Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review

An umbrella review of systematic reviews with meta-analyses evaluating positive and negative outcomes of Hydroxychloroquine and chloroquine therapy

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ABSTRACT

BACKGROUND & AIMS: Hydroxychloroquine (HCQ) and chloroquine (CQ) are anti-malarial drugs frequently used in the rheumatologic field. They were recently identified as potential therapeutic options for Coronavirus Disease (COVID-19). The present study aims to map and grade the diverse health outcomes associated with HCQ/CQ using an umbrella review approach.
METHODS: Umbrella review of systematic reviews of observational and intervention studies. For observational studies, random-effects summary effect size, 95% confidence interval, and 95% prediction interval were estimated. We also assessed heterogeneity, evidence for small-study effect, and evidence for excess significance bias. The quality of evidence was then graded using validated criteria from highly convincing to weak. The evidence from randomized controlled trials (RCTs) was graded using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool.
RESULTS: From 313 articles returned in the literature search, six meta-analyses were included (n = 25 outcomes). Among meta-analyses (MAs) of observational studies, HCQ/CQ are weakly associated with a reduced risk for cardiovascular events and diabetes when used for autoimmune diseases and with spontaneous abortion; they are also associated with a higher risk of death in COVID-19 patients. Among MAs of RCTs, HCQ/CQ are associated with an improvement of articular manifestations of rheumatic diseases.
CONCLUSIONS: There is high evidence of the efficacy of HCQ/CQ in the rheumatologic field. The lack of evidence for efficacy and the risk of death associated with the use of HCQ/CQ for COVID-19 indicate the inappropriateness of their inclusion in recent COVID-19 therapy guidelines and the urgent need for RCTs to determine eventual appropriateness as a COVID-19 therapy.

Introduction

Hydroxychloroquine/chloroquine (HCQ/CQ), broadly used antimalarial medications, are also some of the most widely used immunosuppressant drugs in rheumatology (Schrezenmeier and

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Dorner, 2020); they are included in the therapeutic guidelines for systemic lupus erythematosus (Fanouriakis et al., 2019) and are also considered for the treatment of other autoimmune diseases, such as antiphospholipid syndrome (Tektonidou et al., 2019), Sjogren's syndrome (Ramos-Casals et al., 2020), and rheumatoid arthritis (Smolen et al., 2020).

Recent results from 15 trials reported by Chinese researchers indicate a potential role for HCQ/CQ with the new coronavirus disease (COVID-19) (Yao et al., 2020). Despite limited clinical data on the use of HCQ/CQ in COVID-19, the use of these drugs has attracted considerable attention from the media. Individuals and lobby groups have called for widespread prescription of these drugs (Javelot et al., 2020). Public endorsement of the use of HCQ and other medications (e.g., azithromycin) to treat COVID-19 has led to it becoming one of the most used treatments in this pandemic (Ferner and Aronson, 2020; Jaffe, 2020).

Currently, more than 200 trials of HCQ, CQ, or both, and sometimes in combination with other drugs, are registered worldwide. The translation from laboratory to clinic has led to disappointment, likely due to the complex pharmacokinetics of 4-aminoquinolones, with scarce effects obtained so far (Ferner and Aronson, 2020). In some cell cultures CQ inhibits dengue, shows promising effects on Ebola and influenza virus, and has some effects on SARS-CoV2 (Ferner and Aronson, 2020; Yao et al., 2020).

From a public health perspective, the side effects, as well as the potential benefits, need to be considered before clinicians expose their patients to these drugs. Wide use of HCQ/CQ may expose some patients to harm, ranging from cutaneous adverse reactions to hepatic failure and ventricular arrhythmias, which occur especially when HCQ/CQ is associated with other medications, such as azithromycin (Ferner and Aronson, 2020; Mercuro et al., 2020).

The aim of the present work is to evaluate – through an umbrella review – the strength and credibility of the evidence derived from systematic reviews with meta-analyses (MAs) of observational and intervention studies regarding HCQ/CQ, their importance to health outcomes and their side effects.

