Is hydroxychloroquine safety for COVID-19? a systematic review and meta-analysis of randomized trials

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Abstract

Aim: Many concerns still existed about the safety of hydroxychloroquine (HCQ) in the treatment of Corona Virus Disease 2019 (COVID-19). The purpose of this study was to evaluate the safety of HCQ by performing a systematic review and meta-analysis. Methods: Randomized controlled trials reporting the safety of HCQ in PubMed, Embase, and Cochrane Library were retrieved from the establishment of the database to February 27, 2020. Literature screening, data extraction, and assessment of risk bias were performed independently by two reviewers. Results: We identified 34 eligible studies that involved 3,639 patients. The difference in the cumulative number of AEs between the HCQ and control group was statistically significant (P<0.0001). The pooled incidence of gastrointestinal AEs, which occurred most frequently in the HCQ group was higher than that in the control group (P<0.0001) according to the system organ class. In addition, the risks of skin and subcutaneous tissue AEs (P = 0.011), renal and urinary disorders (P=0.011), ear and labyrinth AEs (P = 0.045) and surgical and medical procedures AEs (P = 0.020) in HCQ group are also significantly increased compared with the control group. Meanwhile, the cumulative number of SAEs was similar between the two groups (P=0.222). Meta-analysis results indicated that the pooled incidences of all the AEs reported by two or more studies were similar except for the treatment discontinuation caused by AEs (RD 0.02, 95% CI: 0.00 to 0.06). Conclusion: HCQ was well tolerated and might be safe for clinical application under the outbreak of COVID-19.

1 INTRODUCTION

Although the war against COVID-19 in China has ushered in the dawn, the worldwide epidemic became more widely over the world. Chloroquine, which is widely used against malaria and autoimmunity diseases, has been reported as a potential broad-spectrum antiviral drug in previous articles. A recent study demonstrated that chloroquine was effective against COVID-19 in vitro[1], and then it was incorporated into antiviral treatment options in the sixth[2] and seventh trial editions of COVID-19 protocol of China against COVID-19[3], with the emergence of a series of clinical trials on chloroquine or HCQ treatment of COVID-19[4,5]. Despite the positive efficacy of chloroquine in the treatment of COVID-19, it also raised concerns about the safety of chloroquine. As a derivative of chloroquine, HCQ has a similar antiviral mechanism with chloroquine, but it is well tolerated[6-9]. The adverse reactions (ADRs) of HCQ involve various systemic organs, among which irreversible retinopathy is the most concerned. Previous studies indicated that the overall prevalence rate of patients receiving HCQ for more than 5 years is 7.5%, which can rise to almost 20% after 20 years[10]. Other frequently reported SAEs were mainly focused on cardiotoxicities such as cardiomyopathy[11-14], and cutaneous toxicity such as acute generalized exanthematous pustulosis[15-17], pigmentation[18-20] and toxic epidermal necrolysis[21,22].

Preliminary results from a small, single-center clinical trial conducted by the People's Hospital of Wuhan University revealed good short-term efficacy for 20 patients treated with HCQ [23]. The experts consensus of

the comprehensive treatment of coronavirus diseases in Shanghai ("Shanghai protocol") agreed that HCQ would also be one of the main antiviral treatment[4]. According to the Shanghai epidemic prevention and control press conference on March 19, 2020, HCQ ranks as the first therapeutic drug in the "Shanghai protocol". The recent clinical trial performed in Shanghai Public Health Clinical Center enrolling 184 patients suggested that HCQ is effective and safe in the treatment of COVID-19[24,25]. The purpose of this study was to investigate the incidence of AEs of HCQ in randomized controlled trials, and then to provide evidence for the safety of COVID-19 therapy.

2 METHODS

We conducted the study following the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines[26]. The study protocol was registered in PROSPERO (CRD42020176407).

2.1 Search strategies

Randomized controlled studies published in English were searched systematically in PubMed, Embase and Cochrane Library up to February 27, 2020. The Medical Subject Headings "HCQ," "Drug-Related Side Effects and Adverse Reactions," "Adverse event," "Adverse drug reaction," and free text word such as "HCQ," "Adverse drug effect," "Adverse event," "Adverse drug reaction," "random," "randomization," "randomized," "randomly" were combined with the Boolean operator "AND" and "OR". See Tables S1-3 for detailed retrieval strategies. Additionally, references cited in the articles were checked for and found to be available.

2.2 Study selections

We had access to all publications which evaluated the safety of HCQ, included randomized controlled studies that were enrolled adult patients and published in English. We excluded studies whose full text was unavailable, as well as studies that not published as randomized controlled studies, studied in children, not reported the safety outcomes, and focused on other irrelevant topics. The primary outcome was the incidence of AEs, which was defined as any undesirable experience associated with the use of a medical product in a patient[27]. The secondary outcome was the incidence of SAEs that defined as death, life-threatening, hospitalization (initial or prolonged), disability or permanent damage, or congenital anomaly/birth defect, or required intervention to prevent permanent impairment or damage (devices)[27]. The literature selection was performed independently by two researchers (C.C and KM. P), and any disagreements were resolved through negotiation or seeking the help of another reviewer.

2.3 Data abstraction

Two researchers (C.C and KM. P) extracted the data of the eligible studies independently, including the author, year of publication, country, region, study type, study population, age, HCQ dosage, follow-up time, the occurrence of AEs and SAEs The extracted AEs were classified according to the Medical dictionary for regulatory activities (MedDRA)[28], and cross-checked by the two researchers (C.C and KM. P). If inconsistencies could not reach a consensus, another reviewer would participate in making a decision. For studies that covered two intervention groups, we will integrate the two intervention groups into one to analyzed[29].

2.4 Risk of bias assessment

The risks of bias of the eligible studies were assessed using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials[30], which including the following 7 domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and anything else.

