who developed HF after RA incidence (HF cases) while controls were RA patients without HF (non-HF controls). Cases and controls were matched 1:1 on year of birth, sex and year of RA incidence. Each non-HF control was assigned an index date corresponding to the HF diagnosis date of the case, which occurred in 1983-2018. Controls were allowed to later become cases to avoid bias. HF was defined using the Framingham Heart Study criteria.[8] Information on HCQ -related retinal toxicity was also obtained from the medical records.

HCQ exposure. To determine the history of HCQ use, medical records were manually reviewed and abstracted. Data extracted included the HCQ start date, dosage, change in dosage, stop date, reason for termination and restart date if applicable. The glomerular filtration rate (GFR) was calculated from creatinine values obtained closest to index date/ HF diagnosis with ±90 days using the CKD-EPI formula. This study was approved by institutional review boards of Mayo Clinic (IRB #17-002593) and Olmsted Medical Center (IRB #017-omc-17).

Data on CV risk factors and RA characteristics. A review of medical records was performed to record the following CV risk factors: age, smoking, hypertension, diabetes mellitus, and dyslipidemia as previously defined.[9] Data on RA disease characteristics such as rheumatoid factor (RF) positivity, anti-cyclic citrullinated peptide antibody (CCP-antibody) and year of RA diagnosis were collected for all patients.

Statistical Analysis. Descriptive statistics (means, percentages, etc.) were used to summarize the data. Characteristics were compared between cases and controls using Chi-square and rank sum tests. Age-adjusted logistic regression models were used to examine the association between HCQ and HF. Cumulative dose was examined as a continuous variable and dichotomously (<300 vs ≥ 300 grams (g). Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

From a cohort of 1078 patients with RA, this study identified 143 RA cases diagnosed with HF who were matched with 143 non-HF RA controls. **Table 1** shows characteristics of both groups at RA incidence. Both groups were similar in respect to demographics and RA characteristics. Hypertension and diabetes mellitus were more prevalent in the HF cases. The median (IQR) GFR (ml/min/1.73 m^2) at index date was 66.5 (53.8, 78.5) and 58.1(41.8, 74.7), in non-HF controls and HF cases respectively. The initial presentation of the HF group based on the Framingham criteria is summarized in **Table 2**.

Duration of HCQ use and risk of HF

Seventy one HF and 69 non-HF patients used HCQ at some point prior to HF diagnosis/index date. The median (IQR) duration of HCQ use prior to index date was 2.8 (0.6, 10) years in HF cases and 2.5 (0.7, 8.2) years in non-HF controls. Age-adjusted logistic models showed that

duration of HCQ use prior to index was not associated with increased risk of developing HF: odds ratio (OR) 0.98, 95% confidence interval (CI) 0.91-1.05. The most recent HCQ discontinuation prior to HF diagnosis/index date was reported to be due to adverse effects in 11 (24%) of 46 HF patients who had any prior discontinuation of HCQ and 10 (22%) of 45 non-HF patients who had any prior discontinuation of HCQ. Retinal toxicity prior to index date was comparable in both HF and non-HF cases and controls, being 4% and 9% respectively (p=0.27)

HCQ dose and risk of HF

The median (IQR) cumulative dose in patients receiving HCQ prior to index date/HF diagnosis was 371 (71, 1159) g and 302 (89, 1043) g respectively. 55% of HF cases received a cumulative dose of at least 300 g or more compared to 54% in non-HF controls. The HCQ cumulative dose was not associated with HF (OR 0.96, 95% CI 0.90-1.03 per 100g). Likewise, no statistically significant association was found for patients with a cumulative dose ≥300g compared to those with <300g, although the 95%CI was wide (OR 0.92, 95% CI 0.41-2.08). **Table 3** shows HCQ characteristics of patients that received HCQ prior to index date.

