EXTENDED REPORT

Metabolic and cardiovascular benefits of hydroxychloroquine in patients with rheumatoid arthritis: a systematic review and meta-analysis

Claire Rempenault,1 Bernard Combe,1 Thomas Barnetche,2 Cécile Gaujoux-Viala,3 Cédric Lukas,1 Jacques Morel,1 Charlotte Hua1

ABSTRACT

Objective Cardiovascular disease (CVD) is the leading cause of mortality in patients with rheumatoid arthritis (RA). Hydroxychloroquine (HCQ) has been shown to improve survival rates in other inflammatory diseases. We aimed to assess the available literature on the cardiovascular impact of HCQ in patients with RA.

Methods We systematically searched for studies evaluating the effects of HCQ on cardiovascular outcomes of known risk factors for CVD in patients with RA. Databases searched were MEDLINE (via PubMed), EMBase, Cochrane Library and the American College of Rheumatology and European League Against Rheumatism annual meetings. A meta-analysis was performed with a random-effects model, estimating mean differences (MDs), HRs and 95% CIs. Data were extracted by one investigator and independently checked by another.

Results The literature search revealed 185 articles and abstracts of interest; further examination resulted in 16 studies fulfilling the criteria. The MDs between HCQ users and non-users in levels of total, low-density and high-density cholesterol and triglycerides were −9.8 (95% CI −14.0 to −5.6), −10.6 (95% CI −14.2 to −7.0), +4.1 (95% CI 2.2 to 6.0) and −19.2 (95% CI −27.2 to −11.1), respectively. Diabetes incidence was lower for HCQ ever users than never users (HR 0.59 (95% CI 0.49 to 0.70)). HCQ seemed to decrease insulin resistance and incidence of CVD, but data were too few for meta-analysis.

Conclusion Besides its limited efficacy for disease activity and progression, HCQ may benefit the metabolic profile and to a lesser extent cardiovascular events in patients with RA, which suggests its usefulness combined with other conventional synthetic disease-modifying antirheumatic drugs.

INTRODUCTION

Mortality is increased in patients with rheumatoid arthritis (RA) as compared with the general population,1 and cardiovascular diseases (CVDs) are the main cause of the mortality. A meta-analysis of 24 studies of mortality in patients with RA showed a 50% increased risk of CVD death due to the disease itself and its treatments.2 Recommendations for RA management include screening, identification of CVD risk factors and CVD risk management.3 Antimalarial agents have been prescribed for many years,4 and their potential uses are still being explored. Chloroquine and hydroxychloroquine (HCQ) are weak basic 4-aminoquinoline compounds; because of reduced toxicity, HCQ is preferred over chloroquine in rheumatology practice.5 The drug has been found to improve survival rates in some other inflammatory diseases, notably systemic lupus erythematosus.6–8 The mechanism of action of HCQ is thought to be related to interference with lysosomal activity, inhibition of antigen presentation and toll-like receptor signalling.9

On the basis of the mechanism of action of HCQ, experimental data suggest that it could have a protective effect on CVD. Indeed, its effects on lysosomes appear to reduce insulin degradation10 and impede cholesterol synthesis.11 HCQ also increases levels of low-density lipoprotein (LDL) receptors in the liver, which in turn increases the catabolism of plasma LDL and lowers the plasma concentration of cholesterol.12 Finally, in vitro and animal studies indicated that the antimalarial improves insulin secretion and peripheral insulin sensitivity.10 11

Some clinical data corroborate these findings. Hypoglycaemia is a known side effect of HCQ.13 14 Several randomised trials of patients with poorly controlled diabetes mellitus have suggested that HCQ may significantly reduce levels of glycated haemoglobin A1c (HbA1c).15 16 A crossover study found that 6 weeks of HCQ improved insulin sensitivity among obese patients with insulin resistance.17 Moreover, HCQ can be a prophylactic agent against some of the major morbidities of systemic lupus erythematosus, namely, hyperlipidaemia, diabetes mellitus and thrombosis.18