2.5 Statistical analysis

We categorized AEs by frequencies according to Council for International Organization of Medical Science (CIOMS) as follows: common AEs (risk per 100 participants [?]1/100 and <1/10), uncommon AEs (risk per 100 participants [?]1/1000 and <1/100)[31]. The pooled incidence of AEs or SAEs was calculated in HCQ

and control group, respectively, and the Chi-square test or Fisher's exact test in SPSS software (version 23.0) was used to evaluate the difference in the pooled incidence of AEs or SAEs between the HCQ and the control group.

For AEs reported in two or more studies, we performed meta-analysis using the Review Manager 5.3.5 software[32], and the Risk Difference (RD) and 95% Confidence Interval (CI) in the pooled incidence of AEs between HCQ and control group was calculated. We used the $\chi 2$ test for the exploration of heterogeneity, and the P-value <0.05 was considered significant. Besides, I^2 statistics was used to quantify heterogeneity, and the random-effect model was used for quantitative synthesis, otherwise, the fixed-effect model was used. If there was significant clinical heterogeneity across studies, descriptive analysis was used to present the results. Furthermore, Funnel plots were used to assess the risk of publication bias for outcomes reported by nine or more studies. A P value of less than 0.05 was considered significant. Subgroup analysis was performed for common AEs based on whether the daily doses of HCQ were greater than 400mg. We considered the daily doses greater than 400mg as high dosage group, and less than 400mg as standard dosage group.

3 RESULTS

A total of 885 articles were identified, of which 58 studies were potentially eligible, and 34 randomized studies[33-68]published in English between 1976 and 2020 were finally included after title/abstract and full-text screening process, the PRISMA 2009 flow diagram in literature screening referred to **Fig 1.** Studies excluded in the full-text screening process were listed in Table S4 in the Supplementary Material.

The 34 randomized controlled trials included subjects from 13 countries with a mean or median age of 33 to 71 years. Nine studies were performed in patients with rheumatoid arthritis[33,35,37,40,52,57,58,62,65,67], three with osteoarthritis[43,46,47], three with lupus erythematosus[45,54,64], two with acquired immune deficiency syndrome[51,53], two with pancreatic cancer[44,55], two with diabetes mellitus[44,55] and each one with COVID-19[68], chronic-phase chronic myeloid leukaemia[37], proteinuria in IgA nephropathy[48], acute brucellosis[48,49], refractory chronic spontaneous urticaria[34], anti-phospholipid antibody positive[36], dyslipidemia[50], primary sjögren syndrome[39], asthma[63], Alzheimer's disease[61], schizophrenia[60], chronic hepatitis-C[57] and fractures of the hip, pelvis, or thoracolumbar spine[41], respectively. HCQ in two of the eligible studies[36,41] were used for thrombosis prophylaxis, and the remaining were for therapeutic use. Twenty-seven studies of the eligibility were placebo-controlled, while seven studies[36,42,44,49,68] reported that no placebo was given to the control group. The daily dosages of HCQ used in five studies[42,44,45,53,55] were exceeded 400 mg, and the maximum dosage, which used in patients with pancreatic cancer, was 1200mg one day[44]. The follow-up times were ranged from 6 days to 40 months across studies, and most studies were followed up less than 6 months[33-35,39-41,43-54,57,58,60,63-66]. The basic characteristics of the included studies are presented in Table 1.

Risks of bias assessment of all eligible studies are presented in**Fig 2, 3** , most of the studies are considered to be at low or moderate risk of bias in the important domains as measured by the Cochrane Collaboration's tool for assessing risk of bias in randomized trials. The reason for the increased risk of bias is mainly that the researchers or those who evaluated the outcomes were not blinded.

3.1 The incidence of AEs

Among 3,639 patients enrolled in the 34 studies, 1,878 patients received HCQ and 1,761 received placebo or not. 933 AEs were reported in HCQ group, while 651 in the control group. The cumulative number of AEs in the two groups was significantly different ($P<0.0001$). When all the AEs were categorized by the system organ class in MedDRA, the gastrointestinal disorders were reported most frequently, of which 290 AEs reported in HCQ group and 199 in control group, and there was a significant difference between the two groups ($P<0.0001$). In addition, the incidences of skin and subcutaneous tissues disorders ($P = 0.011$), ear and ear labyrinthine disorders ($P = 0.045$), renal and urinary disorders ($P=0.011$), as well as surgical and medical procedures ($P = 0.020$) in the HCQ group were significantly higher than that in the control group. We presented the pooled incidences of AEs of each system organ in Table 2. Moreover, the cumulative number of common AEs in the HCQ group (381/1878) was significantly increased compared with that in the control group (268/1761) ($P<0.0001$), among which the pooled incidence of rash was increased obviously

(P=0.037). The pooled incidences of common AEs and all AEs referred to Table 3 and Table S5, respectively. The cumulative number of the treatment discontinuation caused by AEs in HCQ group was greatly raised compared with the control group (P= 0.016).

3.2 The incidence of SAEs

Twenty-four of the 34 included studies[34,35,37,39,41,42,44,46-48,50-54], which contributing to 2,760 patients, reported the incidence of SAEs as an outcome. 1,428 patients in the HCQ group reported 162 SAEs, while 1,332 patients in the control group reported 132 SAEs. The cumulative number of SAEs in the HCQ group was not significantly greater than that in the control group (P=0.222).When all the SAEs were categorized by the system organ class in MedDRA, the pooled incidence of SAEs in all system organs (P>0.05) between the two groups except for gastrointestinal tract (P=0.005). The pooled incidences of SAEs in each system organ were presented in**Table 4** . Of the 2,760 patients, 138 specified SAEs in the HCQ group and 84 in the control group were reported. In HCQ group, the SAE occurred most frequently was neutropenia, but it was not significantly different from the control groups (P = 0.577). Moreover, the patients in HCQ group had low risk of anemia (P = 0.026) and high risk of fatigue (P = 0.045). We listed the pooled incidence of all specified SAEs in**Table 5** .

3.3 Meta-analysis results

The results of the meta-analysis indicated that the pooled incidence of treatment discontinuation caused by AEs (RD 0.02, 95% CI: 0.00 to 0.06, 23 studies) were significantly different between HCQ and control group using the fixed-effect model. However, the pooled incidences of other AEs in HCQ group were similar to that in control group. The meta-analysis results of each AE were listed in **Table 6** .

