EJR European Journal of Rheumatology

DOI: 10.5152/eurjrheum.2020.20193

Original Article

Positive effect of hydroxychloroquine on lipid profiles of patients with rheumatoid arthritis: A Veterans Affair cohort

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Abstract

Objective: Despite remarkable improvements in rheumatoid arthritis (RA) treatment, there is evidence indicating that the mortality gap between patients with RA and the general population is not closing. The increase in mortality rates in patients with RA is predominantly due to cardiovascular disease (CVD). Literature suggests that important links exist between RA inflammation and atherosclerosis in CVD. Dyslipidemia is a well-known risk factor of atherosclerosis. Previous studies have suggested that antimalarials, chloroquine diphosphate, and hydroxychloroquine (HCQ), used in the treatment of autoimmune diseases, have a beneficial effect on the lipid levels. However, the studies had small sample sizes. We analyzed a Veterans Affair RA cohort of 2,925 patients to characterize the effect of 4 months' use of HCQ on the lipid levels.

Methods: Data for this cohort were obtained from the department of Veterans Affairs administrative database. Individuals (age ≥18 years) with a diagnosis of RA (ICD-9 code) at 2 or more outpatient visits from 1999 to 2009 were identified. Only the patients with at least 1 lipid level measured at 120-180 days before staring HCQ were included. Lipids levels on pre- and poststart dates of HCQ (120-180 days) were compared using student's t-test and adjusted for age, sex, race, C-reactive protein (CRP), and statin use with multivariable regression (analysis of variance/analysis of covariance) for the change in different lipid levels. To give equal weightage to covariables, we conducted an analysis of marginal means for race in each lipid level. All analyses were performed using STATA 11.

Results: After adjusting for sex, age, race, statin use, and post CRP values >10 mg/dL using a linear regression, the factor driving the change in the different lipid levels was race (p values for total cholesterol, 0.006; low-density lipoprotein, 0.09; non-high-density lipoprotein [HDL], 0.03; atherogenic index, 0.08; and HDL, 0.17). When considering race individually using marginal means analysis, the race in the subgroup "others" was more influential.

Conclusion: Our results suggest that sex and race influences the HCQ effect on the lipid profiles in patients with RA. Use of HCQ in males is found to be associated with positive changes in the lipid profiles independent from the use of statins. There is a suggestion that whites and African Americans might be less susceptible to HCQ effect on lipid profiles than other races.

Keywords: Antirheumatic agents, rheumatoid arthritis, lipids

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Cite this article as: Guevara M, Ng B. Positive effect of hydroxychloroquine on lipid profiles of patients with rheumatoid arthritis: A Veterans Affair cohort. Eur J Rheumatol 2021; 8(2): 62-6.

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Submitted: October 21, 2019
Accepted: July 30, 2020
Available Online Date: November 5, 2020

Introduction

The most common inflammatory arthritis is rheumatoid arthritis (RA), and it affects 1% of the general population. RA is associated with multiple comorbidities, but one of the most feared is the increased risk for accelerated cardiovascular disease (CVD). The common risk factors affecting the general population, i.e., smoking, diabetes, insulin resistance, dyslipidemia, hypertension, and body mass index, cannot explain the increased CVD risk in RA. Although the traditional CVD risk factors are responsible for some of the increased risk seen in patients with RA, current literature suggests that chronic inflammation seen in RA is more responsible for the development of CVD (1-7).

Ultrasound of the carotid arteries in patients with early and longstanding RA has shown increased deposition of lipid plaques and carotid intima-media thickness (2, 6-10). These studies help us to validate the increased risk of CVD seen in patients with RA. In addition, lipid abnormalities have been noted in patients with positive rheumatoid factor (RF) before the diagnosis of RA (9, 11).

Just like in the general population, dyslipidemia plays an important role in the development of atherosclerosis. However, in chronic inflammation, there is still some confusion as to how the lipid abnormalities seen in patients with RA play a role in the accelerated CVD.