HCQ has been used for treating RA for several decades, but its overall effect appears to be moderate,19 and since the emergence of more efficient conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), such as methotrexate (MTX), HCQ is not recommended as a single disease-modifying antirheumatic drug (DMARD) for patients with RA. However, HCQ is sometimes used in association due to some data suggesting that it might potentiate the effects of MTX.20 21 Nevertheless, since the metabolic effects of HCQ could be of interest in RA management, we performed a systematic review and meta-analysis of the current literature to assess the impact of HCQ on the metabolic profile and CVDs of people with RA.
MATERIALS AND METHODS

Literature search
This systematic review with meta-analysis was based on the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement (see online supplementary table S1).23 We systematically reviewed articles written in English or in French for studies evaluating the metabolic or cardiovascular impact of HCQ that were published up to March 2016 in MEDLINE (via PubMed), EMBase, Cochrane Library and databases for the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) annual meetings since 2013. Keywords were ‘rheumatoid arthritis’, ‘plaquenil’, ‘hydroxychloroquine’ and ‘antimalarial’, with no limit on date of publication. In addition, the reference lists of articles detected were manually searched to identify additional relevant articles. The trials were selected on the basis of their titles and abstracts and then on their full text; duplicates were removed.

Study selection
The population of interest was all patients with RA regardless of disease activity and duration or age. We included studies comparing HCQ users and non-users for the known modifiable factors of CVD (lipid levels, blood pressure, insulin resistance, HbA1c level, diabetes mellitus, metabolic syndrome) and comparing HCQ ever users and never users for incidence of CVD according to the WHO definition (ie, a group of disorders of the heart and blood vessels including coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis and pulmonary embolism). Based on this definition and due to the lack of data, CVD procedures (such as percutaneous coronary intervention or heart surgery) were not included as cardiovascular events. Observational studies and randomised controlled trials (RCTs) but not case reports were eligible. Selection criteria are shown in online supplementary table S2.

Data extraction and quality assessment
Two investigators (CR and CH), using a predetermined form, collected data on the study design, sample size, treatments received, patient and control group characteristics (age, sex, disease duration, biologic agent, prednisone use and dose, exposure time to HCQ and HCQ dose), definition of the outcome measures, timing and unit of measurements, presence of known cardiovascular risk factors (smoking status, body mass index), presence of an established CVD, exposure to statins and statistical analyses performed. Disagreements were resolved by consensus. The quality of studies suitable for meta-analysis was evaluated. We used the Jadad score for RCTs, (see online supplementary table S3) and a score of eight items pre-established and based on the Newcastle-Ottawa scale for cohort studies (see online supplementary table S4).

Data synthesis and analysis
A meta-analysis was performed for three factors: lipid profiles between HCQ users and non-users, change in lipid profiles after HCQ initiation and incidence of type 2 diabetes mellitus (T2DM) by HCQ exposure. The analysis was not adjusted for statin use because these data were available in only one of the included studies. Due to heterogeneity in the results presentation and in the statistical tests performed, meta-analysis was not feasible for three variables: insulin resistance, HbA1c level and CVD incidence. Among included studies, homoeostatic model assessment for insulin resistance (HOMA-IR) was used as a surrogate measure of insulin resistance. HOMA-IR was calculated as fasting glucose (mmol/L) × fasting insulin (µU/mL)/22.5 or fasting glucose (mg/dL) × fasting insulin (µU/mL)/405. High HOMA-IR values were associated with...