Methods

The protocol for this review was registered in PROSPERO on 1 April 2020 in the context of COVID-19 research and is still awaiting formal approval. The submitted protocol is attached in the Supplementary Material.

Data sources and searches

We conducted an umbrella review (Ioannidis, 2009), searching the MEDLINE, Scopus and Embase databases from inception until 27 June 2020 with:

"(Meta-Analysis [ptyp] OR metaanaly*[tiab] OR meta-analy* [tiab] OR Systematic review [ptyp] OR "systematic review" [tiab]) AND (Hydroxychloroquine [tiab] OR Hydroxychlorochin [tiab] OR "chloroquine" [tiab] OR Plaquenil [tiab] OR "Hydroxychloroquine Sulfate" [tiab] OR "Hydroxychloroquine Sulfate (1:1) Salt" [tiab]).

We also hand-searched the reference lists of eligible articles and reviews in this field.

Study selection

We considered eligible: 1) any MA that included people of any age, any risk category, any population, taking any HCQ/CQ medication; 2) MAs of longitudinal design studies (i.e., prospective/cohort or retrospective/case-control) that investigated the association of HCQ/CQ administration with any outcome or MAs of randomized controlled trials (RCTs) that investigated the effects of HCQ/CQ. The study selection was made by two authors independently (JD, SC). Disagreements were resolved through consensus with an independent author (NV). Full-texts of all potentially eligible articles were subsequently evaluated by the same two authors (JD, SC) and any disagreement resolved with another independent author (LS).

MAs were included only if they reported study-specific information (i.e., effect size, 95% confidence intervals (CIs), sample size) or if those metrics could be inferred from the data presented.

Data extraction

For each eligible MA, two independent investigators (JD, SC) firstly extracted data from each eligible MA including: name of first author; year of publication; study population; study design; outcome; number of studies; intervention; comparison; and effect size reported with 95% CI.

The same two authors (JD, SC) then extracted the following information for each original article: PMID/doi; name of MA author; year of MA; name of first author of single studies included in the MA; year of publication; population/main condition of patients exposed to HCQ/CQ; effect size metrics used in the MA; study design of included primary studies (e.g., case-control, prospective, RCT); number of cases and controls for each study; number of people treated with HCQ/CQ with the correspondent number of events and number of people in placebo/control and corresponding number of events in intervention MAs; follow-up; mean age of participant population; medication type (HCQ, CQ); and outcome.

Next, the study-specific estimated relative risk for any side effects or negative outcome were extracted with 95% CI (risk ratio, odds ratio (OR), hazard ratio, incident risk ratio, standardized mean differences, and mean differences (MDs)).

If two MAs were available for the same outcome, the one that included the largest number of studies (or if equal for number of studies, the most recent one) was used. If there were observational and RCT MAs investigating the same outcome, both were included.

Outcomes

Any health outcome, adverse event or side effect potentially associated to HCQ/CQ therapy.

Risk of bias assessment

The methodological quality of each included MA was assessed by two independent investigators (LS, SC) with the Assessment of multiple systematic reviews (AMSTAR) 2 tool (https://amstar.ca/Amstar-2.php). A recent update of AMSTAR (Shea et al., 2017), AMSTAR2 ranks the quality of a MA from critically low to high according to 16 predefined items.

Data synthesis and analysis

For each MA we estimated the summary effect size and its 95% CI through a random-effects model. We also estimated the prediction interval (PI) and its 95% CI, which further accounts for between-study effects and estimates the certainty of the association if a new study addresses the same association (Higgins et al., 2009; IntHout et al., 2016; Serghiou and Goodman, 2018). Between-study inconsistency was estimated with the I^2 metric, with values $\geq$50% indicative of high heterogeneity and $\geq$75% very high heterogeneity (Higgins and Thompson, 2002). We calculated the evidence of small-study effects (i.e., whether small studies inflated effect sizes) using the regression asymmetry test (Egger et al., 1997) with a p-value of <0.10 (Carvalho et al., 2016). Finally,

we applied the excess of significance test (Ioannidis and Trikalinos, 2007). Because of the limited statistical power of this test a lenient significance threshold ($p < 0.10$) was adopted (Ioannidis, 2013). We considered the effect size of the largest dataset and based on this we estimated the power of each constituent study with an algorithm using a non-central *t* distribution. Excess significance for each MA was considered whenever $p < 0.10$.

