



Article title: Current evidence on chloroquine and hydroxychloroquine and their role in the treatment and prevention of COVID-19

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Abstract:

Although chloroquine and hydroxychloroquine have not yet been shown to be safe or effective for the treatment or prevention of COVID-19, regulatory agencies in some countries have authorised their use in Coronavirus disease 2019 (COVID-19) due to the lack of available interventions. Several large clinical trials are currently underway to investigate these agents as potential therapeutic options for COVID-19. Previous research against similar pathogens that cause severe acute respiratory syndrome and Middle East respiratory syndrome has identified chloroquine and hydroxychloroquine as possible antiviral candidates against SARS-CoV-2. Despite promising pre-clinical evidence, data have thus far failed to confirm their efficacy, and recent studies suggest potential dose-related cardiotoxicity and mortality. Close monitoring for cardiac conduction abnormalities is advised with higher-than-approved doses. Additional, robust evidence from randomised controlled trials and meta-analyses are required to make informed risk-benefit assessments. Finally, the off-label prescription of these agents should be judiciously considered, and any such use should be conducted within clinical trials, or under the Monitored Emergency Use of Unregistered and Investigational Interventions framework.

Introduction

Several therapies have been described as a potential treatment of coronavirus disease 2019 (COVID-19). Among them is chloroquine, an antimalarial, anti-inflammatory and immunomodulatory drug, and its derivative, hydroxychloroquine. However, numerous questions have been raised pertaining to the rationale, dosing regimen, and safety profile of these repurposed drugs for COVID-19 treatment and prophylaxis. The World Health Organisation (WHO) and other academic partners have launched large, multi-country, prospective clinical trials which have included chloroquine or hydroxychloroquine to address some of these questions. The hydroxychloroquine arm of the Solidarity study was recently stopped after a review of their data and the recently announced results from the RECOVERY trial in the United Kingdom showed that hydroxychloroquine was ineffective in the reduction of mortality of hospitalised COVID-19 patients when compared with standard care¹. The WHO statement noted that the decision to stop hydroxychloroquine's use in the Solidarity trial does not apply to the evaluation of its role (or that of chloroquine) in pre- or post-exposure prophylaxis, or the outpatient treatment of less severe COVID-19.

In this review, we discuss the pharmacokinetics, pharmacodynamics, safety profile, and evidence for hydroxychloroquine and chloroquine use in the prevention and treatment of COVID-19. We will also discuss the role of off-label prescription of these agents within an ethical framework.

History of chloroquine and hydroxychloroquine

Quinine, the prototypical 4-aminoquinoline, was discovered in 1600 from the bark of the cinchona tree as a cure for malaria². Occupation of the Java plantations in World War II by the Japanese army led to research to synthesise it in the United States. Chloroquine was first synthesised in 1934 by Andersag in an effort to improve the safety and efficacy of quinine³, and this became the drug of choice for the treatment of malaria until the late 1990s when widespread resistance in *Plasmodium falciparum* limited its use. Hydroxychloroquine was synthesised in 1946 and proposed as a safer alternative to chloroquine in 1955⁴. Hydroxychloroquine is an analogue of chloroquine in which one of the N-ethyl groups of chloroquine is hydroxylated⁵. Hydroxychloroquine is now preferred for treating various autoimmune conditions including rheumatoid arthritis, discoid lupus, and systemic lupus erythematosus (SLE), in countries where it is available.

Pharmacokinetics of chloroquine

Absorption after oral administration is rapid and generally reliable (even in unconscious patients)⁶. The total apparent volume of distribution is >100 L/kg, reflecting extensive tissue binding⁷. Thus, the initial plasma concentrations are determined mainly by distribution processes and not by elimination. This is important to understand dose-related adverse effects such as cardiotoxicity. Toxicity can occur if absorption outpaces distribution, leading to transiently toxic plasma concentrations. Due to its large volume of distribution, loading doses are required to treat conditions like malaria, or potentially COVID-19, to ensure that therapeutic concentrations, that would take weeks to achieve without a loading dose, are achieved as rapidly and safely as possible.