We performed a descriptive analysis for the 5 studies[42,44,45,53,55] in high dosage groups. Two studies[44,55] conducted in pancreatic cancer receiving gemcitabine and nab-paclitaxel plus HCQ or not, and the dosage of HCQ was 600mg twice a day. One[44] of two studies concluded that the chemotherapy regimen plus HCQ significantly increased neutropenia (P = 0.03) compared with the chemotherapy regimen without HCQ, however, the other one[55] did not find any difference in the incidence of AEs or SAEs between the two groups. In the remaining three studies[42,45,53], the eligible patients were given a daily dose of 800mg of HCQ, and the incidences of AEs were not significantly increased in two[45,53] of the studies, while the incidence of diarrhea was significantly higher in one study[42]than in the control group.

The funnel plot of the AEs reported by nine or more studies had no obvious asymmetry, indicating that there was no significant publication bias (see figure S1-4).

4 DISCUSSION

This review found that the cumulative number of all AEs in HCQ group was markedly greater than that of the control group. According to the system organ class, the difference in the pooled incidence of gastrointestinal AEs that occurred most frequently in HCQ group, was significant between the two groups. In addition, the pooled incidence of skin and subcutaneous tissue AEs, ear and labyrinthine AEs, and renal and urinary AEs of HCQ group are also significantly higher than that of control group. Furthermore, the cumulative number of the common AEs of HCQ group was also significantly increased compared with that of the control group, among which the pooled incidence of rash was raised up obviously. Compared with the control group, the cumulative number of SAEs in the HCQ group did not reach a significant increase, but the pooled incidence of SAEs in the gastrointestinal tract was significantly different between the two groups. Moreover, the patients in HCQ group had a high risk of fatigue. The meta-analysis suggested that the pooled incidence of treatment discontinuation caused by AEs in the HCQ group was significantly higher than that in the control group.

HCQ or chloroquine, which are currently widely medicated for rheumatoid arthritis, systemic lupus erythematosus and other rheumatic diseases, has been proved to be a potential broad-spectrum antiviral agent[69,70]. Previous studies revealed that HCQ or chloroquine could inhibit retroviruses[51,53,71], dengue virus[72], hand-foot-mouth virus[73], avian influenza A (H5N1) virus[74] and coronavirus[75-77].

The antiviral mechanisms of HCQ or chloroquine include inhibiting multiple processes such as virus invasion, transport, and replication by increasing the pH value of vesicle organelles such as intracellular bodies, as well as inhibiting the production and release of tumor necrosis factor and interleukin-6 that mediate the inflammatory complications of various viral diseases[70]. For SARS, it seems to interfere with the glycosylated terminal of the cell receptor angiotensin-converting enzyme-2, thereby negatively affecting the virus-receptor binding, leading to the failure of infection, and finally influencing the infection and transmission of SARS coronavirus within a certain concentration range[78].

Although a series of studies and case reports[79-86]found that HCQ could increase the risk of retinopathy, this review demonstrated that the pooled incidence of eye AEs in HCQ group was not significantly increased in comparison with the control group and only one specified proliferative retinopathy was reported in eligible studies. The reason might be explained by the follow-up times of randomized studies that included in this review were not abundant enough. one retrospective study found that the potential risk factors for HCQ retinopathy were high dose and long-term (>5 years) treatment by multivariate regression [87]. However, most follow-up times of the included studies were within 12 months, and the longest one was about 40 months. *Fin* bloom et al.[9] assessed the frequency of retinal toxicity in patients receiving either chloroquine or HCQ, and the overall frequency of retinopathy was 6% (7/110). Compared with the chloroquine group, the risk of the retinopathy in HCQ group was lower (6/31 vs. 0/66).

This study found that the most common AEs and SAEs significantly increased in the HCQ group were gastrointestinal events such as diarrhea, nausea, and vomiting, and a retrospective cohort study showed the incidence of skin and subcutaneous tissue disorders in patients with cutaneous lupus and dermatomyositis was the highest[88]. In this review, the patients receiving HCQ also had a high incidence of skin and subcutaneous tissues AEs, which was significantly different from the patients in the control group. The common skin and subcutaneous tissues AE with a relatively increased risk was rash, and other AEs such pigmentation and itching were also reported frequently. There were two SAEs reported in HCQ group, one was erythema multiforme and the other one was acute generalized erythematous pustulosis, while none reported in control group. The difference in pooled incidence was not significant between the two groups. Previous studies revealed that skin ADRs generally occurred 5˜14 days after the beginning of HCQ, and the rash is characterized by lichen-like, urticaria or rash. Additionally, the symptoms are generally mild, which could be relieved after the withdrawal[89,90]. Skin and subcutaneous tissue SAEs of HCQ that were frequently reported in the literature were acute generalized exanthematous pustulosis (AGEP)[15-17,91-94], pigmentation[18,20,95-101], Stevens-Johnson syndrome[22,102], and toxic epidermal necrolysis[21,103,104]. One multinational case-control study suggested that HCQ or chloroquine was highly associated with AGEP[105]. Besides, the risk factors identified in previous studies of HCQ-induced pigmentation were previous treatment with oral anticoagulants and/or antiplatelet agents and with higher blood HCQ concentration[100,101]. In addition, we found that the patients in the HCQ group suffered from more ear and labyrinth AEs than in the control group, and the ADR reported more than once was tinnitus. There was no ear and labyrinth SAE reported in all patients enrolled. A case of hearing loss caused by HCQ in HIV-infected patients was reported in a previous publication, however, the hearing was restored two months after the withdrawal[106]. Moreover, patients who received HCQ had increased incidences of renal and urinary AEs compared with the patients without HCQ, and the frequently reported AE was proteinuria. Meanwhile, the meta-analysis results suggested that the difference in the pooled incidence of proteinuria between the two groups was not significant. One SAE that reported in renal and urinary system was acute kidney injury.