Discussion

In light of the recent global interest in HCQ, considered a potential drug for treatment and/or prophylaxis of coronavirus disease 2019 (COVID-19), cardiovascular safety of HCQ have been a subject of increasing interest.[10] This is the first population-based study to examine the association between chronic HCQ use and HF in patients with incident RA.

Since its approval by U.S Food and Drug Administration (FDA) in 1955, HCQ has been widely used in treatment of RA, systemic lupus erythematous (SLE) and other rheumatic diseases.[4,11] HCQ is believed to exert an immunomodulatory effect by its ability to interfere with the maturation of autophagosomes. Additionally, it hinders the process of antigen presentation and lymphocytic activity, the same mechanism that could explain the drug's known adverse effects .[12]

The inflammatory burden characteristic of RA has been linked to the increase risk of CV disease, including HF.[3,13] HF development in RA patients is multifactorial, with contribution from cardiovascular risk factors and RA disease-related factors.[3]The relationship between HCQ and HF has been controversial, with one argument suggesting a cardioprotective effect of HCQ, while the counterargument supports a cardiotoxic role. In a meta-analysis conducted to associate the use of HCQ and chloroquine (CQ) in rheumatoid patients (RA, SLE, Lupus Nephritis) with cardiovascular risk, Liu et.al reported a reduced risk of CVD development in HCQ users.[14]

Proposed spectrum of cardiotoxic effects of HCQ range from conduction disorders, restrictive cardiomyopathy, left ventricular hypertrophy, ventricular dysfunction and valvular

abnormalities.[5,15] Although this evidence is based on case reports/series and drug surveillance reports rather than population-based longitudinal data, it is supported by two main rationale. First, HCQ cardiotoxicty has been characterized for its specific histological appearance on endomyocardial biopsy (EMB).[16] Second, improvement after withdrawal of HCQ has been reported both clinically and histologically.[17,18]

The standard dose of HCQ in RA patients range from 200 to 400 mg a day, and the treatment is long-term. Assessment of the risk of HF depending on cumulative dose of HCQ showed no statistically significant associations for cumulative doses assessed as a continuous variable or using a cutoff of ≥300g. However, the association for the cumulative dose ≥300g had a wide CI, (OR 0.92, 95% CI 0.41-2.08) including both potentially meaningful benefit and harm.

The risk of retinopathy associated with HCQ has been characterized at a cumulative dose of 1000 g over a period of use over 5-7 years.[19] While retinal toxicity associated with HCQ use was not the primary question of this study, retinal toxicity prior to index date was comparable in both HF and non-HF groups.

With many reviews analyzing the cardiotoxicity of HCQ and CQ in combination, this work focuses only on HCQ.[5,15] HCQ has been known to be less toxic in comparison to CQ, hence is used more frequently today.[20] Furthermore, this population of only RA naturally excludes other rheumatology patients receiving HCQ, in particular SLE patients in whom published reports on HF have been more predominant. In a recent pharmacovigilance analysis, Goldman et al. showed association of HCQ/CQ use for any indication with HF (reporting odds ratio, ROR 2.2). This risk

was largely driven by persons with SLE and Sjorgen's syndrome compared with all other users, including those with RA.

There are several limitations to this study. First, as with any retrospective study, only information available from medical records was used to ascertain exposures and outcomes. However, availability of complete medical records from all healthcare providers in the area and standardized case ascertainment likely minimized this bias. Second, no patient follow up after HCQ discontinuation was performed nor was EMB available in our medical records. Third, the population size, although the largest to date, still limited the study. Fourth, the prevalence of hypertension and diabetes mellitus was higher in patients with HF as compared to those without HF. While both hypertension and diabetes mellitus can affect the risk of HF, this imbalance in baseline characteristics between patients with and without HF is unlikely to have major implications on the main results of the study, as no statistically significant association between HCQ use and risk of HF was detected. Finally, the HF diagnosis was based on retrospective chart review and information on ejection fraction, presence of arrhythmia, biological markers of HF and type of HF was not available However, similarly to our previous studies, all patients with HF fulfilled Framingham criteria which have been shown to have high sensitivity (92%) for HF diagnosis.[21]

In conclusion, this is the first population-based study to quantify the association between HCQ use and HF in patients with RA. We found no increased risk of HF in this RA population receiving HCQ. Larger prospective studies are needed to define the safety of higher cumulative doses of HCQ with regards to HF development, as well as to identify the incidence of HCQ-related cardiotoxicity in RA patients in order to define the subgroups of high-risk patients and the need for cardiovascular screening.

