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In Search for the Truth about Hydroxychloroquine Prophylaxis of Covid-19

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Abstract

Introduction: COVID-19, caused by the coronavirus SARS-CoV-2 has quickly spread around the world. Currently there is an active search for vaccines and therapeutics, including repurposing of well-known drugs. COVID-19 continues to be a challenge with only a few therapeutic and no chemoprophylactic interventions to combat the virus.

Methods: We aimed to review available data for the application of hydroxychloroquine (HCQ) as a chemoprophylactic agent for COVID-19, outline weakness of published trials and assess the objectivity of conclusions regarding the possible benefits of HCQ prophylaxis against the novel coronavirus disease.

Results: Our search turned 15 articles describing trials investigating the application of HCQ as a chemoprophylactic agent for COVID-19. Different cohorts of subjects were used, mainly health care workers exposed to coronavirus patients; people with rheumatic arthritis and systemic lupus erythematosus; cases of household transmission.

Conclusions: Trials investigating the potential of HCQ to be a prophylactic agent for SARS-CoV-2 have quite conflicting results. Further research is required in the form of large randomized trials with carefully considered methodological approach which will help avoid limitations making the potential results unreliable.

Keywords: Hydroxychloroquine; Coronavirus disease; COVID-19; Prophylaxis; Pre-exposure; Post-exposure

Highlights

- No chemoprophylaxis for COVID-19 available to date
- Repurposing of old drug is a viable alternative
- Summary of studies investigating HCQ as prophylaxis in health care workers
- Summary of studies investigating HCQ as prophylaxis in rheumatoid arthritis patients
- A lot methodological inconsistences and limitations mean further research is required

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Introduction

COVID-19, the pulmonary disease caused by the coronavirus SARS-CoV-2 first registered in Wuhan, China at the end of 2019, has quickly spread around the world. While most of the infected develop symptoms only mild (40%) to moderate (40%) in severity, approximately 15% develop severe disease that requires oxygen support, and 5% are critical with complications such as respiratory failure, acute respiratory distress syndrome (ARDS), sepsis and septic shock, thromboembolism, and/or multiorgan failure, including acute kidney injury and cardiac injury [1].

With number of confirmed cases and resulting deaths on the rise responsible parties in almost every country worldwide issue recommendations and guidelines detailing instructions concerning hygiene, social distancing, diagnostics and drug therapies in an attempt to curb the spread of the infection [2]. Currently there is a worldwide active search for vaccines and therapeutics to be used against the newly emergent disease, including repurposing of well-known drugs. However, the disease

caused by the coronavirus SARS-CoV-2, continues to be an immense challenge for the scientific community throughout the world with only a few therapeutic and no chemoprophylactic interventions in our arsenal to combat the virus [3].

In vitro based evidence of suppression of activity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and other coronavirus strains provoked increased interest in the use of hydroxychloroquine (HCQ) and chloroquine for the treatment of COVID-19 [4-8]. A search of the clinicaltrials.gov database by Galvis et al, showed that 90 projects investigating the possible use of HCQ against COVID-19 were registered. A significant percentage of them – 28% (25 projects) were concerned with HCQ use as prophylaxis and were led by institutions in countries all over the world - the United States, Mexico, Spain, France, Turkey, Colombia, Austria, South Korea, Singapore, United Kingdom, Thailand, Australia and Canada [9]. Galvis et al., noted that there were remarkable differences in the proposed designs with respect to number of participants, maintenance dose, frequency of use and inclusion and exclusion criteria [9].

Clinical evidence of prophylactic use of HCQ is conflicting at best. Agarwal et al, attempt to summarize and analyze results from published trials and note that many if not all of the overviewed studies have limitations that may influence the interpretation of results [10]. Therefore, we aimed to review available data for the application of HCQ as a chemoprophylactic agent for COVID-19, outline weakness of published trials and assess the objectivity of conclusions regarding the possible benefits of HCQ prophylaxis against the novel coronavirus disease.

A comprehensive literature search was conducted through electronic databases: Cochrane, eLIBRARY.ru, MEDLINE, PsyInfo, PubMed, Scopus, and registries for data of clinical trials (http://ClinicalTrials.gov and http://www.clinicaltrialsregister.eu) in February 2021 to identify studies that investigate the application of HCQ as a chemoprophylactic agent for COVID-19 both as pre-exposure and post-exposure. The following keywords and various combinations were used in the search: hydroxychloroquine, antimalarial, coronavirus disease, COVID-19, prophylaxis, pre-exposure, post-exposure.