There are some particular changes in the lipid profile of patients with RA that have been recognized. Literature suggests that active, untreated patients with RA have reduced low-density lipoprotein (LDL), triglycerides, total cholesterol (TC), and high-density lipoprotein (HDL) levels; however, not all levels are decreased in the same proportion. In RA, there is a significant decrease in HDL compared with TC, and as a result, patients with RA have increased TC/HDL ratio. In the general population, this ratio represents the atherogenic index (AI), which has been implicated as an important marker for CVD. The data show that an AI>5 is associated with a markedly increased risk of myocardial infarction (MI) and is a better predictor of MI than LDL, triglycerides, TC, or HDL levels. Taking these facts into consideration, we expect that including the TC/HDL ratio may better predict CVD in patients with RA (12-15). Multiple reports have verified that the use of disease-modifying antirheumatic drugs (DMARDs) contribute to a decrease in inflammation and consequently result in a significant reduction of the AI. This phenomenon is primarily due to the increase in serum HDL level. Hydroxychloroquine (HCQ), an antimalarial medication and one of the DMARDs used in RA, has also been shown to have this effect. HCQ has the advantage of being well tolerated, inexpensive, and less toxic than other DMARDs. Furthermore, the fact that HCQ favorably affects dyslipidemia in patients with RA, independent of steroid use, suggests the possibility that it has an important role in reducing the risk for atherosclerosis (16-21).

The purpose of this study was to investigate the association of HCQ use with lipid profiles and AI in a department of Veterans Affairs (VA) cohort of patients with RA.

Main Points

- Rheumatoid arthritis (RA) is associated with an increased risk of cardiovascular disease (CVD).
- Chronic inflammation is associated with the accelerated CVD seen in RA.
- Total cholesterol:High-density lipid (TC/HDL) levels ratio ratio is a better predictor for CVD.
- Hydroxychloroquine can improve TC/HDL ratios in patients with RA.

Methods

Data for this study were extracted from the VA administrative database DSS (inpatient files, outpatient files, vital status files, pharmacy benefits management [PBM], laboratory files, and VA centers for Medicare and Medicaid services). This project had institutional review board approval from the VA Puget Sound healthcare and the University of Washington. All adults (age ≥18 years) with a diagnosis of RA (ICD 9 code of 714) at 2 or more outpatient visits from 1999 to 2009, were identified. To ensure that the patients had not been on other DMARDs before, only those who had been in the VA system for at least 2 years and had not been on any other DMARD before starting HCQ were included. In addition, only patients with at least 1 lipid level checked 120 days before staring HCQ were included with the purpose of allowing HCQ to achieve its full effect.

Outcome

The primary outcome was change in the levels of non-HDL, TC, LDL, HDL, and AI after 4 months' use of HCQ in patients with RA. The secondary outcome was differences in lipid levels in patients treated with HCQ alone and HCQ plus statins.

Variables

Sociodemographic data of the cohort: Age, sex, race (Caucasians, African American, Others, and unknown).

Data on clinical parameters were collected at VA medical centers across the United States and were deposited into the database used for this study.

Laboratory data included were levels of CRP 14 days before staring HCQ and 14 days after staring HCQ. Lipid values included for the analysis were TC, LDL, HDL, non-HDL, and AI (TC/HDL).

The homogeneous enzymatic colorimetric assay on large chemistry analyzer by Roche Cobas was used to measure the lipid levels. Normal range for lipids is TC <200 mg/dL, LDL 0-129 mg/dL, and HDL ≥40 mg/dL.

The LDL direct assay meets the 1995 National Cholesterol Education Program (NCEP) goals of <4% total coefficient of variation bias <4% versus reference method and <12 total analytic error (22, 23).

The Roche cholesterol assay meets the 1992 National Institutes of Health (NIH) goal of ≤3% for both precision and bias (24).

The HDLC4 assay meets the 1998 NIH/NCEP goals for precision and accuracy (25).

CRP was measured with agglutinates with latex particles. The aggregates are determined turbidometrically on a large chemistry analyzer by Roche Cobas. Normal range for CRP is ≤10 mg/L.

The limit of quantitation (functional sensitivity) is the lowest CRP concentration that can be reproducibly measured with an interassay coefficient of variation of <20% (26).

Medications data were the start date for HCQ therapy (indicating an index date) at an unknown dose. Continuous HCQ use was defined by use ≥4 months. The data from PBM, which contains information about filled prescriptions, date of dispensed medication, and duration of treatment, was used to determine HCQ therapy.

