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Chloroquine and hydroxychloroquine for COVID-19: *Perspectives on their failure in repurposing*

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Abstract

What is known and Objective: Non-clinical studies suggest that chloroquine (CQ) and hydroxychloroquine (HCQ) have antiviral activities. Early clinical reports of successful HCQ-associated reduction in viral load from small studies in COVID-19 patients spurred a large number of national and international clinical trials to test their therapeutic potential. The objective of this review is to summarize the current evidence on the safety and efficacy of these two agents and to provide a perspective on why their repurposing has hitherto failed.

Methods: Published studies and rapidly emerging data were reviewed to gather evidence on safety and efficacy of CQ and HCQ in patients with COVID-19 infection or as prophylaxis. The focus is on clinically relevant efficacy endpoints and their adverse effects on QT interval.

Results and Discussion: At the doses used, the two agents, given alone or with azithromycin (AZM), are not effective in COVID-19 infection. The choice of (typically subtherapeutic) dosing regimens, influenced partly by "QT-phobia," varied widely and seems anecdotal without any pharmacologically reliable supporting clinical evidence. A substantial proportion of patients receiving CQ/HCQ/AZM regimen developed QTc interval prolongation, many with absolute QTc interval exceeding the potential proarrhythmic threshold, but very few developed proarrhythmia.

What is new and Conclusion: The strategy to repurpose CQ/HCQ to combat COVID-19 infection is overshadowed by concerns about their QT liability, resulting in choice of potentially subtherapeutic doses. Although the risk of QT-related proarrhythmia is real, it is low and manageable by careful monitoring. Recent discontinuation of HCQ from at least four large studies effectively marks the end of efforts at repurposing of CQ or HCQ for COVID-19 infection. This episode leaves behind important questions on dose selection and risk/benefit balance in repurposing drugs generally.

KEYWORDS

chloroquine, COVID-19, dose-response, hydroxychloroquine, interleukin-6, QT interval, viral infections

1 | WHAT IS KNOWN AND OBJECTIVES

Repurposing old drugs for novel indications has gathered momentum over the last 2 decades in an effort to curb drug development costs and reduce time-lines to regulatory approval of drugs whose safety profile is already well known.[1] This momentum is the result of systematic re-evaluation of many old drugs which are found in non-clinical studies to have activities at targets well beyond the ones

originally investigated.[1] The term 'repurposing' has not been clearly defined but generally means the development of an out-of-patent drug for a novel pharmaco-therapeutic indication.[1,2] An unsubstantiated assumption is that the safety profile of the drug is comparable across all indications, despite potential differences in drug-disease or drug-drug interactions.

Clinical examples of successful repurposing are few. Most prospective randomized clinical trials have failed to confirm expectations from non-clinical investigations or from observational and retrospective clinical studies.[1] Perhaps no drug illustrates this gap better than pravastatin. Statins, widely used in cardiovascular medicine, have been reported to have tissue-specific anticancer properties.[3-7] LUNGSTAR, one of the largest prospective placebo-controlled studies, was carefully planned to investigate the benefits of adding pravastatin 40 mg daily to standard chemotherapy in patients with small-cell lung cancer. Pravastatin performed no better than placebo.[8]

Chloroquine (CQ) is a synthetic analogue of quinine, a muscle-relaxant quinoline found in the bark of *Cinchona* tree (*Cinchona officinalis*). The bark extract was first used in the West to treat malaria in 1631 in Rome. Following isolation of quinine from the bark in 1820, its analogue CQ was first synthesized in 1934 and marketed as RESOCHIN®. Clinical trials showed CQ to be a highly effective anti-malarial drug, and it was introduced clinically in 1947 as treatment and prophylaxis against malaria. Subsequently, hydroxychloroquine (HCQ) was synthesized in 1946 and introduced clinically in 1955 for the same purposes under the brand name of PLAQUENIL®.

Based on earlier non-clinical evidence and the impact of ongoing COVID-19 pandemic, there has been interest in repurposing CQ and HCQ for combating this infection. The virulence, clinical outcomes and the rapid globalization of this pandemic since its origin in Wuhan (China) in December 2019 have led to unprecedented global scientific collaboration. Early release of data from scientific studies has appeared at such an extraordinary rate that it is difficult to keep pace with them.[9] This review is a critical commentary on repurposing CQ and HCQ in combating COVID-19 infection, with particular focus on dose selection and perceived cardiotoxicity.