A number of recent studies have reported the related cardiotoxicity of HCQ[11-14,107-114], especially the cardiomyopathy[12-14,107,110,111,113,114]. The cardiac SAEs of HCQ reported in eligible studies were arrhythmias and heart failure. A systematic review about chloroquine or HCQ cardiac toxicity indicated that the incidence of cardiac AEs is rare, but generally more severe and may be irreversible. The AEs induced by HCQ included cardiomyopathy, atrioventricular block, valve dysfunction, acute myocardial infarction, heart failure, and abnormal left ventricular ejection fraction, and among them, the incidence of cardiomyopathy was higher than chloroquine[115]. However, the study also pointed out that the evidence of cardiotoxicity caused by HCQ was mainly from retrospective studies, and further pharmacovigilance was needed.

For SAEs, although the pooled incidence of neutropenia and neutrophils count decreased were higher in HCQ group, the differences did not reach a statistically significant between the two groups. The publications of Karasic et al.[44] and Zeh et al.[55]contributed to the increased neutropenia and neutrophils count decreased, for all the patients with pancreatic cancer enrolled in were treated with gemcitabine and nab-paclitaxel. Bone marrow suppression is a common ADR to nab-paclitaxel and gemcitabine[116,117]. In this review, the incidence of discontinuation caused by AEs in HCQ group was about 6%, which was significantly higher than that of the control group.

The descriptive analysis suggested that the incidence of neutropenia and diarrhea significantly increased in patients that received HCQ with a daily dose of 800˜1200 mg. The finding of the PLUS study[118] conducted in France indicated that the AEs rates of patients receiving HCQ once daily for 200mg, 400mg, 600mg, and 800mg were 38.9%, 15.5%, 25%, and 27.4%, respectively, and no differences were identified between groups in terms of nausea, vomiting, diarrhea or blurred vision. Moreover, patients who received high HCQ doses for 7 months, including patients with a dose of 800 mg/day, had no significant AEs. Another dose-dependent study enrolled 212 rheumatoid arthritis in a 6-week, double-blind study [38] comparing treatment with HCQ at 400 mg/day, 800 mg/day, and 1,200 mg/day, and the results revealed that gastrointestinal AEs of HCQ were dose-related, while ocular AEs were dose-independent. Besides, another study[119] also proved that there is an association between gastrointestinal AEs and elevated blood HCQ concentrations.

In vitro, based on the PB/PK models, Yao et al. [120]found that a loading dose of 400 mg twice a day of HCQ sulfate given orally, followed by a maintenance dose of 200 mg given twice a day for 4 days reached three times the potency of chloroquine phosphate when given 500 mg twice a day 5 days in advance. Furthermore, in a non-randomized study conducted by Didier Raoulta et al.,[121] 36 patients who infected with COVID-19 were given HCQ 200mg three times daily for 10 days, and the results demonstrated that 70% of HCQ-treated patients were virologically cured comparing with 12.5% in the control group at day 6 post-inclusion ($P<0.001$). Of all the studies included in this review, only one study[68] used HCQ for COVID-19 patients, and the founding revealed that only two mild AEs occurred in patients with a daily dose of 400mg. The dosage of HCQ in the "Shanghai protocol" for the treatment of COVID-19 infection was 400mg daily for 5 days, and the preliminary study on 30 patients with common COVID-19 infection indicated that the HCQ group had no significant increase in the incidence of AEs compared with the control group ($P > 0.05$), and all ADRs disappeared after the withdrawal[25].

There several limitations to this study. Firstly, the quantitative subgroup analysis could not be conducted because of the limited number of AEs reported in a limited number of studies in the high-dose group, thus we could not demonstrate that whether the incidence of AEs or SAEs were significantly increased in high-dose group. Secondly, when we counted the number of AEs in each study, some studies reported the number of AEs, but not the number of patients with AEs. Since different types of AEs might occur simultaneously in a single patient, as a result, the pooled incidence may be overestimated. Thirdly, the unspecified AEs or SAEs in some studies were not accounted for the total number of certain AEs or SAEs, leading to an underestimation of the pooled incidence. Finally, we merely enrolled randomized studies representing the exclusion of patients at high risk of harm[122], the lack of enough time to determine long-term harm and small sample size to detect unusual events[123]. In the forward work, we will supplement the data on the safety of HCQ by incorporating observational studies.

5 CONCLUSION

The short time use of HCQ was well tolerated in other diseases and COVID-19, though there is not much evidence in the treatment of COVID-19. We considered that HCQ might be safe for clinical application under the outbreak of COVID-19. We will then conduct a pooled analysis of the AEs reported in the randomized and observational studies, in the hope of finding more safety information of HCQ in high dosage.

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COMPETING INTERESTS

The authors declare that they have no conflict of interest.

CONTRIBUTORS

Q.L. and X.L. proposed the study protocol and supervised the progress of the work. C.C. and K.P. worked on the literature search and study selection, data extraction, assessment of risk of bias, data synthesis, and manuscript writing. B.W. and Z.C. assisted in solving various professional problems encountered during the work and interpreting the results. X.L. and Q.X. double-checked the manuscript. All authors read and approved the final manuscript.

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Table 1 Basic characteristics of the eligible studies

Author	Year	Population Country	Population Sample size	Population Age (year)[d]	Population Indication	Intervention	Follow-up time
Horne	2020	UK	HCQ:32 C:30	HCQ:50.0 (38.5 to 60.5) C:49.5 (42.0 to 66.0)	Chronic-phase chronic myeloid leukaemia	HCQ: 400 mg bid or 400mg qm + 200mg qn or 200mg bid C: No HCQ treatment	24 months
Zeh	2020	US	HCQ: 52 C: 46	HCQ: 40.48 ± 11.40 C: 40.92 ± 9.83	Pancreatic cancer	HCQ: 600mg bid C: No HCQ treatment	39.7 months[b]
Liu	2019	China	HCQ:30 C:30	HCQ:37.6 ± 11.6 C:35.6 ± 9.6	Proteinuria in IgA nephropathy	HCQ: 0.2 g bid[c] C: Placebo	6 months
Karasic	2019	US	HCQ:55 C:57	65 (43 to 86)	Advanced pancreatic cancer	HCQ:600mg bid C: No HCQ treatment	11 to 12 months[a]
Majzoobi	2018	Iran	HCQ:89 C:88	HCQ:37.6 ± 11.6 C: 42.5 ± 16.4	Acute brucellosis	HCQ: Maximum dosage: 6.5 mg/kg/day C: No HCQ treatment	6 months
Lee	2018	Netherlands	HCQ:98 C:98	HCQ:57.7 ± 8.2 C: 58.3 ± 7.0	Hand osteoarthritis	HCQ: 400 mg qd C: Placebo	6 months