We planned to run several sensitivity analyses (age, duration of therapy/exposure), however, these data were not sufficiently reported in the MAs included, hindering reliable analyses.

All statistical analyses were conducted in Stata, version 14.0 (StataCorp), and R, version 3.3.0 (R Foundation for Statistical Computing).

Grading the evidence

For observational studies, using the criteria mentioned above, significant associations (i.e., $p < 0.05$) were categorized into strong, highly suggestive, suggestive, or weak evidence, following a grading scheme that has already been applied in various fields (Theodoratou et al., 2014; Aromataris et al., 2015; Belbasis et al., 2016; Bellou et al., 2016; Dinu et al., 2017; Kyrgiou et al., 2017; Li et al., 2017; Veronese et al., 2018; Solmi et al., 2020).

Grading of Recommendations, Assessment, Development and Evaluation (GRADE) assessment of observational studies was performed (supplementary table 1 GRADE of observational studies). Based on the GRADE assessment of observational studies (mostly case control), independently from significance of association, one was rated as moderate (Singh et al), nine were rated as low, and all the remaining as very low quality. The rating was impaired mostly due to heterogeneity, unavailable data, and quality assessment of original studies.

Evidence from MAs of RCTs was assessed in terms of the significance of the summary effect, using a p-value <0.05 as the threshold for statistical significance. When the p-value for the random effect was <0.05, we evaluated the evidence using the GRADE assessment (Guyatt et al., 2008). We also reported 95% PI (excluding null or not), the presence of large heterogeneity (I^2 >50%), small study effects ($p > 0.10$), and excess significance ($p > 0.10$) as possible indicators of quality of the available evidence.

Results

Literature review

The initial search yielded 313 articles. After duplicates (61) were removed we evaluated 252 papers. Only 62 papers were eligible for