Review

Our search turned 15 articles [11-25] describing trials investigating the application of HCQ as a chemoprophylactic agent for COVID-19 **(Table 1).** Extracted data encompassed author and date, type of study, type of exposure, dosage regimen used and period of intake, subject population and control group(s), number of occurring infections in test and control groups and authors' conclusions. Of the 15 studies, 5 are randomized [11-15], 4 are retrospective cohort [17,20,23,25], 3 are case control [16,19,22] and 3 are observational [18,21,24]. 11 deal with the application of HCQ as a pre-exposure chemoprophylaxis agent [11,13,16-23,25]

Table 1 Summary of published trials.

Author, year	Type of study	Exposure (time from exposure)	Dose regimen and period of intake	Comparator	Population		COVID-19 infections		Determination of infection
					test	control	test	control	
Abella [11]	randomized, double-blind, placebo-controlled clinical trial in HCW	Pre-exposure	600mg, daily for 8 weeks	placebo	64	61	4	4	RT-PCR from NP swabs
Barnabas [12]	household-randomized, double-blind, controlled trial in household contacts	Post exposure (< 96 hours after exposure)	400 mg/d for 3 days followed by 200 mg/d for 11 days)	ascorbic acid (500 mg/d followed by 250 mg/d)	407	422	53	45	RT RCR from NP
Rajasingham [13]	randomized, double-blind, placebo-controlled clinical trial in HCW	Pre-exposure	400 mg twice separated by 6-8 hours followed by (i) 400 mg once weekly for 12 weeks or (ii) 400 mg twice weekly for 12 weeks	placebo	494 495	494	29 29	39	PCR confirmed or symptomatically compatible illness
Boulware [14]	randomized, double-blind, placebo-controlled trial in cases of household or occupational exposure	Post-exposure (4 days of exposure)	800 mg once followed by 600 mg in 6 to 8 hours, then 600 mg daily for 4 additional days	placebo folate tablets	414	407	49	58	PCR confirmed or symptomatically compatible illness
Mijta [15]	an open-label, cluster-randomized trial in contacts (HCW around 60%)	Post-exposure	800 mg once followed by 400 mg daily for 6 days)	usual-care group (which received no specific therapy)	1116	1198	64	74	RT-PCR from NP swabs

Author, year	Type of study	Exposure (time from exposure)	Dose regimen and period of intake	Comparator	Population		COVID-19 infections		Determination of infection
					test	control	test	control	
Revollo [16]	observational cross-sectional case-control study in HCW	Pre-exposure	400 mg twice daily on the first day and 200 mg twice daily for an additional 4 days, with a maintenance dosing of 200 mg weekly	No HCQ	69	418	16	65	RT-PCR from NP swabs
Jung [17]	population-based retrospective cohort study in patients with RA or SLE	Pre-exposure	200 - 400 mg/ day	No HCQ	649	1417	15	31	RT-PCR from NP swabs
Simova [18]	observation of the use of HCQ as prophylaxis of COVID-19 in HCW	Pre-exposure	200 mg daily for 14 days	No HCQ	156	48	0	3	RT-PCR from NP swabs
Gianfrancesco [19]	cross-sectional case series from a physician reported registry of patients with rheumatic diseases who have contracted COVID-19	Pre-exposure	Not specified	Not specified	Not specified		600		Hospitalizations
Sbidian [20]	nationwide, retrospective, matched 'exposed/ unexposed' cohort study	Pre-exposure	Not specified	No HCQ	54873	155689	128	195	Hospitalizations
Favalli [21]	observational data from a cohort of rheumatic patients	Pre-exposure	Not specified	No HCQ	112	802	19	119	RT-PCR from NP swabs or symptomatically compatible illness
Chatterjee [22]	a case control study among HCW	Pre-exposure	Not specified	No HCQ	378	373	172	193	RT-PCR from NP swabs or symptomatically compatible illness
Bhattacharya [23]	retrospective cohort study among HCW	Pre-exposure	Not specified	No HCQ	54	52	4	20	RT-PCR from NP swabs
Lee [24]	observation of patients and careworkers in a long-term care hospital	Post-exposure	400 mg daily for 14 days	No HCQ	211	101	0	0	RT-PCR from NP swabs
Gendelman [25]	retrospective study in patients with rheumatic diseases/autoimmune disorders	Pre-exposure	Not specified	Not specified	14520		1317		RT-PCR from NP swabs or symptomatically compatible illness

and 4 explore HCQ ability to act as a post-exposure prophylactic drug [12,14,15,24]. All studies explore different dosing regimens ranging from 200 mg to 800 mg daily (see Table 1 for details).