Approximately 30-50% of an administered dose of chloroquine is transformed in the liver via cytochrome P450 enzymes⁸. Upon absorption, chloroquine is rapidly dealkylated into the pharmacologically active metabolites, desethylchloroquine, bisdesethylchloroquine and 7-chloro-4-aminoquinoline⁹. Following single oral doses of chloroquine in healthy volunteers, desethylchloroquine and bisdesethylchloride are rapidly detected, reaching plasma concentrations of 40% and 10% of chloroquine concentrations respectively, which adds to the pharmacological effect. Chloroquine has been shown to be a substrate of the CYP2C8, CYP3A4 and CYP3A5 enzymes, as well as a potent inhibitor of CYP2D6 and CYP2D1^{10, 11}. Furthermore, chloroquine and hydroxychloroquine are both inhibitors of the P-glycoprotein (P-gp) transport system¹². P-gp is an efflux transporter found most notably in the endothelial cells of the gut lumen and blood-brain barrier. Metabolism of concomitantly administered drugs that are substrates of CYP2D6 and/or P-gp may potentially be inhibited.

Mechanism of action of chloroquine

Chloroquine and its congener, hydroxychloroquine, are approved for first-line use as anti-malarial and amoebicidal agents¹³, and are also used as anti-inflammatory adjuvants for rheumatoid arthritis, discoid lupus and SLE¹⁴. These agents have been described to possess a broad range of antiviral activities – Chloroquine's mild antiviral action was initially demonstrated against avian reticuloendotheliosis virus, as well as human immunodeficiency virus-1. This is thought to be mediated through inhibition of pH-dependent endocytosis and interference of viral glycoprotein glycosylation pathways¹⁵. In 2003, chloroquine and hydroxychloroquine were investigated as possible treatments for the severe acute respiratory

syndrome (SARS) as SARS-CoV, a coronavirus which also involves pH-dependent endocytosis, was found to be the aetiological agent¹¹.

SARS-CoV-2 and other coronaviruses are a diverse group of enveloped, positive-sense strand RNA viruses that can cause a wide spectrum of disease in their host species including respiratory, enteral and neurological disease. Coronavirus particles contain four main structural proteins: spike, membrane, envelope, and nucleocapsid proteins. SARS-CoV and SARS-CoV-2 attachment to the host cell is initiated by binding of the spike protein to the host cell receptor, angiotensin-converting enzyme-2 (ACE2)¹⁶. Following attachment, the virus fuses with the host cell membrane through acid-dependent cleavage of the spike protein. This cleavage-facilitated fusion allows for the release of viral contents into the host cell cytoplasm^{16, 17}. This process usually occurs within acidified endosomes without which viral internalization cannot occur. The acidification of endosomal content to an average pH of 6.0-6.5 is primarily generated by a vacuolar-type ATPase transporter, which uses ATP hydrolysis to drive protons against their electrochemical gradient¹⁸. Chloroquine diffuses readily in its unprotonated form across plasma cell membranes and cellular organelles like endosomes, lysosomes, or Golgi vesicles. Upon entry into the acidic environment, the molecule becomes more protonated and less lipophilic, which results in decreased diffusion and drug trapping¹⁹. This accumulation increases the endosomal pH and prevents fusion and viral entry into the cell²⁰. Chloroquine is also thought to interfere with the glycosylation of cellular receptors, including ACE2 receptors^{10, 20}. These 4-aminoquinolines may also have immunomodulatory properties that affect the regulation of pro-inflammatory cytokines¹⁰ such as the inhibition of tumour necrosis factor alpha and interleukin-6 production, which has been suggested as a mechanism for its potential efficacy against the COVID-19 related acute respiratory distress syndrome¹¹.

Safety profile of chloroquine

Chloroquine is generally well tolerated, with an established safety profile at the doses recommended for its approved uses; for instance, SLE can be treated safely with 500 mg chloroquine sulphate for 10 days, followed by a daily maintenance dose of 250 mg^{12, 14}. Total doses of 25 mg/kg over 3 days have also safely been used for the treatment of uncomplicated malaria, and higher total doses are reportedly tolerated in children with uncomplicated malaria²¹. Irreversible retinopathy has been described with higher doses and long-term use. The risk of ophthalmological complications is less than 1% after 5 years of use at recommended

doses, with the risk doubling after 10 years of use²². Hydroxychloroquine is associated with less ocular toxicity and is therefore preferred over chloroquine if available²³. Haemolytic anaemia in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency has been reported in patients with concomitant use of primaquine and chloroquine, an effect which has been mainly attributed to primaquine²⁴. Monitoring for haemolysis in patients with known G6PD deficiency and chloroquine use is therefore recommended. The spectrum of toxicity with accidental or intentional overdosage is dependent on the dose, duration of treatment, concomitant drugs as well as underlying renal function. The main concern with high dosages is cardiovascular toxicity, which can present with conduction abnormalities, cardiomyopathy, and hypotension with sudden collapse¹³. Conduction abnormalities include a prolonged QT interval, impaired ventricular conduction that can result in widened QRS complexes, and increased automaticity that can induce arrhythmias. Chloroquine causes dose-dependent prolongation of the corrected QT (QT_c) interval by potassium-channel blockade and prolongation of the cardiac repolarization time. This can lead to fatal complications such as sudden cardiac death²⁵⁻²⁸.