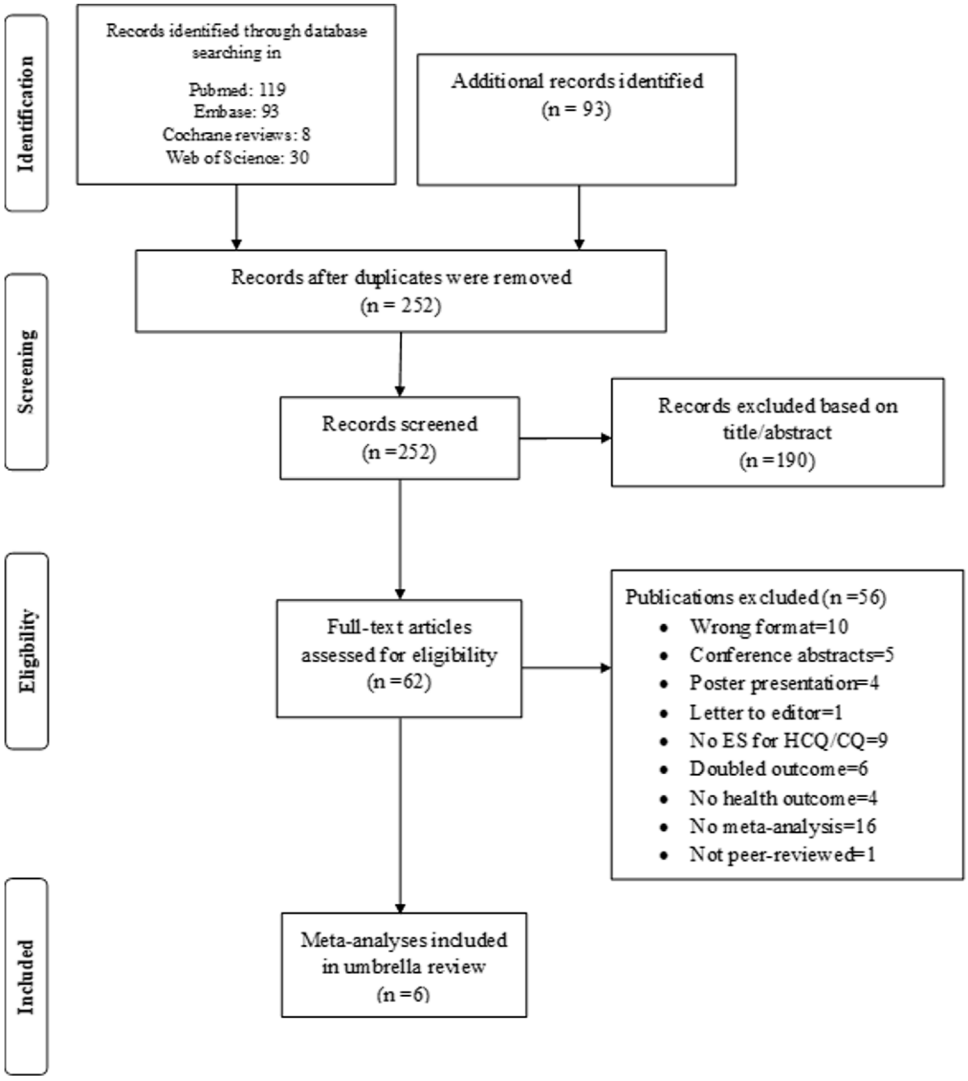

Figure 1. Flow of studies through review selection.

Table 1
Findings from the observational studies.

Intervention	Population	Outcome	Number of studies	Events	Sample size	Type of ES	Mean ES	Lower 95% CI	Higher 95% CI	P-value	I^2	Small study	Excess significance bias	Largest study	95% low PI	95% high PI	Grade of evidence
HCQ	RA	DM incidence	3	273	16,885	HR	0.59	0.49	0.7	1.04E-08	0	no	no	yes	0.18	1.92	**IV**
HCQ	Autoimmune disease	CVD	7	NA	3447	OR	0.43	0.26	0.71	0.001	50.2	yes	NA	NA	0.1	1.79	**IV**
HCQ/CQ	Autoimmune disease	CVD	10	NA	NA	RR	0.73	0.56	0.94	0.01	42.8	no	NA	NA	0.38	1.89	**IV**
HCQ	Autoimmune disease + pregnancy	Spontaneous abortion	4	82	1090	OR	1.86	1.1	3.14	0.02	12.3	no	no	yes	0.45	7.68	**IV**
HCQ	Autoimmune disease + pregnancy (no APLS)	Spontaneous abortion	4	79	1055	OR	1.77	1.09	2.89	0.02	0	no	no	yes	0.61	5.18	**IV**
HCQ/CQ	SLE	CVD	7	NA	NA	OR	0.71	0.53	0.96	0.03	43.5	no	NA	NA	0.34	1.5	**IV**
HCQ	Autoimmune disease + pregnancy	Prematurity	5	260	1343	OR	1.75	0.95	3.23	0.07	71.6	no	no	yes	0.21	14.29	**NS**
HCQ	Autoimmune disease + pregnancy	LBW	2	83	252	OR	0.88	0.22	3.6	0.1	62.1	NA	no	no	NA	NA	**NS**
HCQ	SLE pregnancy	Prematurity	6	230	871	OR	0.58	0.29	1.16	0.12	46.7	no	no	no	0.09	3.54	**NS**
HCQ	SLE pregnancy	IUGR	5	143	831	OR	0.6	0.22	1.64	0.32	69.1	no	no	no	0.03	14.2	**NS**
HCQ	Autoimmune disease + pregnancy	Stillbirth	4	41	1467	OR	0.72	0.36	1.41	0.33	0	no	no	no	0.24	2.18	**NS**
HCQ	Autoimmune disease + pregnancy	nervous system malformation	5	4	1295	OR	1.9	0.32	11.31	0.48	0	no	no	no	0	20,000	**NS**
HCQ	Autoimmune disease + pregnancy	craniofacial malformation	5	5	1295	OR	0.63	0.13	3.2	0.58	0	yes	no	no	0.02	22.22	**NS**
HCQ	Autoimmune disease + pregnancy	genitourinary malformation rates	5	12	1295	OR	1.41	0.42	4.67	0.58	0	no	no	no	0.01	19.59	**NS**
HCQ	Autoimmune disease + pregnancy	major congenital malformation rates	7	58	1800	OR	1.12	0.58	2.15	0.74	17	no	no	no	0.3	4.19	**NS**
HCQ	Autoimmune disease + pregnancy	cardiovascular malformation rates	5	15	1295	OR	1.06	0.29	3.86	0.93	0	no	no	no	0.06	18.12	**NS**
HCQ	COVID-19	Death	2	52	446	OR	1.84	0.74	4.55	0.19	40.7	NA	NA	yes	NA	NA	**NS**