Author	Year	Population	Population	Population	Population	Intervention	Follow-up time
Kingsbury	2018	UK	HCQ:124 C:124	HCQ:62.8±9.1 C:62.5±9.2	Hand Osteoarthritis	HCQ: 200, 300 or 400 mg[e] (maximum 6.5 mg/kg/day) C: Placebo	6 months
Yokogawa	2017	Japan	HCQ:77 C:26	HCQ:43.1±12.8 C:41.6±12.7	Cutaneous lupus erythematosus	HCQ: 400 mg/day[e] C: Placebo	4 months
Boonpiyathad	2017	Thailand	HCQ:28 C:27	HCQ:33.0 ± 12.1 C:34.0 ± 11.9	Refractory chronic spontaneous urticaria	HCQ: 400 mg/day C: Placebo	3 months
Erkan	2016	US	HCQ:9 C:11	HCQ:48.9±9.6 C:44.7±10.4	Antiphospholipid antibody positive patients without systemic autoimmune disease	HCQ: 200mg qd or 200mg bid[e] C: No HCQ treatment	25 months
Helal	2016	Egypt	HCQ: 60 C: 60	HCQ: 40.48 ± 11.40 C: 40.92 ± 9.82	Genotype-4 chronic hepatitis-C	HCQ: 200mg bid C: Placebo	3 months
Pareek	2015	India	HCQ:161 C:167	HCQ:49.2±9.6 C:50.1±9.7	Dyslipidemia	HCQ: 200mg qd C: Placebo	6 months
Gottenberg	2014	France	HCQ:56 C:64	HCQ: 56.3±11.9 C: 55.6±13.9	Primary sjögren syndrome	HCQ: 400 mg/day C: Placebo	6 months
Jokar	2013	Iran	HCQ:23 C:21	HCQ: 48.3±11.1 C: 47.6±8.5	Knee Osteoarthritis	HCQ: 200mg bid C: Placebo	6 months
Paton	2012	UK	HCQ:42 C:41	HCQ: 37.1±7.7 C: 38.3±10.8	HIV-infected patients	HCQ: 400 mg/day C: Placebo	12 months

Author	Year	Population	Population	Population	Population	Intervention	Follow-up time
Das	2007	India	HCQ: 61 C: 61	HCQ: 40.3 ± 9.7 C: 40.0 ± 10.9	Rheumatoid arthritis	HCQ: 400mg/day C: Placebo	2 months
Desta	2002	Ethiopia	HCQ: 28 C: 33	HCQ:28.5±7.0 C: 31.2±7.9	Schizophrenia	HCQ: 200mg/day C: Placebo	2 months
Gerstein	2002	Canada	HCQ: 69 C: 66	HCQ:58±9.6 C: 57±10.1	Type 2 diabetes mellitus	HCQ: 6.5 mg/kg/day C: Placebo	18 months
Van Gool	2001	Netherlands	HCQ: 83 C: 85	HCQ:70.4±8.3 C: 70.7±8.5	Alzheimer's disease	HCQ: 400mg/day or 200mg/day[e] C: Placebo	18 months
Van Jaarsveld	2000	Netherlands	HCQ: 120 C: 67	HCQ:37.9 ± 4.0 C: 44.7 ± 5.2	Rheumatoid arthritis	HCQ: 400mg/day C: No HCQ treatment	59 weeks[b]
Charous	1998	US	HCQ: 8 C: 9	HCQ:37.9 ± 4.0 C: 44.7 ± 5.1	Asthma	HCQ: <6.5 mg/kg/day[e] C: Placebo	7.5 months
Kavanaugh	1997	US	HCQ 1: 6 HCQ 2: 6 C: 5	HCQ 1: 37.9 ± 4.0 HCQ 2: 37.9 ± 4.0 C: 44.7 ± 5.2	SLE	HCQ 1: 400mg/day HCQ 2: 800mg/day C: Placebo	1 months
Sperber	1995	US	HCQ: 20 C: 20	HCQ: 39.1± 6.6 C: 40.6±12.5	HIV Type 1	HCQ: 800mg/day C: Placebo	2 months
Esdaile	1995	Canada	HCQ: 59 C: 60	HCQ: 53±13.5 C: 53 ±14.8	Early rheuma-toid arthritis	HCQ: Maximum dosage 400mg/day C: Placebo	9 months
Blackburn	1995	US	HCQ: 124 C: 118	HCQ: 53.1±1.19 C:50.2±1.20	Rheumatoid arthritis	HCQ: 200mg bid C: Placebo	6 months