Cumulative doses calculated where possible vary greatly in the range 2800 mg [18] to 33600 mg [11] **(Table 2).** Number of participants also varies a lot between studies – from around 50 [11,16,23] to 150000 [20]. Control groups differ in treatments used – from no HCQ without any specifics [16-25], through placebo [11,13,14] to active comparators [12,15]. All these aforementioned variables and others also concerning design should be carefully evaluated when results from these studies are examined or incorporated into further analysis.

Table 2 Cumulative doses.

Author, year	Cumulative doses where available, mg
Abella [11]	33600
Barnabas [12]	3400
Rajasingham [13]	5600 10400
Boulware [14]	3800
Mijta [15]	3200
Simova [18]	2800
Lee [24]	5600

Many of the studies examining the potential of HCQ to act as a chemoprophylaxis for COVID-19 choose as their population health care workers (HCW) exposed to coronavirus patients. Abella et al planned a randomized, double-blind, placebo-controlled clinical trial at 2 tertiary urban hospitals in the period April-July 2020. Subjects involved included 132 physicians, nurses, certified nursing assistants, emergency technicians, and respiratory therapists with a median age 33 years. Authors reported that 4 subjects in the HCQ group and 4 in the placebo group contract COVID-19 and conclude that there is no clinical benefit of HCQ [11]. However, there were several limitations that have to be taken into account when interpreting these results. First of all, the trial was terminated prematurely without reaching the prespecified sample size, therefore not reaching the necessary statistical power. Another drawback that can explain the low number of infections is the young age of the included participants. The study of Rajasingham et al also evaluated HCQ prophylaxis in HCW performing aerosol generating procedures from United States and Canada. They declare that the incidence of Covid-19 (laboratory-confirmed or symptomatic compatible illness) was 0.27 events per person-year with once-weekly and 0.28 events per person-year with twice-weekly hydroxychloroquine compared with 0.38 events per person-year with placebo and conclude that pre-exposure prophylaxis with hydroxychloroquine once or twice weekly did not significantly reduce laboratory-confirmed Covid-19 or Covid-19-compatible illness among healthcare workers [13]. Here enrollment was also stopped early and the initial sample size planned (3150) was not reached. 97 of the 1483 subjects included developed infection during the study. It should be noted that only 18% of the subjects declared to have Covid-19 had a confirmatory PCR, 43% were not tested at all and 39% had negative tests during illness. It remains unclear what the objective coronavirus infection rates were. Revollo et al performed an observational cross-sectional case-control study to evaluate the efficacy of HCQ pre-exposure prophylaxis among hospital HCWs. The crude rates of SARS-CoV-2 infection with (versus without) HCQ pre-exposure prophylaxis were, respectively, 23.19% (16/69) versus 15.55% (65/418) by reverse real-time PCR and 28.33% (17/60) versus 15.35% (62/404) by serology [16]. The authors concluded that hydroxychloroquine pre-exposure prophylaxis did not prevent confirmed COVID-19 but did not elaborate on the limitations of the study. Apart from its retrospective design which they point out it should be noted that no study period is defined which makes it hard to determine cumulative HCQ doses involved in the trial. There is no confirmation provided that subjects were negative at least by serology at the time of their inclusion in the study. The retrospective cohort study among 106 HCW exposed to COVID-19 patients, at a tertiary care hospital in India by Bhattacharya et al demonstrated that voluntary HCQ consumption as pre-exposure prophylaxis by HCWs is associated with a statistically significant reduction in risk of SARS-CoV-2 - (4 out of 54 HCW with HCQ), compared to those who were not on it (20 out of 52 HCW), $\chi 2 = 14.59$, $p<0.001$ [23]. Lack of randomization and blinding are part of the limitations declared by the authors. The small sample size and the unclear dose regimen should be added to those. Chatterjee et al adopted a case-control design and investigated if HCQ consumption reduced rates of SARS-CoV-2 infection in HCW in India. Their results showed that cases were slightly older than controls and were predominantly males. HCW performing endotracheal intubation had higher odds of infection. Authors reported that consumption of four or more maintenance doses of HCQ was associated with a significant decline in the odds of getting infected (AOR: 0.44; 95% CI: 0.22-0.88) and that a dose-response relationship existed between frequency of exposure to HCQ and such reductions [22]. Although results here are positive with regard to HCQ prophylaxis, it should be noted that sample size was not achieved in this either. Another drawback is its retrospective design. The Bulgarian Cardiac Institute also share their experience with HCQ prophylaxis. Among 204 HCW, 156 took HCQ and 48 did not. None of the HCW who took HCQ tested positive for SARS-CoV-2 infection [18]. The authors concluded that HCQ could possibly provide protection against infection with SARS-CoV-2 but limitations should not be omitted here either. Lack of specifics about study design and the unclear study period are to be mentioned.