Statin use was classified at 2 different points, 180 days before the index date of HCQ use and at 120 days after the index date of HCQ use (to allow the pre-lipid profile of this subgroup to reflect the full effect of statin use at the time of measurement). Here we made the assumption that because statins constitute chronic therapy, the patients did not discontinue the statin therapy between the 2 points of measurement (Figure 1).

Statistical analysis

Mean and standard deviation (SD) for each lipid level and 2 time points, pre- and postindex dates for all participants (HCQ users) and for the subgroups of statin users+HCQ users versus HCQ users, were obtained.

Differences in the mean for each lipid levels, pre- and postindex HCQ use, were evaluated using the student's t-test.

To explore the effect of the variables, considering effect modifiers (age, sex, race, statin use, post CRP values >10 mg/L), a multivariable regression model was performed (analysis of variance/analysis of covariance) for the change in different lipid levels.

For sensitivity analysis, marginal means of change were calculated for each lipid level by race and by controlling other variables.

All analyses were performed using STATA 11 for Windows (StataCorp; College Station, TX, USA).

Results

Our initial database consisted of 12,939 patients with a diagnosis of RA. For the purpose of our study, we selected patients with RA who started HCQ as their first and only

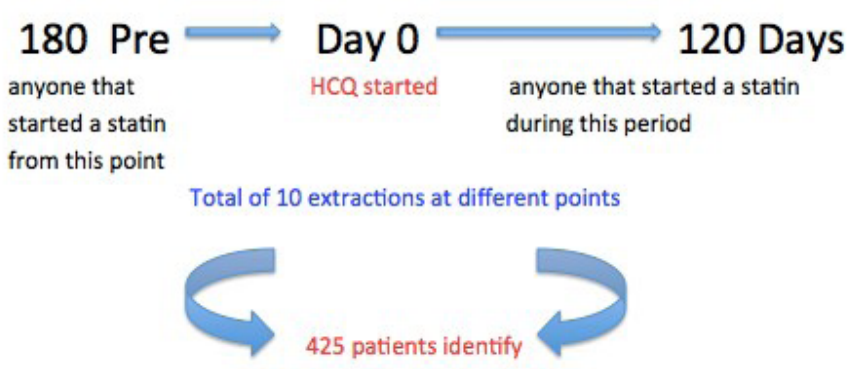

Figure 1. This represents how the data were extracted from the Veterans Affair database. Any patient on the system 180 days before starting hydroxychloroquine (HCQ) (day 0) was included. Any patient starting statin 180 days before starting HCQ and any patient starting statin during the 120 days after starting HCQ was extracted. In total, 425 patients were extracted with pre- and postlipid profiles.
HCQ: hydroxychloroquine.

Table 1. Demographics of 2925 RA patients who started HCQ stratified on stain users versus non-users.

	Yes on statin	No on statin	Total (n)
Gender			
Female (%)	23 (6.6)	326 (93.4)	349
Male (%)	402 (15.6)	2174 (84.3)	2576
Age mean (SD)	69 (9.7)	64 (12.2)	
Race			
White	369 (16.5)	1868 (83.5)	2237
Black	28 (8.2)	312 (91.8)	340
Others	28 (8.0)	320 (92.0)	348
Pre-starting statin CRP mean (SD) mg/L	16.13 (13.53)	5.16 (12.14)	
Post-starting statin CRP mean (SD) mg/L	11.23 (37.91)	5.9 (17.94)	

SD: standard deviation; CRP: C-reactive protein; R: rheumatoid arthritis; HCQ: hydroxychloroquine.