Author	Year	Population	Population	Population	Population	Intervention	Follow-up time
Williams	1994	US	HCQ: 40 C: 31	HCQ:41 mean C:43	SLE	HCQ :200 mg bid C: Placebo	12 months
Haar	1993	Denmark	HCQ: 25 C: 27	HCQ: 64.0(37 to 84) C: 58.3(31 to 86)	Rheumatoid arthritis	HCQ: 250mg qd C: Placebo	6 months
Clark	1993	Canada	HCQ: 65 C: 65	HCQ: 39 C: 36	Rheumatoid arthritis	HCQ: 400mg/day C: Placebo	6 months
Faarvang	1993	Denmark	HCQ: 31 C: 29	61 (18 to 82)	Rheumatoid arthritis	HCQ :250 mg/day C: Placebo	6 months
Quatraro	1990	Italy	HCQ: 22 C: 16	HCQ:57.4±4.4 C:57.6±4.7	Diabetes Mellitus	HCQ :200 mg tid C: Placebo	6 months
Scott	1989	UK	HCQ: 52 C: 49	HCQ: 52.7±3.0 C: 54.7±3.2	Rheumatoid arthritis	HCQ: 200mg bid for 6 months + 200mg qd C: Placebo	12 months
Bunch	1984	US	HCQ: 17 C: 21	HCQ:48.1±13.7 C:48.2±10.8	Rheumatoid arthritis	HCQ :2.2 mg/kg/day C: Placebo	24 months
Hansen	1976	Denmark	HCQ: 75 C: 78	HCQ: NA C: NA	Fractures of the hip, pelvis, or thora-columbar spine	HCQ :200 mg/day tid C: Placebo	3 weeks

HCQ: hydroxychloroquine; C: Control; HIV: Human Immunodeficiency Virus; SLE: Systemic lupus erythematosus; NA: Not available; qd once a day; bid twice a day; tid three times a day; qm once in morning; qn once in night.

a Median follow-up time b Mean follow-up time c adjusted by eGFRs : eGFR $>$ 60 mL/min/1.73 m2: 0.2 g bid, 45˜59 mL/min/1.73 m2: 0.1g tid, 30 ˜44 mL/min/1.73 m2: 0.1g bid d expressed as mean ± standard or median or mean (range) e Weight-adjusted

Table 2 Differences in the pooled incidence of AEs between the HCQ and control groups classified by system organ

System organ	HCQ group (n=1,878)	HCQ group (n=1,878)	Control group (n=1,761)	Control group (n=1,761)	P value	No. of studies
	No. of AEs	Incidence per 100 pts	No. of AEs	Incidence per 100 pts		
Gastrointestinal disorders	290	15.44	199	11.30	<0.0001*	18
General disorders and administration site conditions	87	4.63	67	3.80	0.215	13
Nervous system disorders	86	4.58	70	3.98	0.368	17
Skin and subcutaneous tissue disorders	83	4.42	50	2.84	0.011*	20
Blood and lymphatic system disorders	73	3.89	63	3.58	0.623	7
Infections and infestations	46	2.45	31	1.76	0.149	5
Investigations	36	1.92	36	2.04	0.783	6
Eye disorders	31	1.65	20	1.14	0.187	15
Metabolism and nutrition disorders	23	1.22	15	0.85	0.269	9
Psychiatric disorders	22	1.17	25	1.42	0.508	7
Musculoskeletal and connective tissue disorders	17	0.91	20	1.14	0.489	8
Renal and urinary disorders	16	0.85	4	0.23	0.011*	5
Ear and labyrinth disorders	9	0.48	2	0.11	0.045*	4
Immune system disorders	7	0.37	4	0.23	0.419	4
Cardiac disorders	6	0.32	3	0.17	0.509	6

System organ	HCQ group (n=1,878)	HCQ group (n=1,878)	Control group (n=1,761)	Control group (n=1,761)	P value	No. of studies
Vascular disorders	6	0.32	5	0.28	0.845	1
Respiratory, thoracic and mediastinal disorders	4	0.21	5	0.28	0.747	3
Hepatobiliary disorders	4	0.21	1	0.06	0.376	4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	0.11	0	0.00	0.500	2
Pregnancy, puerperium and perinatal conditions	1	0.05	0	0.00	1.000	1
Injury, poisoning and procedural complications	1	0.05	0	0.00	1.000	1
Surgical and medical procedures	107	5.70	71	4.03	0.02*	23
Others, unspecified	83	4.42	30	1.70	<0.0001*	7

pts: patients

*P value < 0.05 and difference was statistically significant.

Table 3 Differences in the pooled incidence of the common AEs between the HCQ and control groups

AEs	HCQ group (n=1,878)	HCQ group (n=1,878)	Control group (n=1,761)	Contr
	No. of AEs	Incidence per 100 pts	No. of AEs	Incid
Nausea	78	4.15	61	3.46
Diarrhea	72	3.83	49	2.78
Fatigue	47	2.50	33	1.87
Headache	47	2.50	34	1.93
Rash	29	1.54	14	0.80
Dyspepsia	24	1.28	18	1.02
Respiratory tract infection	22	1.17	16	0.91

AEs	HCQ group (n=1,878)	HCQ group (n=1,878)	Control group (n=1,761)	Contr
Abdominal pain	21	1.12	19	1.08
Flu-like illness	21	1.12	14	0.80
Neuropathy	20	1.06	10	0.57

pts: patients

*P value < 0.05 and difference was statistically significant.

Table 4 Differences in the pooled incidence of SAEs between the HCQ and control groups classified by system organ

System organ	HCQ group (N=1,428)	HCQ group (N=1,428)	Control group (N=1,332)	Control group (N=1,332)	P value
	No. of SAEs	Incidence per 100 pts	No. of SAEs	Incidence per 100 pts	
Blood and lymphatic system disorders	32	2.24	37	2.78	0.367
Investigations	30	2.10	24	1.80	0.571
Gastrointestinal disorders	25	1.75	8	0.60	0.005*
General disorders and administration site conditions	17	1.19	14	1.05	0.728
Nervous system disorders	9	0.63	6	0.45	0.521
Metabolism and nutrition disorders	7	0.49	2	0.15	0.181
Vascular disorders	6	0.42	5	0.38	0.852
Skin and subcutaneous tissue disorders	5	0.35	4	0.30	1.000
Cardiac disorders	4	0.28	2	0.15	0.688
Musculoskeletal and connective tissue	4	0.28	0	0.00	0.126
Psychiatric disorders	4	0.28	6	0.45	0.669
Eye disorders	3	0.21	1	0.08	0.626
Respiratory, thoracic and mediastinal disorders	2	0.14	4	0.30	0.438

System organ	HCQ group (N=1,428)	HCQ group (N=1,428)	Control group (N=1,332)	Control group (N=1,332)	P value
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	0.14	0	0.00	0.500
Renal and urinary disorders	2	0.14	0	0.00	0.500
Hepatobiliary disorders	2	0.14	0	0.00	0.500
Immune system disorders	1	0.07	1	0.08	1.000
Injury, poisoning and procedural complications	1	0.07	1	0.08	1.000
Surgical and medical procedures	0	0.00	1	0.08	0.483
Infections and infestations	0	0.00	12	0.90	$< 0.0001^*$
Others, unspecified	6	0.42	4	0.30	0.836

pts: patients

*P value < 0.05 and difference was statistically significant.