Figure 1 Flow chart of the systematic literature review with meta-analysis. ACR, Annual College of Rheumatology; EULAR, European League Against Rheumatism.
Clinical and epidemiological research

Insulin resistance. In some studies, pancreatic β-cell function was also evaluated by measure of homeostatic model assessment of β-cell function (HOMA-B). HOMA-B was defined as $20 \times$ fasting insulin ($\mu$U/mL)/fasting glucose (mmol/L)–3.5 or $360 \times$ fasting insulin ($\mu$U/mL)/fasting glucose (mg/dL)–63. Low HOMA-B values were associated with β-cell dysfunction. Pooled mean differences (MDs) and pooled HRs, with 95% CIs, were estimated by the meta-analysis, using the generic inverse-variance approach, and are shown by forest plots for each outcome studied. Estimates and their SEs could be entered directly. Statistical heterogeneity of studies was assessed by the $\chi^2$ Cochran’s Q test, at p<0.05, and the I² statistic, with high values indicating high heterogeneity. All meta-analyses involved a random-effects model, in case of significant heterogeneity. RevMan V.5.1.6 was used for statistical analysis. A p value <0.01 was considered statistically significant. Publication bias was assessed with funnel plots and Egger’s test.

<table>
<thead>
<tr>
<th>Study</th>
<th>Group</th>
<th>N</th>
<th>MTX</th>
<th>Non-HCQ csDMARDs</th>
<th>TNFi</th>
<th>CS</th>
<th>TC (mean (SD) or median (IQR))</th>
<th>LDL (mean (SD) or median (IQR))</th>
<th>HDL (mean (SD) or median (IQR))</th>
<th>TG (mean (SD) or median (IQR))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kerr et al25</td>
<td>Group 1</td>
<td>150</td>
<td>NR</td>
<td>95</td>
<td>21</td>
<td>41</td>
<td>186.1 (31.8)</td>
<td>108.6 (3)</td>
<td>53.0 (10.9)</td>
<td>124.1 (39.3)</td>
</tr>
<tr>
<td></td>
<td>Group 2</td>
<td>638</td>
<td>NR</td>
<td>71</td>
<td>25</td>
<td>40</td>
<td>204 (41.8)</td>
<td>119.7 (48.7)</td>
<td>46.7 (15.7)</td>
<td>153.5 (59.9)</td>
</tr>
<tr>
<td>Penn et al26</td>
<td>Group 1</td>
<td>31</td>
<td>NR</td>
<td>26</td>
<td>23</td>
<td>47</td>
<td>201 (33)</td>
<td>112 (30)</td>
<td>63.7 (15.6)</td>
<td>116 (94, 142)</td>
</tr>
<tr>
<td></td>
<td>Group 2</td>
<td>146</td>
<td>NR</td>
<td>52</td>
<td>33</td>
<td>40</td>
<td>210 (37)</td>
<td>123 (35)</td>
<td>60.5 (14.4)</td>
<td>121 (84, 156)</td>
</tr>
<tr>
<td>Restrepo et al27</td>
<td>Group 1</td>
<td>109</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>181.2 (35.6)</td>
<td>97.5 (29.7)</td>
<td>60.4 (18.4)</td>
<td>115.1 (56.9)</td>
</tr>
<tr>
<td></td>
<td>Group 2</td>
<td>836</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>185.6 (40.4)</td>
<td>106.5 (33.6)</td>
<td>52.7 (16.3)</td>
<td>132.2 (81.2)</td>
</tr>
<tr>
<td>Solomon et al28</td>
<td>Group 1</td>
<td>23</td>
<td>70</td>
<td>30</td>
<td>57</td>
<td>9</td>
<td>179.7 (44.3)</td>
<td>101.7 (36.7)</td>
<td>59.4 (18.2)</td>
<td>92.4 (41.7)</td>
</tr>
<tr>
<td></td>
<td>Group 2</td>
<td>23</td>
<td>70</td>
<td>30</td>
<td>57</td>
<td>9</td>
<td>189.4 (37.9)</td>
<td>109.9 (33.1)</td>
<td>60.3 (17.8)</td>
<td>91.6 (44.9)</td>
</tr>
<tr>
<td>Rho et al29</td>
<td>Group 1</td>
<td>42</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>103.7 (27.8)</td>
<td>50.4 (14.1)</td>
<td>105.5 (50.5)</td>
</tr>
<tr>
<td></td>
<td>Group 2</td>
<td>127</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>115.6 (34.7)</td>
<td>45.3 (13.7)</td>
<td>157.7 (202.6)</td>
</tr>
</tbody>
</table>