Another cohort of patients chosen to be involved in trials investigating the prophylactic use of HCQ in COVID-19 is that of people with rheumatic arthritis and systemic lupus erythematosus. Jung et al conducted a population-based retrospective cohort study using the records of the Korean Health Insurance Review and Assessment (HIRA) claim records to investigate the attack rate of COVID-19 between those who underwent HCQ therapy within 14 days before the test for SARS-CoV-2 (HCQ users) and HCQ non-users. The authors declare that the rates of infection are not statistically different between users and non-users – 2.3% to 2.2%, and conclude that HCQ prophylactic use at a usual dose did not prevent COVID-19 in patients with rheumatic disease [17]. A case series of individuals with rheumatic disease and COVID-19 from the COVID-19 Global Rheumatology Alliance registry described 600 COVID-19 cases from 40 countries. The authors did not find significant connection between antimalarials use and hospitalization rates after adjusting for sex, age, rheumatic disease, smoking status, comorbidities [19]. No evidence supporting prophylactic use of HCQ found Favalli et al. after conducting an observation of cohort of rheumatic patients from the Research Center for Adult and Paediatric Rheumatic Diseases of the ASST Gaetano Pini-CTO in Milan. The study population comprised of 914 patients stratified in HCQ-users (n=112) and non-HCQ-users (n=802) with the incidence of COVID-19 positive subjects was comparable in the two groups - 0.89% in HCQ-users vs. 0.62% in non HCQ-users; p=0.64 [21]. Gendelman et al perform a retrospective study in patients with rheumatic diseases or autoimmune disorders screened for SARS-CoV-2 comparing them in terms of rates of use of HCQ. The authors found no significant difference in terms of rates of usage of HCQ between those who were found positive for SARS-CoV-2 and those who were found negative (0.23% versus 0.25% for HCQ [25]. All these studies have major limitations originating from their retrospective design and lack of defined dosing regimens; study periods are not specified in Jung et al and Gendelman et al [17,25]. Risk of bias due to the reporting method and unknown confounders [19,21,25], unclear diagnostic method for SARS-CoV-2 infections can be added as limitation in [19]. Favalli et al. also report lack of complete matching between the two groups in

their study [21]. All these limitations are a plausible explanation for the conflicting results of studies investigating the prophylactic use of HCQ in Covid-19.

There are also several studies checking the prophylactic potential of HCQ in cases of household transmission of COVID-19. Barnabas et al conducted a household-randomized, double-blind, controlled trial of hydroxychloroquine post exposure prophylaxis. The authors declared that there was no clinically meaningful effect of hydroxychloroquine as post exposure prophylaxis to prevent SARS-CoV-2 infection [12]. However, pertaining limitations should be taken into account when interpreting results. First of all, there is a delay between exposure, baseline testing and HCQ intake. Additionally, participants have to do self-application of swabs without supervision by a professional. At finally, the comparator used is another active substance with a known positive effect on SARS-CoV-2 infection [26,27]. A randomized, double-blind, placebo-controlled trial across the United States and parts of Canada enrolling 821 asymptomatic participants showed that there were not significant differences in rates of infection between participants receiving hydroxychloroquine (49 of 414 [11.8%]) and those receiving placebo (58 of 407 [14.3%]). The authors declared that in moderate and high risk exposure to SARS-CoV-2 HCQ did not provide protection [14]. It should be noted that only 18% of reported COVID-19 cases had a confirmatory PCR test. Mijta et al conducted an open-label, cluster-randomized trial involving asymptomatic contacts of patients with polymerase-chain-reaction (PCR)–confirmed Covid-19 in Catalonia. They involved 2314 healthy contacts of 672 index case patients with Covid-19 and assigned 1116 contacts were randomly assigned to receive hydroxychloroquine. Infection rates were not significantly different between the two groups 5.7% and 6.2%, respectively and authors conclude that post exposure therapy with hydroxychloroquine did not prevent SARS-CoV-2 infection or symptomatic Covid-19 in healthy persons exposed to a PCR-positive case patient [15]. One of the limitations of this study is the lack of blinding; another significant one is the fact that around 12% of contacts had a positive PCR at screening which makes the design from the perspective of inclusion/exclusion criteria pretty unclear.