2 | PREVIOUS EFFORTS AT REPURPOSING CQ AND HCQ IN VIROLOGY

Chloroquine and HCQ are approved for both treatment and prophylaxis against malaria. Both have wide-ranging activities against bacteria, fungi, protozoa, parasites and viruses.[10,11] Clinically, CQ is also approved for the treatment of hepatic amoebiasis.

In non-clinical studies, CQ and HCQ have shown a variety of pharmacological effects, leading to their use in other conditions.[12] For example, based on different mechanisms of action, both are approved for use in rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and light-sensitive skin eruptions. Therefore, it could be argued that CQ and HCQ have already been repurposed for use in novel pharmaco-therapeutic indications unrelated to infections. Furthermore, CQ is reported to have antitumour activity[13] and in November 2014, preliminary findings led the European Commission to grant CQ an orphan drug designation for the treatment of glioma.[14]

Chloroquine and HCQ have attracted much attention for their antiviral activity. CQ was first investigated as an antiviral agent in 1963.[15] The exact mechanism(s) of their antiviral activity is not clear but evidence suggests that 4-aminoquinolines such as CQ and HCQ have at least four mechanisms by which they may act against diverse RNA viruses and reduce the cytokine storms they generate. These are (a) inhibition of viral entry; (b) inhibition of viral release into the host cell; (c) reduction of viral infectivity; and (d) immunomodulation.[13,16] They inhibit viral release into the host cell by increasing late endosomal and lysosomal pH, resulting in impaired release of the virus from the endosome or lysosome. Since the release of the virus requires a low pH, the virus is unable to release its genetic material into the cell and replicate. CQ also seems to act as a zinc ionophore that allows extracellular zinc to enter the cell and inhibit viral RNA-dependent RNA polymerase. CQ inhibits thiamine uptake[17] but the significance of this effect in terms of its antiviral activity is unclear at present.

Not surprisingly, both drugs have been investigated for use in various viral infections and have demonstrated in vitro antiviral activity against herpes simplex virus type 1, ZIKA, HIV, MERS, SARS-CoV, HCoV-OC43, Chikungunya, hepatitis C and several other viruses.[13,16,18] However, very few randomized clinical studies have investigated their antiviral efficacy. Rodrigo et al[18] have summarized 13 clinical studies that investigated the efficacy of these agents in four viral infections and concluded that the benefit of either drug was either lacking or doubtful. To date, there is no evidence of CQ having successfully treated any acute viral infection in man.[19]

3 | CURRENT EFFORTS AT REPURPOSING CQ AND HCQ FOR COVID-19 INFECTION

Chloroquine was shown in vitro to have antiviral activity against severe acute respiratory syndrome (SARS) associated with coronavirus infection.[20] Since the appearance of the current pandemic with COVID-19, a virus closely related to SARS, there has been an unparalleled resurgence of interest in the potential value of CQ and HCQ against this infection which is associated with high morbidity and mortality.[21] This interest intensified following an endorsement of HCQ as a safe and effective prophylactic medication by US President Donald Trump despite little reliable evidence of its efficacy or safety. This endorsement was associated with an abrupt increase in the number of prescriptions for HCQ.[22,23] A survey of 1197 professionals by the Heart Rhythm Society revealed substantial use of HCQ, with or without azithromycin (AZM), among the respondents in the treatment of COVID-19 patients.[24]

3.1 | Current evidence concerning efficacy of HCQ

The pharmacokinetics of CQ and HCQ are complex but comparable.[12] In the indications approved, their efficacy is also comparable but in animal studies, HCQ has been reported to be significantly less toxic than CQ.[25] In humans, HCQ has also been reported to have lower retinal toxicity than CQ.[26] Therefore, HCQ has been studied more widely than CQ, both alone and in combination with AZM, as a potential therapy against COVID-19 infection. AZM is a macrolide antibiotic reported to be immunomodulatory and antiviral. It is also reported to reduce production of pro-inflammatory cytokines such as interleukin (IL)-8, IL-6 and tumour necrosis factor (TNF)-alpha, reduce oxidative stress and modulate T-helper functions.[27]