Table 5 Differences in the pooled incidence of all specified SAEs between the HCQ and control groups

SAEs	HCQ group (N=1,428)	HCQ group (N=1,428)	Control group (N=1,332)	Control group (N=1,332)	P value
	No. of SAEs	Incidence per 100 pts	No. of SAEs	Incidence per 100 pts	
Neutropenia	23	1.61	18	1.35	0.574
Neutrophils count decreased	10	0.70	10	0.75	0.876
Fatigue	9	0.63	2	0.15	0.045^*
Nausea	7	0.49	1	0.08	0.071
Peripheral neuropathy	7	0.49	3	0.23	0.401
White blood cell count decreased	7	0.49	6	0.45	0.879

SAEs	HCQ group (N=1,428)	HCQ group (N=1,428)	Control group (N=1,332)	Control group (N=1,332)	P value
Anemia	5	0.35	14	1.05	0.026*
Death	5	0.35	2	0.15	0.455
Dehydration	5	0.35	1	0.08	0.220
Thrombocytopenia	4	0.28	5	0.38	0.746
Severe diarrhea	4	0.28	2	0.15	0.688
Alanine aminotransferase increased	4	0.28	1	0.08	0.376
Neuropsychiatric symptoms	4	0.28	6	0.45	0.669
Visual changes	3	0.21	0	0.00	0.251
Aspartate transferase increased	3	0.21	2	0.15	1.000
Lymphocyte count decreased	3	0.21	0	0.00	0.251
Hypertension	3	0.21	4	0.30	0.718
Cardiac rhythm disorder	3	0.21	0	0.00	0.251
Vomiting	2	0.14	1	0.08	1.000
Dyspnea	2	0.14	0	0.00	0.500
General muscle weakness	2	0.14	0	0.00	0.500
Hypotension	2	0.14	0	0.00	0.500
Platelet count Decreased	1	0.07	3	0.23	0.358
Diverticulosis-relayed gastrointestinal bleeding	1	0.07	0	0.00	1.000
Abdominal pain	1	0.07	0	0.00	1.000
Edema Limb	1	0.07	0	0.00	1.000
Lipothymia	1	0.07	0	0.00	1.000
Erythema multiforme	1	0.07	0	0.00	1.000
Acute generalized erythematous pustulosis	1	0.07	0	0.00	1.000
Bone pain	1	0.07	0	0.00	1.000
Pain in extremity	1	0.07	0	0.00	1.000

SAEs	HCQ group (N=1,428)	HCQ group (N=1,428)	Control group (N=1,332)	Control group (N=1,332)	P value
Breast cancer	1	0.07	0	0.00	1.000
Multiple myeloma	1	0.07	0	0.00	1.000
Urinary lithiasis	1	0.07	0	0.00	1.000
Acute kidney injury	1	0.07	0	0.00	1.000
Heart failure	1	0.07	0	0.00	1.000
Hypoalbuminemia	1	0.07	0	0.00	1.000
Severe hypoglycemia	1	0.07	0	0.00	1.000
Allergic reaction	1	0.07	1	0.08	1.000
Blood bilirubin Increased	1	0.07	1	0.08	1.000
Lipase increased	1	0.07	0	0.00	1.000
Cholelithiasis	1	0.07	0	0.00	1.000
Thromboembolic event	1	0.07	1	0.08	1.000

pts: patients

*P value < 0.05 and difference was statistically significant.

Table 6 Meta-analysis results of the incidence of AEs between HCQ and control group

AEs	No. of studies	No. of pts	Models	Meta-analysis results (RD, 95%CI)	*P* value
Gastrointestinal disorders	**Gastrointestinal disorders**	**Gastrointestinal disorders**	**Gastrointestinal disorders**	**Gastrointestinal disorders**	
Diarrhea	9	1051	Random	0.03 [-0.02, 0.08]	0.24
Nausea	11	1348	Fixed	0.02 [-0.01, 0.05]	0.16
Abdominal pain	8	790	Fixed	-0.00 [-0.03, 0.03]	0.79
Gastrointestinal bleeding	4	544	Fixed	0.01 [-0.01, 0.03]	0.30
Dyspepsia	4	476	Fixed	0.02 [-0.03, 0.07]	0.36
Constipation	3	700	Fixed	0.01 [-0.01, 0.03]	0.43
Vomiting	4	656	Fixed	0.00 [-0.03, 0.03]	0.89
Bloating	3	363	Fixed	0.03 [-0.01, 0.07]	0.12