Abbreviations: HCQ: Hydroxychloroquine; CQ: chloroquine; RA: Rheumatoid arthritis; APLS: Antiphospholipid syndrome; SLE: Systemic Lupus Erythematosus; DM: Diabetes Mellitus; CVD: Cardiovascular disease; LBW: Low birth weight; IUGR: intrauterine growth restriction.

Table 2
Descriptive (and ancillary) findings of the meta-analyses of the randomized controlled trials.

Population	Outcome	N of studies	N HCQ/CQ	Controls	Sample size	Type of ES	Mean ES (RE)	LL	UL	P	I^2	Small study	Largest study	95% LL PI	95% UL PI
RA	Swollen joints	4	290	281	571	MD	−3.71	−4.86	−2.57	2.21E-10	0	no	yes	−6.23	−1.2
RA	Physician global assessment	2	185	180	365	MD	−0.39	−0.56	−0.21	0.00002	0	NA	yes	NA	NA
RA	Tender joints	4	290	281	571	MD	−2.66	−4.19	−1.13	0.001	0	yes	no	−6.01	0.69
RA	Withdrawals and dropouts	4	299	292	591	OR	0.58	0.4	0.86	0.006	4.8	no	no	0.23	1.59
RA	Withdrawals and dropouts lack of efficacy	4	235	232	467	OR	0.54	0.32	0.92	0.02	7.9	no	no	0.01	24.54
RA	Patient global assessment	4	185	180	365	MD	−0.41	−0.77	−0.05	0.03	51.4	NA	yes	NA	NA
RA	Pain	4	247	237	484	MD	−3.75	−7.8	0.3	0.07	88.2	no	yes	−51.35	48.35
RA	Withdrawals AE	4	297	289	586	OR	0.81	0.38	1.69	0.57	0	yes	no	0.16	4.1

Abbreviations: HCQ/CQ: Hydroxychloroquine/Chloroquine; RA: Rheumatoid arthritis; AE: Adverse Events; GI: Gastrointestinal.

full text screening. As reported in the PRISMA flow-chart (Figure 1), we identified six MAs as eligible: Suarez-Almazor et al., 2000; Kaplan et al., 2016; Guillotin et al., 2018; Liu et al., 2018; Rempenault et al., 2018; and Singh et al., 2020.

Meta-analyses of observational studies

As shown in Table 1, the MAs of the observational studies included 17 outcomes. Two outcomes included HCQ/CQ, whilst the other 15 included only HCQ. Most (16/17) of the outcomes included patients with autoimmune diseases, including during pregnancy (n = 10 outcomes). As a consequence, obstetrical outcomes were the most frequently included. One other outcome was mortality in people with COVID-19. The median number of studies included was five (range: 2–10), the median number of events was 93 (range: 4–273), and the median sample size was 2311 (range: 252−16,885).