Among the earliest studies claiming benefits of HCQ in patients with COVID-19 were two, one each from France and China,[28,29] both with significant impact on expectations of the clinical community. However, the French study[29] that used the combination of HCQ and AZM attracted much criticism of the bold conclusions drawn there from because of its small sample size, lack of a placebo or control arm and other limitations. Although published in its journal, the International Society of Antimicrobial Chemotherapy later issued an official statement, emphasizing that the article reporting the French study did not meet the Society's various expected standards.[30] Notwithstanding, based on the results of this study, the French Ministry of Health allowed the use of HCQ to treat COVID-19 patients, pending results from ongoing trials. Furthermore, on 21 March 2020, President Trump claimed the drug combination to have '… a real chance of being one of the biggest game-changers in the history of medicine'. Reluctantly or otherwise, regulators in several countries also allowed HCQ to be used as a potential treatment of COVID-19. To encourage the development of CQ and HCQ in a safe and efficient manner, the US Food and Drug Administration (FDA) also issued Emergency Use Authorization (EUA) on 28 March 2020, intended to facilitate the availability of CQ and HCQ to physicians during the COVID-19 pandemic to treat patients for whom a clinical trial is not available, or participation in a clinical trial was not feasible.[31]

However, the early evidence of efficacy was poor, resulting in proliferation of a number of other trials, investigating the benefits of HCQ and other treatment options. Among these trials are many national and international studies with large sample sizes such as the

- SOLIDARITY trial,[32] investigating disease progression or improvement in survival, co-ordinated by the World Health Organization (WHO),
- DISCOVERY trial[33] (French segment of SOLIDARITY), investigating clinical endpoints focussing on death and hospitalization, co-ordinated in France,
- PRINCIPLE trial,[34] investigating community population at higher risk of complications, co-ordinated at the University of Oxford (UK),
- RECOVERY trial,[35] investigating survival, discharge, need for ventilation and need for renal replacement therapy, co-ordinated at the University of Oxford (UK) and
- ORCHID trial,[36] investigating clinical endpoints focussing on death and hospitalization, sponsored by the National Heart, Lung, and Blood Institute (US).

The principal findings of the main representative studies, reported as of 10 July, 2020, are summarized in Table 1. A critical review of the earlier of these studies can be found elsewhere.[47] These studies, including to date the largest RECOVERY trial, show that at the doses used, CQ or HCQ (with or without AZM) is not effective in reduction of viral load, post-exposure prophylaxis, improving survival or reducing the need for respiratory support in hospitalized patients. However, these studies varied widely in terms of design, patient populations studied, intended indications (prophylactic or curative), sample size and the severity of infection. Although the US FDA had recommended 800 mg on day 1, followed by 400 mg daily for 4-7 days for the EUA, the dosing schedules of HCQ in these studies also varied widely as shown in Table 2 in terms of loading dose (range 400-2400 mg), maintenance dose (range 400-800 mg) and duration of maintenance treatment (range 1-14 days). Four studies also reported concomitant treatment with AZM (typically 500 mg on day 1 followed by 250 mg daily for 4 days).

Critically, based on anecdotal reports of efficacy in COVID-19 infection, HCQ began to be hoarded, thereby increasing its worldwide demand and creating a shortage for its approved use in RA and SLE with potentially serious consequences for these patients.[48,49] In anticipation of product shortages, the FDA also issued product-specific guidance for CQ phosphate and for HCQ sulphate for generic drug manufacturers.

Although the study was retracted within 2 weeks of its (initial online) publication on 22 May 2020, it is relevant to consider here the multinational registry analysis by Mehra et al[50] because, like its earlier French counterpart,[29] it further demonstrates the adverse impact of premature application of inadequately validated data. This study of CQ and HCQ, with and without a macrolide, in 96 032 patients hospitalized with COVID-19, reported that each of these drug regimens was associated with decreased in-hospital survival and an increased frequency of ventricular arrhythmias. Consequently, almost immediately, the use of HCQ in the DISCOVERY and the SOLIDARITY trials was temporarily suspended. Other European governments also followed suit, dealing further blows to the hopes promoted by the US President. However, on 4 June 2020, Mehra et al[51] retracted their study following several concerns regarding the veracity of the data and analyses. Consequently, the WHO resumed the HCQ arm of the SOLIDARITY trial. On 5 June 2020, however, the RECOVERY investigators concluded following an interim analysis that HCQ had no beneficial effect and discontinued with immediate effect enrolment of patients to the HCQ arm of the trial.[52] During mid-June 2020, the FDA also determined that CQ and HCQ are unlikely to be effective in treating COVID-19 and revoked the EUA[53] and the HCQ arm was once again discontinued not only from the SOLIDARITY trial but also from the ORCHID trial.