AEs	No. of studies	No. of pts	Models	Meta-analysis results (RD, 95%CI)	*P* value
Stomatitis	2	429	Random	0.02 [-0.00, 0.06]	0.20
Skin and subcutaneous tissue disorders	**Skin and subcutaneous tissue disorders**	**Skin and subcutaneous tissue disorders**	**Skin and subcutaneous tissue disorders**	**Skin and subcutaneous tissue disorders**	
Rash	10	1176	Fixed	0.02 [-0.00, 0.04]	0.10
Dry skin/itching	7	486	Fixed	0.00 [-0.02, 0.03]	0.81
Skin pigmentation	3	245	Random	0.04 [-0.04, 0.12]	0.33
Alopecia	3	355	Fixed	0.00 [-0.03, 0.04]	0.84
Nervous system disorders	**Nervous system disorders**	**Nervous system disorders**	**Nervous system disorders**	**Nervous system disorders**	
Dizziness	9	1182	Fixed	0.00 [-0.01, 0.02]	0.80
Headache	11	1523	Random	0.02 [-0.01, 0.05]	0.24
Neuropathy	2	299	Random	0.09 [-0.29, 0.46]	0.65
Blood and lymphatic system disorders	**Blood and lymphatic system disorders**	**Blood and lymphatic system disorders**	**Blood and lymphatic system disorders**	**Blood and lymphatic system disorders**	
Anemia	5	579	Random	-0.01 [-0.06, 0.05]	0.81
Thrombocytopenia	4	571	Random	-0.00 [-0.07, 0.07]	0.96
Neutropenia	3	330	Random	0.05 [-0.14, 0.24]	0.64
General disorders and administration site conditions	**General disorders and administration site conditions**	**General disorders and administration site conditions**	**General disorders and administration site conditions**	**General disorders and administration site conditions**	
Fatigue	7	813	Fixed	0.03 [-0.00, 0.07	0.08
Chest pain	4	663	Fixed	-0.01 [-0.03, 0.00]	0.12
Asthenia	2	570	Fixed	0.00 [-0.01, 0.02]	0.71
Pyrexia	3	478	Fixed	0.02 [-0.00, 0.05]	0.11
Edema	3	527	Fixed	0.00 [-0.02, 0.02]	0.79

AEs	No. of studies	No. of pts	Models	Meta-analysis results (RD, 95%CI)	*P* value
Flu-like illness	2	203	Random	0.08 [-0.12, 0.28]	0.44
Respiratory, thoracic and mediastinal disorders	**Respiratory, thoracic and mediastinal disorders**	**Respiratory, thoracic and mediastinal disorders**	**Respiratory, thoracic and mediastinal disorders**		
Dyspnea	3	356	Fixed	0.02 [-0.01, 0.04]	0.22
Eye disorders	**Eye disorders**	**Eye disorders**	**Eye disorders**	**Eye disorders**	
Blurred vision	5	630	Fixed	-0.01 [-0.04, 0.02]	0.67
Visual impairment	4	700	Fixed	0.00 [-0.01, 0.02]	0.59
Ocular pain	3	309	Fixed	0.01 [-0.02, 0.04]	0.68
Retinopathy	4	422	Fixed	0.00 [-0.02, 0.03]	0.66
Psychiatric disorders	**Psychiatric disorders**	**Psychiatric disorders**	**Psychiatric disorders**	**Psychiatric disorders**	
Insomnia	4	575	Fixed	-0.01 [-0.05, 0.02]	0.53
Depression	3	399	Fixed	0.01 [-0.02, 0.05]	0.42
Neuropsychiatric symptoms	2	231	Random	0.03 [-0.13, 0.18]	0.71
Musculoskeletal and connective tissue disorders	**Musculoskeletal and connective tissue disorders**	**Musculoskeletal and connective tissue disorders**	**Musculoskeletal and connective tissue disorders**	**Musculoskeletal and connective tissue disorders**	
Musculoskeletal pain	3	607	Fixed	-0.01 [-0.03, 0.02]	0.54
Back pain	3	607	Random	0.00 [-0.03, 0.04]	0.86
Joint pain	2	524	Fixed	-0.00 [-0.03, 0.02]	0.77
Pain in extremity	2	426	Fixed	0.01 [-0.01, 0.03]	0.37
Ear and labyrinth disorders	**Ear and labyrinth disorders**	**Ear and labyrinth disorders**	**Ear and labyrinth disorders**	**Ear and labyrinth disorders**	
Tinnitus	2	372	Fixed	0.03 [-0.00, 0.06]	0.08
Cardiac disorders	**Cardiac disorders**	**Cardiac disorders**	**Cardiac disorders**	**Cardiac disorders**	

AEs	No. of studies	No. of pts	Models	Meta-analysis results (RD, 95%CI)	*P* value
Cardiac rhythm disorder	5	664	Fixed	0.01 [-0.01, 0.03]	0.36
Metabolism and nutrition disorders	**Metabolism and nutrition disorders**	**Metabolism and nutrition disorders**	**Metabolism and nutrition disorders**	**Metabolism and nutrition disorders**	
Anorexia	5	631	Fixed	0.02 [-0.00, 0.05]	0.28
Immune system disorders	**Immune system disorders**	**Immune system disorders**	**Immune system disorders**	**Immune system disorders**	
Allergic reaction	4	414	Fixed	0.01 [-0.02, 0.05]	0.47
Investigations	**Investigations**	**Investigations**	**Investigations**	**Investigations**	
eGFR reduction	3	575	Fixed	0.00 [-0.02, 0.02]	0.84
Hepatobiliary disorders	**Hepatobiliary disorders**	**Hepatobiliary disorders**	**Hepatobiliary disorders**	**Hepatobiliary disorders**	
Hepatitis	3	551	Fixed	0.00 [-0.01, 0.02]	0.68
Renal and urinary disorders	**Renal and urinary disorders**	**Renal and urinary disorders**	**Renal and urinary disorders**	**Renal and urinary disorders**	**Renal and urinary disorders**
Proteinuria	2	225	Fixed	0.06 [-0.01, 0.12]	0.10
Infections and infestations	**Infections and infestations**	**Infections and infestations**	**Infections and infestations**	**Infections and infestations**	**Infections and infestations**
Respiratory tract infection	3	479	Random	0.02 [-0.20, 0.25]	0.84
Surgical and medical procedures	**Surgical and medical procedures**	**Surgical and medical procedures**	**Surgical and medical procedures**	**Surgical and medical procedures**	
Treatment discontinuation caused by AEs	23	2505	Fixed	0.02 [0.00, 0.04]	0.02*

pts: patients

*P value < 0.05 and difference was statistically significant.

Figure legends

Figure 1 The PRISMA 2009 Flow Diagram in literature screening

Figure 2 Risk of bias graph of the included studies

A plot of the distribution of the judgements across studies for each risk of bias item.

Figure 3 Risk of bias summary of the included studies. Green means “low risk,” yellow means “unclear risk,” and red means “high risk.”

A summary table of the judgements for each risk of bias item for each study.