CS, corticosteroid; csDMARD, conventional synthetic disease-modifying antirheumatic drug; HCQ, hydroxychloroquine; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MTX, methotrexate; NR, not reported; TC, total cholesterol; TG, triglycerides; TNFi, TNF inhibitors.

Figure 2  Forest plot of mean differences between hydroxychloroquine users and non-users in levels of total cholesterol (A), low-density lipoprotein (B), high-density lipoprotein (C) and triglycerides (D).
RESULTS

Literature search results and study characteristics

Initially, 8294 potentially relevant articles were screened and 8281 were excluded. After manually searching reference lists and ACR and EULAR annual meeting databases, reports of 16 studies were included; 9 were selected for meta-analysis (figure 1). Among these nine studies, seven were cohort studies and two were clinical trials. The methodological quality was good for eight studies and poor for one study due to lack of randomisation and blinding (see online supplementary tables S3 and S4). No publication bias was highlighted (see online supplementary figure S1–3).

This systematic review involved 35213 patients: 12245 HCQ users or ever users and 22968 HCQ non-users or never users. Lipid levels analyses were performed on 6536 HCQ users and 9760 non-users, diabetes incidence analyses on 4811 ever users and 12074 never users, insulin resistance analyses on 80 users and 243 non-users, HbA1c analyses on 33 users and 31 non-users and CVD analyses on 824 ever users and 1029 never users. Patient characteristics are shown in online supplementary table S5. Except for three studies, the information on history of an established CVD was often not available and so patients both with and without CVD might have been included.

Lipid profiles between HCQ users and non-users

Seven studies compared lipid profiles, namely, levels of total cholesterol (TC), LDL cholesterol, HDL cholesterol and triglycerides (TG) between HCQ users and non-users. Five studies were included for meta-analysis (table 1). Lipid profile was better for HCQ users, with pooled MD for TC, LDL, HDL and TG of −9.8 mg/dL (95% CI −14.0 to −5.6) (−0.25 mmol/L), −10.6 mg/dL (95% CI −14.2 to −7.0) (−0.27 mmol/L), +4.1 mg/dL (95% CI +0.10 mmol/L), respectively (figure 2). The analysis was not adjusted for statin

<table>
<thead>
<tr>
<th>Study</th>
<th>Group</th>
<th>N</th>
<th>Total person-years</th>
<th>T2DM incident cases</th>
<th>Non-HCQ csDMARDs</th>
<th>TNFi</th>
<th>CS</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bili et al</td>
<td>Group 1</td>
<td>333</td>
<td>484</td>
<td>3</td>
<td>48</td>
<td>24</td>
<td>77</td>
<td>0.31 (0.10 to 1.0)</td>
</tr>
<tr>
<td>Group 2</td>
<td>794</td>
<td>2041</td>
<td>45</td>
<td>61</td>
<td>30</td>
<td>77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Holmqvist et al</td>
<td>Group 1</td>
<td>2670</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>0.59 (0.48 to 0.73)</td>
</tr>
<tr>
<td>Group 2</td>
<td>8183</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wasko et al</td>
<td>Group 1</td>
<td>1808</td>
<td>10364</td>
<td>54</td>
<td>64</td>
<td>0</td>
<td>72</td>
<td>0.62 (0.42 to 0.92)</td>
</tr>
<tr>
<td>Group 2</td>
<td>3097</td>
<td>19313</td>
<td>171</td>
<td>49</td>
<td>0</td>
<td>58</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CS, corticosteroid; csDMARD, conventional synthetic disease-modifying antirheumatic drug; HCQ, hydroxychloroquine; NR, not reported; T2DM, type 2 diabetes mellitus; TNFi, TNF inhibitors.