QT_c interval prolongation can be prevented by avoiding use in those with genetic predispositions (congenital long QT syndrome or family history of sudden death) or electrolyte abnormalities (hypokalaemia, hypocalcaemia, and/or hypomagnesaemia)²⁹. Additionally, concomitant use with other medicines with QT_c interval prolonging properties, including macrolide and fluoroquinolone antibiotics, oseltamivir and certain antipsychotics, should be avoided. Baseline and routine follow-up electrocardiograms with use of higher doses of chloroquine are recommended³⁰. Although generally safe and well-tolerated with appropriate administration, chloroquine is potentially lethal in overdose, and incidents of self-medication and consequent accidental poisoning with chloroquine in response to COVID-19 have recently been reported in some countries including the United States of America and Nigeria^{31, 32}. Additionally, recent literature has suggested that chloroquine may be associated with significant adverse effects when used in high dosages in the management of hospitalised COVID-19 patients (Takla, preprint, 2020)³³, as the dosages required to reach therapeutic concentrations may increase the risk of adverse outcomes in this patient population³⁰. Until results on the safety of chloroquine for the treatment of COVID-19 from high-quality randomised clinical trials (RCT) have been appraised, no specific recommendations on the

safety of chloroquine in the management of patients with SARS COV-2 can be made, but it is advised that clinicians should avoid its use in patients with risk factors for QT prolongation.

Pre-clinical evidence supporting the use of 4-aminoquinolines including chloroquine & hydroxychloroquine in coronaviruses

The first data demonstrating chloroquine's antiviral activity against coronaviruses published in 2001 showed that this drug was able to inhibit cellular infection with HCoV-229E, a coronavirus, in a time-dependent manner (Table 1)³⁴. Other studies have also shown that chloroquine effectively inhibited viral replication of SARS-CoV and MERS-CoV *in-vitro*^{35,36}. In 2014, a mouse model study reported that chloroquine administered at doses of 15, 5, and 1 mg/kg improved the survival of new-born mouse pups infected with HCoV-OC43 infection (100%, 92.9%, 33.3% survival respectively)³⁷. This study provided some evidence that higher doses may be required for successful treatment of coronaviruses. By contrast, a study conducted by Barnard and colleagues was unable to demonstrate chloroquine as an effective antiviral agent at doses up to 50 mg/kg *in-vivo* but simultaneously conducted *in-vitro* experiments showed that chloroquine was an effective inhibitor of SARS-CoV replication. The authors concluded that this discrepancy suggested that chloroquine may have insufficient activity on its own as a therapeutic antiviral agent³⁸.

Early in the COVID-19 pandemic, an *in-vitro* study demonstrated that chloroquine was also effective against SARS CoV-2 at a low-micromolar concentration³⁹. Hydroxychloroquine is also thought to have similar action to chloroquine, but evidence regarding their relative potency is conflicting^{40, 41}. These data provided the rationale for Gautret et. al. to conduct a non-randomised trial of hydroxychloroquine in the treatment of COVID-19⁴².

Clinical evidence for chloroquine and hydroxychloroquine use in COVID-19

In an observational study, Gao J et al. reported that chloroquine was effective in the treatment of COVID-19 in 100 Chinese patients compared to a control group, with a dosing regimen of 500 mg twice daily for 10 days⁴³. The reasoning behind this dosing regimen is not well documented⁴⁴. By contrast, another observational study using data from a large medical centre in New York City in the United States of America failed to show an association between

hydroxychloroquine administration and a decreased probability of intubation or death (adjusted hazard ratio = 1.04, 95% Confidence interval [95% CI]: 0.82-1.32)⁴⁵. It is important to note that, although the analysis was adjusted for differences in baseline characteristics, hydroxychloroquine-treated patients were more severely ill at baseline compared to the standard care group⁴⁵.

The earliest clinical trial data suggesting a possible benefit from hydroxychloroquine in COVID-19 came from a non-randomised study conducted in France that was published in March 2020, which found that 70% in the intervention arm had virological cure compared to 12.5% in the control group by day 6 ($p < 0.001$) (Table 2)⁴². Despite significant limitations, this study was a key catalyst which prompted further research into the efficacy and subsequent emergency use authorisation (EUA) of these agents by the U.S. Food and Drug Administration (FDA). Two small RCTs by Chen Z and Chen J subsequently reported conflicting results, with Chen Z reporting improved clinical resolution with hydroxychloroquine use, while Chen J showed similar swab conversion rates on day 7 between hydroxychloroquine and placebo groups^{46, 47}.