Sbidian et al. conducted a nationwide, retrospective, matched 'exposed/unexposed' cohort study using information from the French national health data system in patients using synthetic antimalarial drugs. The authors gathered data for 54873 long term users of antimalarial drugs and matched them to 155689 non-users from the general population. The primary end point of hospitalisation with COVID-19 occurred in 323 patients (128 patients in the synthetic AMD group and 195 in the unexposed group) leading the authors to conclude that there was no evidence supporting prophylactic use of HCQ [20]. However, this study also has some limitations including its retrospective design, increased risk of bias and unspecified dosing regimens and diagnostic methods. Lee et al describe the outbreak response strategy used in a long-term care hospital following the diagnosis of a hospital social worker. Among 193 patients and 121 hospital staff, post exposure prophylaxis with HCQ was offered to 193 patients and 29 care workers. All patients and staff were tested by PCR one or two days prior to discontinuation of the 14-day quarantine and all tests were negative. The authors considered HCQ was an effective option for COVID-19 prophylaxis [24]. However, this study was an observation only with significant differences in the demographic parameters of patients and staff.

All in all, trials investigating the potential of HCQ to be a prophylactic agent for SARS-CoV-2 have quite conflicting results which could be partially explained by the significant differences in design, treatment regimens and cumulative doses applied. Additionally, all studies have some major limitations which have to be carefully considered when results are interpreted. Despite this, several reviews and meta-analysis have attempted to base their conclusions on an assortment of trials. Lewis et al performed a systematic review and meta-analysis to determine the efficacy and safety of HCQ as prophylaxis for COVID-19. They calculated relative risks using random effects model with data from 4 RCTs and concluded that the existing body of evidence does not show any potential of a clinical benefit for prophylaxis with HCQ [28]. However, one of the trials included was terminated early and did not reach its predefined sample size [11], in two very few of the alleged COVID-19 cases had confirmatory PCR tests [13,14] and the last one had inconsistencies in design [15]. Another review by Mehta et al, based on some of the same trials as the meta-analysis of Lewis et al reaches the exact opposite conclusion and recommends pre-exposure prophylaxis with HCQ but emphasizes the need for large-scale randomized controlled studies [29]. Monti et al reviewed literature and available data on the prophylactic use of HCQ and found a substantial amount of preclinical data and very little reliable clinical evidence. The authors report that a search in clinical trials databases turned up 77 ongoing clinical trials using a multiplicity of HCQ schedules between January and October 2020. Most of the trials were randomized with placebo as comparator and loading doses up to 1200 mg. However, results are not published yet and the authors concluded that further developments can only be derived from large prospective randomized clinical trials, and that a correct methodological approach is the key to understanding whether prophylactic HCQ can really represent an effective strategy in preventing COVID-19 [30].Garcia-Albeniz et al performed a systematic review and meta-analysis of randomized trials in order to study the effectiveness of HCQ prophylaxis for COVID-19. The authors based their conclusions on 5 trials also featured in the aforementioned analysis [28-30]. However, Garcia-Albeniz et al refrained from giving a strong recommendation either in favour of or against the use of HCQ. Instead, they pointed out that benefit cannot be ruled out based on the available data but the wide publicity given to early findings strongly claiming lack of effect has disrupted the recruitment and completion of other trials and generation of precise estimates for HCQ efficacy [31].

Conclusion

In summary, there is an assortment of trials either randomized or not investigating the potential of HCQ to be a prophylactic agent against COVID-19. Results published so far are conflicting and a strong recommendation for or against cannot be issued based on the available data. There are authors attempting to do so but in most cases their conclusions have to be carefully interpreted due to the many limitations of the studies they base them on. Further

research is required in the form of large randomized trials with carefully considered methodological approach which will help avoid limitations making the potential results unreliable.

Ethics Approval and Consent to Participate

Not applicable

Consent for Publication

Not applicable

Availability of Data And Materials

Not applicable

Competing Interests

EF, EG, KU, VP and SH are employees of Tchaikapharma High Quality Medicines Inc. The other author reports no competing interests.

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None

Authors' Contributions

EF, EG, KU, VP, SH and TV were involved in literature search EF, EG were involved in data extraction. EF, EG, KU, VP, SH, KK and TV were involved in interpretation of results. All authors read and approved the final version of the manuscript.

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