References:

1. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. Lancet Lond Engl. 2016;388:2023-38.

2. Aviña-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: A meta-analysis of observational studies. Arthritis Care Res. 2008;59:1690-97.

3. Nicola PJ, Maradit-Kremers H, Roger VL, Jacobsen SJ, Crowson CS, Ballman KV, et al. The risk of congestive heart failure in rheumatoid arthritis: a population-based study over 46 years. Arthritis Rheum. 2005;52:412-20.

4. Schrezenmeier E, Dörner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. Nat Rev Rheumatol. 2020;16:155-66.

5. Tönnesmann E, Kandolf R, Lewalter T. Chloroquine cardiomyopathy - a review of the literature. Immunopharmacol Immunotoxicol. 2013;35:434-42.

6. Kremers HM, Myasoedova E, Crowson CS, Savova G, Gabriel SE, Matteson EL. The Rochester Epidemiology Project: exploiting the capabilities for population-based research in rheumatic diseases. Rheumatol Oxf Engl. 2011;50:6-15.

7. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The american rheumatism association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31:315-24.

8. Ho KKL, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: The Framingham Study. J Am Coll Cardiol. 1993;22:A6-A13.

9. Myasoedova E, Crowson CS, Matteson EL, Davis JM, Therneau TM, Gabriel SE. Decreased Cardiovascular Mortality in Patients with Incident Rheumatoid Arthritis (RA) in Recent Years: Dawn of a New Era in Cardiovascular Disease in RA? J Rheumatol. 2017;44:732-39.

10. Goldman A, Bomze D, Dankner R, Hod H, Meirson T, Boursi B, et al. Cardiovascular adverse events associated with hydroxychloroquine and chloroquine: A comprehensive pharmacovigilance analysis of pre-COVID-19 reports. Br J Clin Pharmacol. 2020

11. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM et al. 2012 Update of the 2008 American College of Rheumatology (ACR) Recommendations for the use of Disease-Modifying Anti-Rheumatic Drugs and Biologics in the treatment of Rheumatoid Arthritis (RA). Arthritis Care Res. 2012;64:625-39.

12. Frustaci A, Morgante E, Antuzzi D, Russo MA, Chimenti C. Inhibition of cardiomyocyte lysosomal activity in hydroxychloroquine cardiomyopathy. Int J Cardiol. 2012;157:117-119.

13. Crowson CS, Nicola PJ, Kremers HM, O'Fallon WM, Therneau TM, Jacobsen SJ et al. How much of the increased incidence of heart failure in rheumatoid arthritis is attributable to traditional cardiovascular risk factors and ischemic heart disease? Arthritis Rheum. 2005;52:3039-44.

14. Liu D, Li X, Zhang Y, Kwong JS-W, Li L, Zhang Y et al. Chloroquine and hydroxychloroquine are associated with reduced cardiovascular risk: a systematic review and meta-analysis. Drug Des Devel Ther. 2018;12:1685-95.

15. Chatre C, Roubille F, Vernhet H, Jorgensen C, Pers Y-M. Cardiac Complications Attributed to Chloroquine and Hydroxychloroquine: A Systematic Review of the Literature. Drug Saf. 2018;41:919-31.

16. Ratliff NB, Estes ML, Myles JL, Shirey EK, McMahon JT. Diagnosis of Chloroquine Cardiomyopathy by Endomyocardial Biopsy. N Engl J Med. 1987;316:191-93

17. Cotroneo J, Sleik KM, Rene Rodriguez E, Klein AL. Hydroxychloroquine-induced restrictive cardiomyopathy. Eur J Echocardiogr J Work Group Echocardiogr Eur Soc Cardiol. 2007;8:247-51.