The first well-designed RCT that assessed hydroxychloroquine in COVID-19 found similar probabilities of viral swab conversion by day 28 between the hydroxychloroquine (85.4%, 95% CI: 73.8-93.8%) and standard of care arms (81.3%, 95% CI: 71.2-89.6%) in patients admitted to hospital with mild to moderate COVID-19⁴⁸. Unfortunately, the analysis was significantly underpowered as enrolment was terminated early due to recruitment difficulties. Preliminary results from the RECOVERY trial, a multi-intervention RCT, have so far only been reported in a statement on 5 June 2020 which showed that 28-day mortality was similar between the hydroxychloroquine (25.7%) and standard of care treatment arms (23.5%, hazard ratio [HR] = 1.11 [95% CI, 0.98-1.26]; $p = 0.10$)⁴⁹. As a result, enrolment to the hydroxychloroquine arm has been stopped for futility. The authors state that “these data convincingly rule out any meaningful mortality benefit of hydroxychloroquine in patients hospitalised with COVID-19”⁴⁹. These results are preliminary and will require a review of the full data once published, but they provide significant evidence that hydroxychloroquine might not be a viable candidate for treatment in hospitalised COVID-19 patients.

The role of chloroquine as post-exposure prophylaxis in COVID-19 is also being investigated and results from one “pragmatic” RCT in which 821 participants were recruited through social media and almost all data were self-reported by participants, showed that hydroxychloroquine was not effective in preventing illness compatible with COVID-19 disease or confirmed SARS-CoV-2 infection (only 3% were confirmed) in participants that had reported recent exposure⁵⁰. These data may indicate that post-exposure hydroxychloroquine use for prophylaxis might not significantly alter the course of infection, although the long delay between perceived SARS-CoV-2 exposure and the initiation of hydroxychloroquine (≥ 3 days in most participants) suggests that the prevention of symptoms or progression of COVID-19 was being assessed, rather than prevention of SARS-CoV-2 infection⁵¹. Other pre- and post-exposure prophylaxis studies are currently ongoing⁵².

One of the critical issues in assessing the role of chloroquine or hydroxychloroquine in COVID-19 is the dose that can be used to reach therapeutic concentrations without compromising patient safety. Although numerous countries have incorporated the off-label use of these drugs in their treatment policies, data guiding the rational dosing of these drugs in COVID-19 are lacking. A systematic review found that at least 4 different treatment regimens have been used thus far in studies assessing the use of chloroquine in COVID-19, with total dosages ranging from 3 000 mg to 20 000 mg over the course of treatment (Takla, preprint, 2020)³³. Pre-clinical evidence suggests that relatively high dosages may be required in order to reach therapeutic tissue concentrations quickly⁵³. This may be problematic, however, as a recent publication reported higher rates of mortality when a high dosage regimen was compared with a low dosage regimen³⁰. ChloroCovid-19 was a double-blind RCT that aimed to assess two treatment regimens: (a) 600 mg chloroquine base twice daily for 10 days (total dosage = 12 000 mg) or (b) 450 mg chloroquine base twice on day 0, followed by 450 mg once daily for 4 days (total dosage = 2 700 mg). The trial was terminated early after an unplanned safety analysis showed a significant increase in mortality in the high dosage group (39.0% in the high dosage group vs. 15.0% in the low-dosage group) with an odds ratio of 3.6 (95% CI: 1.2-10.6). Additionally, a higher proportion of participants developed QT prolongation in the high dosage group compared to the low dosage group; two of 41 patients given the higher dose regimen developed ventricular tachycardia before death. Importantly, some patients were treated with other QT-prolonging drugs in this trial such as azithromycin and oseltamivir³⁰.

These data highlight a few key points: (1) Chloroquine has largely failed to show a clinical benefit in hospitalized patients with COVID-19, (2) The dose potentially required for therapeutic efficacy may be associated with unacceptable toxicity and increased mortality, and (3) potential drug interactions require careful consideration in the cautious prescription of these agents. A recently published, and subsequently retracted paper had reported an association between hydroxychloroquine administration and increased mortality, which prompted WHO to temporarily suspend the hydroxychloroquine arm from the Solidarity trial pending further assessments⁵⁴. The suspension was lifted after the available mortality data was reviewed, but this arm was terminated on 17 June 2020 after a further review of available data showed that hydroxychloroquine was not effective compared to the standard of care^{53, 55}. Similarly, the Medicines and Healthcare products Regulatory Agency (MHRA) has instructed UK clinical trialists using hydroxychloroquine to treat or prevent COVID-19, to suspend recruitment of further participants⁵⁶. These latest developments, combined with the recently reported mortality benefit with the use of dexamethasone⁵⁷, will most likely see a reduction in hydroxychloroquine use for the treatment of COVID-19 in hospitalised patients going forward.