Figure 3 Forest plot of change in levels of total cholesterol (A), low-density lipoprotein (B), high-density lipoprotein (C) and triglycerides (D) after hydroxychloroquine initiation.
use because these data were available in only one of the included studies.

**Change in lipid profiles after initiation of HCQ**

Two studies that evaluated lipid levels before and after 2 months\(^2\) or 3 months\(^3\) of HCQ treatment were included in the meta-analysis (see online supplementary table S6). On pooled analysis (figure 3), after initiation of HCQ, mean decrease in level of TC, LDL and TG was \(-13.1\, \text{mg/dL} (95\% \text{CI} \, -20.9\, \text{to} -5.3) (-0.34\, \text{mmol/L}), -12.3\, \text{mg/dL} (95\% \text{CI} \, -20.2\, \text{to} -4.6) (-0.32\, \text{mmol/L}) \) and \(-12.5\, \text{mg/dL} (95\% \text{CI} \, -28.9\, \text{to} 3.9) (-0.14\, \text{mmol/L}),\) respectively, and mean increase in HDL level was \(1.6\, \text{mg/dL} (95\% \text{CI} \, -0.96\, \text{to} 4.3) (+0.04\, \text{mmol/L}).\)

**Diabetes incidence by HCQ exposure**

Three studies that compared diabetes incidence between HCQ ever users and never users were included in the meta-analysis (table 2).\(^2\,2^6\,3^2\,3^5\) Diabetes incidence was lower for HCQ ever users than never users (pooled HR 0.59 (95\% CI 0.49 to 0.70)) (figure 4).

**Glycosylated haemoglobin level between HCQ users and non-users**

We included only one RCT.\(^3^7\) Change in HbA1c level from baseline to 3 months was \(-0.19\, \text{±} 0.13\%\) in HCQ users versus \(-0.08\, \text{±} 0.03\%\) in MTX users, without any statistical comparison.

**Insulin resistance and β-cell function between HCQ users and non-users**

Three studies compared HOMA-IR and HOMA-B between HCQ users and non-users.\(^2^6\,3^2\,3^5\) Due to variability in the outcomes, meta-analysis was not feasible. In the included studies, there was no statistically significant difference between the groups for both HOMA-IR and HOMA-B. In the two studies assessing it,\(^2^6\,3^2\) HOMA-B values were numerically higher in the HCQ users group than in the non-users group, which might suggest that HCQ could possibly reduce β-cell dysfunction (see online supplementary table S7).

**CVD according to HCQ exposure**

We included three studies comparing CVD prevalence or incidence between HCQ ever users and never users.\(^3^8\,3^9\,4^0\) (see online supplementary table S8). In a retrospective study, presented as an abstract at the 2014 ACR annual meeting,\(^3^8\) risk of cardiovascular morbidity was reduced among patients with RA with HCQ use (OR \(0.27\) (95\% CI 0.16 to 0.46)). In a case-control study,\(^3^9\) CVD risk was reduced with HCQ treatment (adjusted OR \(0.45\) (95\% CI 0.10 to 2.0)). In a recent retrospective study of an incident RA cohort,\(^4^0\) HCQ use was associated with reduced incidence of CVD (adjusted HR \(0.60\) (95\% CI 0.41 to 0.94), \(p=0.02\)) and incidence of a composite of coronary artery disease, stroke and transient ischaemic attack (adjusted HR \(0.67\) (95\% CI 0.42 to 1.070), \(p=0.09\).

**DISCUSSION**

To our knowledge, this is the first systematic review with meta-analysis of the metabolic and cardiovascular impact of HCQ in patients with RA. According to our results, HCQ has a positive impact on metabolic and cardiovascular outcomes in patients with RA, both by decreasing modifiable factors for CVD, namely, lipid profile, diabetes incidence and glycosylated haemoglobin level, and by decreasing the incidence of cardiovascular events.