Table 2. Change in means of lipids pre and post after starting HCQ.*

Lipids mg/dL	Pre-mean (SD)	Post-mean (SD)	Total difference	p (CI)
Total cholesterol	176.17 (0.87)	171.65 (0.90)	4.52	0.00 (3.50-6.20)
LDL	103.77 (0.76)	98.86 (0.76)	4.91	0.00 (3.7-6.3)
HDL	45.80 (0.32)	46.18 (0.32)	-0.38	0.06 (-0.08-0.03)
Non-HDL	130.37 (0.85)	125.46 (0.86)	4.91	0.00 (3.80-6.40)
AI	4.17 (0.38)	4.0 (0.03)	0.17	0.00 (0.08-0.21)

*The lipid profile and AI improved after the use of HCQ. There was an insignificant increase in HDL with HCQ use from 45.80 mg/dL to 46.18 mg/dL (p=0.06).
HCQ: hydroxychloroquine; SD: standard deviation; LDL: low-density lipoprotein; HDL: high-density lipoprotein; AI: atherogenic index; CI: confidence interval.

DMARD after 180 days of being in the system (2,925 out of the 12,939 patients met this criteria). Lipid profiles were extracted 180 days before and 120 days after starting HCQ and/or statin (Figure 1).

Our study subject demographics were representative of the VA population. They were predominantly men, mostly white (75%) and above 60 years of age (mean age 66.5 years). Majority of the cohort did not use statin (84.3%), and the majority of the statin nonusers were African Americans (91.74%). Statin users had higher CRP levels, both pre- and post-HCQ treatment, and they had greater reduction of CRP levels after the initiation of HCQ (Table1).

The lipid profile and AI improved after the use of HCQ. Mean LDL reduced significantly from 103.77 mg/dL to 98.86 mg/dL (p<0.01). Non-HDL levels reduced significantly from 130.37 mg/dL to 125.46 mg/dL (p<0.01). There was an insignificant increase in the HDL level with HCQ use from 45.8 mg/dL to 46.18 mg/dL (p=0.06).

The AI ratio had a total decrease of 0.17 (p<0.01) (Table 2).

The study cohort was stratified into statin users versus nonusers. Statin users were defined as having started statin use 180 days or more before day zero and had continued taking statin till at least 120 days after starting HCQ (Figure 1).

To assess if there was a synergistic effect between the use of statin and HCQ, we adjusted for statin use. The major difference was in the non-HDL levels being less significant in statin+HCQ users versus nonstatin users (2.92 versus 5.52 mg/dL total difference, respectively) (Table 3).

After adjusting for sex, age, race, statin use, and post CRP values >10 mg/L using linear regression, the factor driving the change in the different lipids levels was race (p values for TC, 0.006; LDL, 0.09; non-HDL, 0.03; AI, 0.08; and HDL, 0.17). When we evaluated for race individually using marginal means analysis, the race in the subgroup of others, nonwhite or African Americans was more influential.

Discussion

Regardless of all the recent success in the treatment of RA, the standardized mortality ratio in RA is still more than 1, mostly because accelerated CVD. Our study assessed the effect of HCQ on the lipid levels in a large cohort of mainly older Caucasian men with RA. HCQ use was associated with positive changes in the lipid profiles. There were decreases in the levels of LDL, non-HDL, and AI (17).

After treatment with DMARDs, a significant reduction in the lipid profiles as well as AI has been observed in the literature (2, 17, 18). Previous studies have shown that this is also true for antimalarials like HCQ in RA (17-21, 27). To avoid confounding, we limited the patients with RA in our study to those who were only on HCQ, allowing for a clearer evaluation of the effect of HCQ on the lipid profiles.

Table 3. Change in means of lipids pre and post after starting HCQ by statin use.*

Change in lipid md/dL	Statin user-Total change	Non statin user-Total change
Change in total cholesterol	2.32	2.41
Change in LDL	4.76	5.09
Change in HDL	-0.35	-0.41
Change in non-HDL	2.92	5.52
Change in AI	0.07	0.16

*To assess if there was a synergistic effect between the use of statin and HCQ, we adjusted for statin use. The major difference was in non-HDL levels being more less significant in statin +HCQ users ersus nonstatin users (2.92 vs. 5.52 mg/dL total difference).
HCQ: hydroxychloroquine; HDL: high-density lipoprotein; LDL: low-density lipoprotein; AI: atherogenic index.

Till date, it is uncertain how HCQ affects the lipid levels. We know that the predecessor and a structurally similar drug to HCQ, chloroquine, is an inhibitor of cholesterol biosynthesis in rat hepatocytes. It also stimulates the capacity of LDL receptors and the activity of β-hydroxy β-methylglutaryl (HMG)-CoA reductase and slows the degradation of HMG-CoA reductase (17, 20).