Only four outcomes reported a high heterogeneity, with an I^2 of 50–75%. The small-study effect was present in 2/17 of the outcomes included, whilst no outcome presented excess significance bias. Four of the 17 outcomes presented the largest studies in terms of a statistically significant number of participants ($p < 0.05$). None of the outcomes included had 95% PI, excluding the null.

Using the criteria mentioned before, 7/17 outcomes reported a statistically significant effect size ($p < 0.05$) and were all rated as weak. One outcome reported a higher risk of death in people with COVID-19. Three outcomes reported a lower incidence of cardiovascular disease (CVD) in patients with autoimmune diseases, one outcome showed a lower incidence of type 2 diabetes in patients with rheumatoid arthritis, and two outcomes revealed a higher rate of spontaneous abortion in women with autoimmune rheumatologic conditions.

Meta-analyses of randomized controlled trials versus placebo

Eight outcomes were explored by the RCTs with a placebo as the control group. No outcome presented active medications as the control group.

Table 2 reports descriptive findings regarding the MAs of the RCTs. Only one condition was included, rheumatoid arthritis (n = 8).

Four RCTs were included with a median number of participants of 528 (in median, 269 randomized to HCQ/CQ and 259 to placebo). The largest study was statistically significant in 4/8 outcomes and one outcome included a 95% PI (lower number of swollen joints). Overall, 6/8 outcomes were statistically significant and consequently rated using the GRADE.

As shown in Table 3 we found that the use of HCQ/CQ compared to placebo was associated with an improvement of the measure of articular inflammation, i.e. a lower number of swollen joints (n = 4 RCTs; MD -3.71; 95% CI: -4.86 to -2.57) with a high certainty of evidence. HCQ/CQ was also associated, when compared to placebo, to a lower incidence of withdrawals and dropouts (0.58; 95% CI: 0.40−0.86), and also to lower withdrawals and dropouts due to lack of efficacy (OR 0.54; 95% CI: 0.32-0.92). A moderate certainty of evidence was present for improvement in the clinician's global assessment of the disease and of subjective measures of inflammation, the number of painful joints (namely, tender joints). A low grade of evidence was found for improvement in the patient's global assessment of the disease.

Risk of bias

The assessment of the risk of bias in the MAs included is reported in Supplementary Table 1. Four MAs were rated as critically low, with two rated low. The main reasons for these ratings were the absence of a list of excluded studies (item 7), poor information regarding the source of funding in the studies included (item 10), and the lack of assessment of publication bias (item 15).

Discussion

In this umbrella review, we report the current research regarding HCQ/CQ in humans, including its efficacy and tolerability in rheumatologic disorders, its safety during pregnancy, and its impact on viral diseases. Overall, our findings suggest that these medications are useful in the treatment of rheumatologic conditions, and their use is associated with adverse events when administered for viral diseases. We believe that our findings are important for the current COVID-19 pandemic.

HCQ/CQ in rheumatology

The efficacy of HCQ/CQ in rheumatoid arthritis has been confirmed and supported by our study showing an improvement in the number of swollen and tender joints, and in the clinician's global assessment of the disease. As an additional effect, we found that HCQ/CQ is able to reduce the incidence of type 2 diabetes in patients with rheumatoid arthritis. This effect might be explained by a decrease in insulin clearance and degradation rate, and an increase in the secretion of C-peptide (Powrie et al., 1991; Emami et al., 1998). The role of HCQ/CQ should be considered while balancing efficacy and side-effects, even if this study suggests that