Evidence to date indicates that hydroxychloroquine (and by extension chloroquine) may not be effective in hospitalised COVID-19 patients, and possibly also not for post-exposure prophylaxis. However, their role in the outpatient treatment of COVID-19 and pre-exposure prophylaxis remain unresolved. Peer-reviewed results from ongoing RCTs are needed to address these critical knowledge gaps.

Off-label, compassionate and emergency use of medicines in pandemics – The role of chloroquine or hydroxychloroquine in COVID-19

The COVID-19 pandemic has prompted important discussions regarding the off-label, and compassionate, use of medicines. Numerous considerations are involved in the use of therapeutic agents for indications that have not been investigated adequately, and this needs to be conducted ethically and rationally. Off-label medication use is defined by the FDA as the use of an approved medicine for an unapproved indication to treat a medical condition which does not have any proven treatments, or where approved treatments have been unsuccessful⁵⁸. Compassionate use of medicines, on the other hand, also known as expanded access, involves

the use of an unapproved, investigational/experimental drug⁵⁹. Compassionate use can be applied when a patient has a serious condition whose life is immediately threatened by their condition, and no comparable or satisfactory alternative intervention is available. Importantly, the potential benefit should justify the potential risks of treatment⁵⁹.

The EUA regulation allows the FDA to facilitate the availability of an unapproved medical product or device in a health-related emergency to diagnose, treat, or prevent serious or life-threatening conditions⁶⁰. Since its establishment in 2004, the FDA has issued a limited number of EUAs in response to public health emergencies such as Zika disease, Ebola, Middle East Respiratory Syndrome (MERS), and the Avian flu. In response to COVID-19, the FDA has issued EUAs to allow the use of hydroxychloroquine and remdesivir for the treatment of hospitalized patients⁶¹. On 15 June 2020 however, the FDA revoked the EUA for hydroxychloroquine, citing a lack of efficacy and ongoing safety concerns⁶². In South Africa, the health products regulatory authority (SAHPRA) approved an application by a pharmaceutical company in March 2020 to donate 500 000 chloroquine tablets for use in COVID-19⁶³. However, the regulatory authority also cautioned practitioners against the irrational and overzealous prescription of chloroquine due to the lack of evidence in COVID-19, and because the depletion of available drug stock may limit its access for other, approved indications⁶³. Numerous regulatory bodies, including SAHPRA, have advocated that chloroquine should be reserved for use within the context of clinical trials; at the minimum, it should be administered within a well-monitored setting, such as that defined by the Monitored Emergency Use of Unregistered and Investigational Interventions (MEURI) framework^{64, 65}. The MEURI framework specifies that it may be ethical to treat patients with an experimental intervention outside a clinical trial context in certain circumstances⁶⁶. This framework requires that: (i) treatment with a potential intervention is approved by local authorities and appropriately qualified ethics committees, (ii) adequate resources are available to ensure that risks are minimized, (iii) informed consent is obtained from the patient or an appropriate proxy, (iv) the emergency use of the intervention is monitored, and (v) data are collected and shared in a timely manner with the medical and scientific community⁶⁶. The MEURI framework, which has similar principles to the concept of compassionate use, was developed by the WHO during the Ebola pandemic as a means to provide some form of treatment for an illness for which no proven treatment existed, while simultaneously providing a method for data collection to contribute to the body of research. Such regulatory policies are important as they

enable the healthcare sector to utilize the best available interventions in an emergency within an approved, legal and ethical setting, which can improve access to potentially, life-saving interventions. Withholding interventions when there is plausible evidence of therapeutic benefit could be argued as unethical, and this may justify the use of an unapproved therapeutic agent. However, this should not override the need for robust evidence generated from RCT or other appropriate study designs such as adaptive trial designs. South Africa is currently involved in various clinical trials, including the Solidarity trial, which aims to compare the safety and effectiveness of various agents against COVID-19 including remdesivir; lopinavir/ritonavir with, or without, interferon beta 1a; and previously, chloroquine or hydroxychloroquine⁶⁷.