Our meta-analysis showed lower levels of TC, LDL and TG and higher HDL level for HCQ users than HCQ non-users. Our literature search highlighted two other studies consistent with these findings but not fulfilling our selection criteria for meta-analysis.\(^3^4\,3^6\) The meta-analysis also showed reduced diabetes incidence in patients with RA who ever used HCQ. This finding was confirmed in a recent publication from Ozen et al.,\(^4^1\) reporting reduced diabetes incidence with HCQ use among patients with RA (adjusted HR 0.67 (95\% CI 0.57 to 0.80)).

Our systematic review with meta-analysis has several strengths. The studies we included showed high-quality scores (over 70\% except for one study) and no significant heterogeneity among studies included in the meta-analysis. Apart from two analyses (figure 3C,D), all pooled ORs were strongly significant and correlated in favour of a positive impact of HCQ on CVD risk. However, most of the studies were observational studies, for possible indication bias and no certainty of comparability of groups. Moreover, HCQ was often combined with other csDMARDs, so concluding on the sole impact of HCQ was difficult. The fact that we were unable to include CVD interventions as cardiovascular events is also a limitation of our study due to the risk of minimisation of CVD incidence. Indeed, according to the European Guidelines on prevention of CVD, all patients who underwent a CVD procedure should receive preventive medication as secondary prevention and should be considered as patients with CVD.\(^4^2\) Finally, our results should be tempered by the possibility of confounding bias. Indeed, because of its moderate efficacy in RA, HCQ might be more likely prescribed to patients with RA with benign disease than to patients with RA with severe and erosive disease who are, however, the most at risk for CVD. Consequently, the lower cardiovascular risk noted for the patients belonging to the ‘HCQ users’ is perhaps linked to the characteristics of these patients’ disease and not to the HCQ treatment in itself.

However, HCQ might not have a high efficacy in RA treatment,\(^4^0\) but it is a well-tolerated drug. Therefore, according to our results, adding HCQ to other DMARDs could have some benefit for metabolic and cardiovascular comorbidities in patients with RA, without major side effects. Yet, studies of other known cardiovascular risk factors (blood pressure, metabolic syndrome etc) are lacking, and these results should be confirmed by RCTs comparing csDMARDs alone with csDMARDs associated with HCQ for quantifiable CVD outcomes.
In conclusion, with limited efficacy for RA disease activity, HCQ may benefit lipid profiles and diabetes incidence and, to a lesser extent, cardiovascular events and insulin resistance in patients with RA. Adding HCQ, a safe and inexpensive treatment, to other csDMARDs may comprise a useful adjunct in the prevention of metabolic and cardiovascular events for patients with RA.

Acknowledgements The authors thank AbbVie because this work was initiated during CME sessions on performing meta-analysis (ASLER) organised by AbbVie. AbbVie had no role in the study design or the collection, analysis, or interpretation of the data, the writing of the manuscript or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by AbbVie. The study was not financially supported by AbbVie. This work has previously been published as a conference abstract at the 2016 American College of Rheumatology annual meeting and the 2017 European League Against Rheumatism annual meeting.


Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES
Metabolic and cardiovascular benefits of hydroxychloroquine in patients with rheumatoid arthritis: a systematic review and meta-analysis
Claire Rempenault, Bernard Combe, Thomas Barnetche, Cécile Gaujoux-Viala, Cédric Lukas, Jacques Morel and Charlotte Hua

Ann Rheum Dis published online September 25, 2017

Updated information and services can be found at:
http://ard.bmj.com/content/early/2017/10/06/annrheumdis-2017-211836

These include:

References
This article cites 41 articles, 8 of which you can access for free at:
http://ard.bmj.com/content/early/2017/10/06/annrheumdis-2017-211836#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/