Table 3
Effect of hydroxychloroquine and/or chloroquine in rheumatoid arthritis.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CQ/HCQ	placebo	Relative (95% CI)	Absolute (95% CI)		
Swollen joints												
4	randomised trials	not serious	not serious	not serious	not serious	none	290	281	-	MD **3.71 lower** (4.86 lower to 2.57 lower)	⊕⊕⊕⊕ HIGH	
Physician global assessment												
2	randomised trials	not serious	not serious	not serious	serious [a]	none	185	180	-	MD **0.39 lower** (0.56 lower to 0.21 lower)	⊕⊕⊕ MODERATE	
Tender joints												
4	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected [b]	290	281	-	MD **2.66 lower** (4.19 lower to 1.13 lower)	⊕⊕⊕ MODERATE	
Patient global assessment												
Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CQ/HCQ	placebo	Relative (95% CI)	Absolute (95% CI)		
4	randomised trials	not serious	serious [c]	not serious	serious [a]	none	185	180	-	MD **0.41 lower** (0.77 lower to 0.05 lower)	⊕⊕ LOW	
Withdrawals and dropouts												
4	randomised trials	not serious	not serious	not serious	not serious	none	63/299 (21.1%)	90/292 (30.8%)	**OR 0.58** (0.40 to 0.86)	**103 fewer per 1.000** (from 157 fewer to 31 fewer)	⊕⊕⊕⊕ HIGH	
Withdrawals and dropouts lack of efficacy												
4	randomised trials	not serious	not serious	not serious	not serious	none	32/235 (13.6%)	58/232 (25.0%)	**OR 0.54** (0.32 to 0.92)	**97 fewer per 1.000** (from 154 fewer to 15 fewer)	⊕⊕⊕⊕ HIGH	

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. Sample size < 400 participants

b. Egger's test (p-value) <0.05

c. I^2 between 50 and 74%

people randomized to HCQ/CQ were less at risk to being lost at follow-up compared to placebo, implying that HCQ/CQ is a generally well tolerated treatment even in the long term. In general, considering their use in rheumatic diseases, we confirmed the efficacy of HCQ/CQ in reducing CVD risk, probably due to the immunomodulatory and anti-thrombotic effect of these drugs (Petri, 2011). Different mechanisms of action are deemed to be responsible for these effects, namely the reduction of platelet aggregation (Kinlough-Rathbone, 1975), the increase in blood fluidity (Ernst et al., 1984), and the inhibition of prothrombotic mechanism mediated by antiphospholipid antibodies (Espinola et al., 2002). The anti-inflammatory action of HCQ/CQ is developed through the reduction of factors such as IL-6 and TNF-α (Wallace, 1994) and a reduction of dyslipidemia and atherosclerosis was demonstrated in an animal model (Shi et al., 2019). These might explain the impact on the cardiovascular system and arguably represent the reason why its role in COVID-19 was considered initially, since many of the mechanisms involved are shared with SARS-CoV-2 infection (Yang et al., 2020).

HCQ/CQ in pregnancy

HCQ/CQ seem to be safe in pregnancy, as also confirmed by our findings, even if our work found an increase of spontaneous abortion in women taking HCQ/CQ. An increase in the risk of premature delivery and intrauterine growth restriction has been

seen, however, these associations are not significant. The increase of spontaneous abortion is more likely to be attributed to the underlying autoimmune diseases rather than drug consumption (Bundhun et al., 2017). In rheumatic diseases HCQ is commonly used during pregnancy (Birru Talabi and Clowse, 2020). HCQ is recommended in systemic lupus erythematosus pregnancies to control disease flares and reduce the risk of poor obstetrical outcomes, however, more data are needed to support the use of HCQ during pregnancy in patients with antiphospholipid syndrome (Andreoli et al., 2017).

HCQ/CQ in COVID-19

In this paper we highlight the absence of any evidence supporting the broad use of HCQ/CQ to treat viral diseases, while suggesting a higher risk of death when used for treating COVID-19 (Singh et al., 2020). Recently HCQ/CQ was used, alone or in combination with azithromycin, for treating COVID-19 in both hospitals and primary care settings, based on the promising results it had *in vitro* (Yao et al., 2020). However, to date, there is no evidence of efficacy, since the only outcome that could be considered as a proxy (the reduction of viral load) was not statistically significant. As shown in a recent systematic review, the findings regarding COVID-19 are sparse overall and the few intervention studies available are of poor quality (Cortegiani et al., 2020).