The continued use of chloroquine and hydroxychloroquine within a MEURI framework requires periodical review as more data on its efficacy and safety become available. Available evidence concerning chloroquine or hydroxychloroquine use has largely failed to demonstrate a significant benefit in the treatment of COVID-19, and safety concerns have been raised. Additionally, the widespread use of these agents has also resulted in varying, often unintentional consequences, including supply shortages for other conditions that they are approved for, such as rheumatoid arthritis and SLE⁶⁸. Bearing these facts in mind, it is important to exercise caution when considering the use of these agents in the management of COVID-19 outside of clinical trials until further, conclusive, evidence becomes available.

Conclusion

The COVID-19 pandemic has required a united effort to identify therapeutic agents that may be useful for treatment or prophylaxis. Previous research on SARS and MERS have identified 4-aminoquinolines such as chloroquine and hydroxychloroquine as agents with potential, but weak, antiviral activity against SARS-CoV-2. Despite promising pre-clinical evidence suggesting potential efficacy against COVID-19, clinical data have thus far failed to show that these agents are effective in hospitalised patients. Additionally, potentially life-threatening cardiotoxicity has been associated with higher doses, and the small, potential benefit (if any) from these agents currently do not appear to justify these risks associated with these drugs. Various gaps in knowledge that still need to be addressed include their role in pre- and post-exposure prophylaxis, outpatient treatment of COVID-19, as well as the appropriate dosage and timing whenever these agents are used. Robust evidence from RCTs and meta-analyses are

required to make informed assessments for the early treatment or prophylaxis of COVID-19 that consider the potential benefit and harm. Finally, the off-label prescription of these agents should be judiciously considered and should be limited to a clinical trial environment, or in exceptional cases, used within the MEURI framework.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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Abbreviations

95% CI – 95% confidence interval

ACE2 – Angiotensin-converting enzyme 2

CC₅₀ – 50% Cytotoxicity concentration

CCID₅₀ – 50% cell culture infective dose

COVID-19 – Coronavirus disease 2019

EC₅₀ – 50% Effective concentration

EUA – Emergency use authorisation

FDA – U.S. Food and drug administration

G6PD - glucose-6-phosphate dehydrogenase

HIV-1 – Human immunodeficiency virus-1

Hpi – Hours post-infection

HR – Hazard ratio

IC₅₀ – 50% inhibitory concentration

MERS – Middle East respiratory syndrome

MERS-CoV – Middle East respiratory syndrome coronavirus

MEURI - Monitored Emergency Use of Unregistered and Investigational Interventions framework

MHRA - Medicines and Healthcare products Regulatory Agency

P-gp – P-glycoprotein

QT_c - Corrected QT interval

RCT – Randomised controlled trial

SAHPRA – South African health products regulatory authority

SARS – Severe acute respiratory syndrome

SI – Selectivity index

SLE – Systemic lupus erythematosus

WHO – World Health Organization

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Table 1: *In-vitro* studies for the use of chloroquine in SARS-CoV/SARS-CoV-2