18. Joyce E, Fabre A, Mahon N. Hydroxychloroquine cardiotoxicity presenting as a rapidly evolving biventricular cardiomyopathy: key diagnostic features and literature review. Eur Heart J Acute Cardiovasc Care. 2013;2:77-83.

19. Wolfe F, Marmor MF. Rates and predictors of hydroxychloroquine retinal toxicity in patients with rheumatoid arthritis and systemic lupus erythematosus. Arthritis Care Res. 2010;62:775-84.

20. Avina-Zubieta J, Galindo-Rodriguez G, Newman S, Suarez-Almazor M, Russell A. Long term effectiveness of antimalarial drugs in rheumatic diseases. Ann Rheum Dis. 1998;57:582-87.

21. Maestre A, Gil V, Gallego J, Aznar J, Mora A, Martín-Hidalgo A. Diagnostic accuracy of clinical criteria for identifying systolic and diastolic heart failure: cross-sectional study. J Eval Clin Pract. 2009;15:55-61.

Table 1. Patient Characteristics at RA incidence in patients who developed HF during the follow up and those who did not

Variable	HF N= 143	Non-HF N=143	P-Value
Age at RA diagnosis (years), mean ± SD	65.8 ± 12.3	64.5 ± 12.5	0.42
Female	88 (62%)	88 (62%)	1.00
BMI (kg/m^2), mean ± SD	28.6 ± 6.5	27.7 ± 5.4	0.37
Smoking status			0.62
Never	46 (32%)	53 (37%)	
Former	66 (46%)	59 (41%)	
Current	31 (22%)	31 (22%)	
RA characteristics			
RF/CCP positivity	96 (68%)	94 (66%)	0.80
Year at RA diagnosis, mean ± SD	1993 ± 8.6	1994 ± 8.6	0.33
CVS risk Factors			
Hypertension	81 (57%)	56 (39%)	0.003
DM	22 (15%)	11 (8%)	0.042
Dyslipidemia	91 (64%)	88 (62%)	0.71
Lipid lowering drugs	26 (18%)	24 (17%)	0.76

Table 2: Heart failure Characteristics in HF group based on the Framingham criteria

Criterion	Number of Subjects who fulfilled the criteria (%)
Major Criteria	
Paroxysmal nocturnal dyspnea or orthopnea	26/113 (23%)
Elevated jugular venous pressure	78/119 (66%)
Pulmonary Rales	121/139 (87%)
Cardiomegaly on chest x-ray	80/132 (61%)
Pulmonary edema on chest x-ray	88/133 (66%)
Third heart sound	15/121 (12%)
Hepatojugular reflux	14/111 (13%)
Minor Criteria	
Ankle edema	109/136 (80%)
Nocturnal cough	18/112 (16%)
Dyspnea on exertion	122/139 (88%)
Hepatomegaly	3/115 (3%)
Pleural effusion	80/132 (61%)
Tachycardia (heart rate >120 beats / min)	7/142 (5%)

Table 2: Fulfillment of the Framingham criteria for heart failure required the presence of 2 major or 1 major and 2 minor criterion.

Table 3. HCQ use prior to index date/HF diagnosis in patients with RA by HF status

Variable	HF N=71	Non-HF N=69	P-Value
Cumulative duration of HCQ use (years), median (IQR)	2.8 (0.6, 10)	2.5 (0.7, 8.2)	
Years from first ever HCQ start to index date, median (IQR)	9.9 (5.4, 16.9)	8.2 (3.8,15.0)	0.26
HCQ cumulative dose, grams, median (IQR)	371 (71, 1159)	302 (89, 1043)	0.98
Patients with HCQ cumulative dose ≥ 300 grams	39 (55%)	37 (54%)	0.88