A recent large observational study (Geleris et al., 2020) on 1776 hospitalized consecutive patients, shows that HCQ administration neither increases nor decreases the risk of intubation or death in COVID-19.

The administration of HCQ/CQ should be carefully evaluated, as it is known to have several side effects, the most worrisome being cardiovascular (torsade de pointes consequent to QT_c prolongation) and ocular (bulls-eye retinopathy) (Ben-Zvi et al., 2012). Proper dosing of maximum 5 mg/kg/die and regular screening according to risk factors are considered necessary for minimizing the risk of adverse reactions (Kim et al., 2017). The extensive use of HCQ, especially in combination with azithromycin, may increase the risk of QT_c prolongation and eventually torsade de pointes (TdP) and death (Javelot et al., 2020). Many experts consider monitoring the QT_c interval as mandatory due to HCQ's well-known arrhythmogenic cardiotoxicity (Haeusler et al., 2018), and monitoring electrolytes, particularly in those already on treatment with beta-blockers or calcium channel blockers (Page et al., 2016), since hypokalaemia, frequently described in COVID-19, predisposes to patients to cardiac conduction disorders (Xu et al., 2020). However, only a few clinical studies have analyzed the cardiovascular effects of HCQ/CQ (Hancox et al., 2013). In a large cohort of COVID-19 patients treated with HCQ/CQ, with or without azithromycin, no instances of TdP or arrhythmogenic death were reported and although the use of these medications resulted in QT_c prolongation clinicians seldom needed to discontinue therapy (Saleh et al., 2020).

There is a need for high quality RCT studies to define more precisely the role of HCQ/CQ during the COVID-19 pandemic. Considering the side-effects that HCQ/CQ may be responsible for, and the lack of evidence for success in improving the prognosis of COVID-19 patients, it may be considered as inappropriate to include HCQ/CQ in the current guidelines or protocols for treatment of COVID-19.

Limitations

The use of pre-established tools for quality assessment of evidence in both interventional and observational studies, which rely on the data reported in the included MAs, can create cumulative bias and shortcomings. We used an I^2 <50% as one of the criteria for class I evidence (convincing) in order to assign the best-evidence grade only to robust associations without hints of bias. However, I^2 estimates can also carry substantial uncertainty and clinical heterogeneity may be substantial even in the absence of statistical heterogeneity. It is known that MAs have considerable limitations (Ioannidis, 2016) and their results depend on the choice of the estimate from each primary study and its representation in the MA (e.g., in the included MA clarity about duration of the studies and the dosage of HCQ/CQ were missing). Applying the criteria suggested by the AMSTAR 2 for evaluating the quality of MAs, we observed the presence of low/critically low ratings, highlighting several potential biases. This evidence is mainly driven by missing information in item 2 (protocol published before the MA), 7 (list of excluded studies), or 15 (publication bias quantitative synthesis was not performed).

Conclusions

In conclusion, in this umbrella review including six meta-analyses and 25 outcomes, we confirmed that HCQ/CQ has an important role in rheumatoid arthritis, reducing joint pain and swelling and lowering the incidence of type 2 diabetes. When used for autoimmune diseases it lowers CVD risk. We also found that HCQ/CQ is associated with an increase of spontaneous abortion, though this may be due to the underlying autoimmune disease more than the pharmacological therapy (Bundhun et al., 2017). When used for treating COVID-19, HCQ/CQ seems to be associated with a higher risk of death. These aspects should be taken into consideration before widespread utilization of HCQ, even when pre-clinical results suggest its usefulness, as a therapy for new, and still unknown, viral diseases.

The results of our study highlight the lack of evidence and the presence of side effects associated with the use of HCQ/CQ for viral diseases, including COVID-19, indicating the urgent need for RCTs to determine their eventual appropriateness as a therapy for COVID-19.

Conflicts of interest

All authors have no conflicts of interest.

Funding

None.

Ethics

Not required.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2020.12.018.

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