Reference	Study design	Treatment	Main findings
Blau et al. [34]	<ul style="list-style-type: none"> Cell culture model with MRC-5 lung epithelial cells HCoV-229E challenge 	<ul style="list-style-type: none"> CQ 50 μM Bafilomycin A 	<ul style="list-style-type: none"> 28 \pm 1.4% 229E antigen expression (-1 to 1 hour post infection [hpi]) – CQ 98 \pm 0.8% 229E antigen expression (1 to 3 hpi) – CQ 80 \pm 0.9% 229E antigen expression (8 to 12 hpi) – CQ
Keyaerts, 2004 [35]	<ul style="list-style-type: none"> Cell culture model with Vero E6 cells SARS-CoV challenge 	<ul style="list-style-type: none"> CQ 0.1, 1, and 10 μM 	<ul style="list-style-type: none"> IC₅₀ = 8.8\pm1.2 μM; CC₅₀ = 261.3\pm14.5 μM; SI = 30 Dose-dependent increase in cell viability at 0.1, 1, and 10 μM Decreased antiviral effect with prolonged time to addition of CQ
De Wilde [36]	<ul style="list-style-type: none"> Cell culture model SARS-CoV, MERS-CoV challenge and HCoV-229E-GFP 	<ul style="list-style-type: none"> Numerous compounds including CQ from 0-50 μM 	<ul style="list-style-type: none"> SARS-CoV: EC₅₀ = 3.0\pm1.1 μM; CC₅₀ = 58.1\pm1.1 μM; SI = 19.4 MERS-CoV: EC₅₀ = 4.1\pm1.0 μM; CC₅₀ > 128 μM; SI > 31 HCoV-229E-GFP: EC₅₀ = 3.3\pm1.2 μM; CC₅₀ >50 μM; SI >15
Keyaerts, 2009 [37]	<ul style="list-style-type: none"> HCoV-OC43 challenge HRT-18 cells Female pregnant C57BL/6 mice treated with CQ for 2 days before labour 	<ul style="list-style-type: none"> In-vitro: CQ at various concentrations Murine: CQ 1, 5, 15 mg/kg subcutaneously, or no CQ treatment groups 	<ul style="list-style-type: none"> In vitro: EC₅₀ = 0.306\pm0.091 μM; CC₅₀ = 419.0\pm192.5 μM; SI: 1,369 Murine: 100%, 88%, 83% & 0% new-born pup survival when given 15, 5, 1 mg/kg CQ and no CQ respectively, with a significant difference in survival between the 15mg/kg compared to the 5 mg/kg (p=0.0237) and 1 mg/kg treatment groups (p<0.0001)
Barnard et al. [38]	<ul style="list-style-type: none"> Cell culture model with Vero 76 cells SARS-CoV challenge (four strains) Cytopathic effect inhibition assay Mouse infection study with BALB/c mice 	<ul style="list-style-type: none"> In-vitro: Numerous antivirals, including CQ, CQ monophosphate and CQ diphosphate at four or eight half log₁₀ dilutions In-vivo: Intraperitoneal (i.p.) or intranasal (i.n.) 1, 10 and 50 mg/kg CQ administration, beginning 4h pre-virus exposure 	<ul style="list-style-type: none"> CQ: IC₅₀ = 1-5 μM; CC₅₀ = 10-20 μM; SI = 2-20 CQ monophosphate: IC₅₀ = 4-6 μM; CC₅₀ = 20-30 μM; μM; SI = 3-8 CQ diphosphate: IC₅₀ = 3-8 μM; CC₅₀ = 10-30 μM; SI = 2-10 50 mg/kg i.n. reduced viral lung titres from 5.4 \pm 0.5 to 4.4 \pm 1.2 in log₁₀ CCID₅₀/g at Day 3 – not statistically significant. 1, 10 mg/kg and i.p. administration did not reduce viral titres
Wang et al. [39]	<ul style="list-style-type: none"> Cell-culture model with Vero E6 cells SARS-CoV-2 challenge 	<ul style="list-style-type: none"> Numerous antivirals, including CQ at various concentrations 	<ul style="list-style-type: none"> EC₅₀ = 1.13 μM; EC₉₀ = 6.9 μM; CC₅₀ > 100 μM ; SI > 88.50
Liu et al. [41]	<ul style="list-style-type: none"> Cell-culture model with Vero E6 cells Dose response analysis at multiplicities of infection of 0.01, 0.02, 0.2, and 0.8 	<ul style="list-style-type: none"> CQ at various concentrations HCQ at various concentrations 	<ul style="list-style-type: none"> CC₅₀ (CQ) = 273.20 μM; CC₅₀ (HCQ) = 249.50 μM; EC₅₀ (CQ) = 2.71, 3.81, 7.14, and 7.36 μM at all respective MOIs EC₅₀ (HCQ) = 4.51, 4.06, 17.31, and 12.96 μM at all respective MOIs The differences in EC₅₀ values between CQ and HCQ were statistically significant at an MOI of 0.01 (P < 0.05) and 0.2 (P < 0.001)

Table 2: Studies exploring the use of chloroquine and hydroxychloroquine in prophylaxis and treatment of COVID-19