Our findings are similar to those of previous studies showing a decrease from baseline levels of 4.52 mg/dL for TC, 4.91 mg/dL for LDL/non-HDL, and a decrease of 0.17 for AI, all statistically significant ($p<0.01$), except for an insignificant increase in HDL of 0.38 mg/dL from baseline. In 1997, Munro et al. (28) showed that in a cohort of 100 patients with active RA, HCQ had a significant overall improvement in their lipid profile compared with injectable gold (median HDL +15% for HCQ, -12% for gold). In 2011, Morris et al. (17) showed a decrease in TC of 7.7 mg/dL, LDL 7.5 mg/dL, AI of 0.191, and a statistically insignificant increase in HDL. In 2017, Restrepo et al. (20) showed that the use of HCQ was associated with lowering lipid levels in the RA cohort (LDL decrease of 9.3 mg/dL, TC 4.7 mg/dL, and AI of 0.59 [$p<0.001$]).

As we know, statins generally cause a 20%-30% decrease in cholesterol and 15% increase in HDL levels. A 10% decrease in the serum TC concentration reduces the risk of death from CVD by 10% and of nonfatal MI by 21% (29). For LDL, there has been a well-documented linear association between decrease in LDL levels and decrease in the rate of CVD (30).

Given these facts, one may be able to associate the positive effects of antimalarial drugs on lipids, even if small, with some clinical significance, particularly in secondary prevention. Further retrospective studies are required to prove this.

Because HCQ and statin affect the lipid profiles through different mechanisms of action, one may hypothesize that combining their use could produce a synergistic effect on the improvement of lipid profiles in patients with RA. However, in our study, we were not able to identify such a synergism, which could be because of the relatively small number of statin users in our cohort.

From our results, HCQ has less effect on the lipid profiles in Caucasian and African American patients with RA than that in the other ethnic groups. These findings concur with those by Kerr et al. (21), where race played a role in the effect of HCQ on the lipid profiles. One of the limitations in the VA database is that a large proportion of ethnic groups are either missing or unknown. To better evaluate the disparate effects on the lipid profile by HCQ in different ethnic groups, we need to study a population where there are better representations of African Americans, Asians, and Hispanics (21).

Ours is a retrospective study using the VA administrative database. Therefore, we encountered several limitations, such as the lack of RA disease activity, years of disease, other comorbidities, and concomitant use of nonsteroidal anti-inflammatory drugs. Because HCQ is primarily used in milder RA, it was possible that our cohort had patients with less severe disease and that could have confounded our results. Another challenge in this study was our inability to identify if the lipid profiles were measured by considering fasting or not. Hence, we included non-HDL and AI in our study. Non-HDL is defined as the difference between TC and HDL. Non-HDL includes all the cholesterol present in the lipoprotein particles considered atherogenic and is believed to be a better measurement of risk of CVD by some, and its level is not affected by fasting (31). Furthermore, as described in the 2009 European League against Rheumatism recommendations, the TC/HDL ratio is a better CVD risk predictor in RA than individual lipid components (32).

Despite these limitations, we believe that our study adds to the current literature in supporting the positive effects of HCQ on atherogenic lipid profiles in patients with RA. Our findings and other findings reported elsewhere about HCQ antiplatelet aggregation effect and favorable effect on glucose metabolism make HCQ an attractive complement to the therapy for patients with RA.

Ethics Committee Approval: Ethics committee approval was received for this study from the Institutional Review Board of VA Puget Sound Healthcare and the University of Washington (Approval Date: December 19, 2013; Approval Number: MIRB #00671).

Informed Consent: Informed consent was not obtained due to the nature of this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.G., B.N.; Design - M.G., B.N.; Supervision - B.N.; Data Collection and/or Processing - M.G.; Analysis and/or Interpretation - M.G., B.N.; Literature Search - M.G., B.N.; Writing Manuscript - M.G., B.N.; Critical Review - M.G., B.N.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study is the result of work supported with resources and the use of facilities at the VA Puget Sound Health Care System and funding from training grant T32HL007028.

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