Reference	Study design	Population	Intervention	Comparator	Main findings
Borba et al. [30]	Randomized, double-blind	Hospitalized adults in Brazil with SARS-CoV-2 infection. N= 81 (41 in high dosage group, 40 in low dosage group).	CQ base 600mg twice daily for 10 days. Concomitant administration of azithromycin and oseltamivir was allowed.	HCQ base 450 mg twice on day 0, followed by 450 mg once daily for 4 days (total dose = 2700 mg). Concomitant administration of azithromycin and oseltamivir was allowed.	Mortality was 39.0% (16/41 patients) in the high dosage group compared to 15.0% (6/40 patients) in the low dosage group (odds ratio = 3.6; 95% CI: 1.2-10.6). The high dose CQ arm had more patients with QTc>500ms (7/37, 18.9%) than the low dose arm (4/36, 11.1%). 89.6% received oseltamivir, 100% received azithromycin
Gautret et al. [42]	Non-randomized, open-label	Hospitalized adults in France with confirmed COVID-19. N=42 (26 HCQ, 16 control)	HCQ sulphate 200 mg three times daily for 10 days. Azithromycin was added depending on clinical presentation.	Standard of care without HCQ. Azithromycin was added depending on clinical presentation	Viral titres were significantly reduced in the HCQ arm on day 6 - 70% compared to 12.5% PCR negative, p=0.001). Of those that received HCQ, 100% that azithromycin achieved viral clearance compared to 57.1% that did not receive azithromycin (p<0.001)
Geleris et al. [45]	Observational, prospective	Hospitalized adults in the USA with confirmed COVID-19. N=1376 (811 HCQ, 565 control).	HCQ 600 mg twice daily on day 1, then 400 mg daily for 4 days. Azithromycin and sarilumab were added depending on the clinician discretion and medical condition.	All other treatment except HCQ.	346 patients (25.1%) had a composite endpoint event of intubation or death, and there was no significant association between HCQ use and intubation or death. HR = 1.04 (95% CI: 0.82-1.32)
Chen Z et al. [46] (pre-print)	Randomized, controlled trial	Hospitalized adults in China with confirmed COVID-19 and mild illness. N= 62 (31 HCQ, 31 control) Patients with severe disease excluded	HCQ sulphate 200 mg 12 hourly orally for 5 days plus standard of care (Oxygen therapy, antiviral agents, antibacterial agents, and immunoglobulin. Corticosteroids were optional)	Standard of care only: Oxygen therapy, antiviral agents, antibacterial agents, and immunoglobulin. Corticosteroids were optional.	Fever resolution time was improved in the HCQ group (mean ± SD): 2.2 ± 0.4 vs. 3.2 ± 1.3 days. Cough resolution time was significantly reduced in the HCQ group (2.0 ± 0.2 vs. 3.1 ± 1.5 days). Progression to severe disease was reduced in the HCQ group (0/31 vs 4/31). Proportion of patients with improved CT results on day 6 was significantly higher in the HCQ group: 25/31 in HCQ group and 17/31 in control group (p=0.0476)
Chen J et al. [47]	Randomized, controlled trial	Hospitalized adults in China with confirmed COVID-19. N= 30 (15 HCQ, 15 control).	HCQ 400 mg daily orally for 5 days plus other treatments:	Other treatments: inhaled interferons, abidor, umifenovir, and lopinavir/ritonavir	Time to body temperature normalization was similar

		Patients with severe disease excluded	inhaled interferons, umifenovir, and lopinavir/ritonavir		(median [Interquartile range]): 1 [0 to 2] day in HCQ group vs. 1 [0 to 3] day in the control group. SARS-CoV-2 nucleic acid conversion rate on pharyngeal swab similar at Day 7: negative in 13/15 in HCQ group, and 14/15 in control group (p>0.05).
Tang et al. [48]	Randomized, open-label	Hospitalized adults in China with confirmed COVID-19. N= 150 (75 HCQ, 75 control)	HCQ sulphate loading dose of 1200 mg daily for three days followed by a maintenance dose of 800 mg daily for 2-3 weeks plus supportive and symptomatic treatment. No antivirals permitted.	Supportive and symptomatic treatment. No antivirals permitted.	The probability of negative conversion by 28 days in the HCQ group was 85.4% (95% CI: 73.8% to 93.8%), similar to the standard of care group (81.3%, 95% CI: 71.2% to 89.6%). The difference between groups was 4.1% (95% CI: -10.3% to 18.5%).
Horby and Landray [49]	Randomized, double-blind, adaptive trial design	Hospitalized adults and children with confirmed COVID-19 (n=1542 in HCQ arm, 3132 in usual care arm at the time of early discontinuation)	HCQ sulphate 2.4 g loading dose over 24 hours, then 800 mg daily for 9 days. Simultaneously randomized to possibly receive convalescent plasma	Usual standard of care. Simultaneously randomized to possibly receive convalescent plasma	Similar 28-day mortality rate (25.7% HCQ vs. 23.5% usual care; HR = 1.11 [95% CI: 0.98 to 1.26]; p=0.10). No evidence of beneficial effects on hospital stay duration or other outcomes found either.
Boulware et al. [50]	Randomized, double-blind	Participants with household or occupational exposure to confirmed Covid-19 where the risk of transmission was considered moderate to high. Conducted in the United States of America. N=821 (414 HCQ, 407 placebo)	HCQ sulphate 800 mg once, then 600 mg 6-8 hours later, then 600 mg daily for 4 more days	Placebo (folate) tablet regimen prescribed identically to the intervention group	Incidence of new illness compatible with Covid-19 or confirmed SARS-CoV-2 infection was similar between participants receiving HCQ (49/414 [11.8%]) and those receiving placebo (58/407 [14.3%]). The absolute difference was -2.4% (95% CI: -7.0 to 2.2; p = 0.35)