TABLE 1 Efficacy findings from key HCQ trials

Study	COVID indication	Study design	Drugs tested	Principal efficacy findings	Ref
Chen et al	Infection	Randomized, parallel groups	HCQ	Use of HCQ was associated with shorter time to clinical recovery and improvement in pneumonia	28
Gautret et al	Infection	Non-randomized, open label	HCQ + AZM	Significant reduction/elimination of viral load in association with HCQ treatment, an effect that that was augmented by AZM	29
RECOVERY	Infection	Prospective, randomized, open label, controlled	HCQ	No significant difference between HCQ and control groups in 28-d mortality and no evidence of beneficial effects on hospital stay duration or other outcomes	35
Lee et al	Prophylaxis	Observational	HCQ	Post-exposure prophylaxis with HCQ was effective	37
Molina et al	Infection	Prospective, uncontrolled	HCQ + AZM	No evidence of a strong antiviral activity or clinical benefit	38
Chen et al	Infection	Prospective, randomized	HCQ	No evidence of a strong antiviral activity or clinical benefit	39
Gautret et al	Infection	Pilot observational	HCQ + AZM	Rapid fall of nasopharyngeal viral load	40
Million et al	Infection	Retrospective analysis	HCQ + AZM	Virologic cure, reduced number of transfers to intensive care unit and lower mortality rate	41
Mahévas et al	Infection	Comparative observational	HCQ	No survival benefit without transfer to the intensive care unit	42
Tang et al	Infection	Randomized, controlled, open label	HCQ	No difference between HCQ and control groups in negative conversion by 28 d	43
Geleris et al	Infection	Observational	HCQ	No evidence of benefit in terms of the need for intubation or death	44
Boulware et al	Prophylaxis	Randomized, double-blind, placebo-controlled	HCQ	HCQ did not prevent confirmed infection or an illness compatible with COVID-19	45
Mitja et al	Infection	Open label, randomized controlled	HCQ	No significant differences in the mean reduction of viral load, reduction in risk of hospitalization or time to complete resolution of symptoms	46

Abbreviations: AZM, azithromycin; HCQ, hydroxychloroquine.

3.2 | Current evidence concerning QT liability and proarrhythmic potential of CQ/HCQ

Both CQ and HCQ have serious adverse effects,[54-56] particularly on cardiac repolarization that results in prolongation of the QT interval of the surface electrocardiogram (ECG). Drug-induced prolongation of QT interval is commonly due to inhibition of IKr, the principal outward current responsible for cardiac repolarization. When excessive (typically ≥ 500 ms) or in presence of other risk factors such as bradycardia or hypokalaemia, prolonged QT interval is often a precursor of potentially fatal ventricular tachyarrhythmia known as the torsade de pointes (TdP). TdP is usually self-terminating but in rare cases can degenerate into ventricular fibrillation.

Hydroxychloroquine, and to a lesser extent AZM, blocks the IKr current and their combination has a greater effect.[57] In addition, AZM also increases peak and late sodium current, thereby further delaying cardiac repolarization.[58] Clinically, CQ, HCQ and AZM have long been known to prolong QT interval and induce ventricular tachyarrhythmias including TdP.[59-62] AZM dose-dependently increases CQ-induced QTc interval prolongation.[61,63]

Early observations suggestive of efficacy of HCQ had already led to widespread off-label use of CQ and HCQ, with or without AZM, in routine clinical medicine to treat COVID-19 patients.[22-24] Consequently, there was a rapid increase in the number of reports of QTc interval prolongation and serious ventricular tachyarrhythmias in association with these drugs. Gerard et al[64] reported receiving 120 reports of cardiac adverse drug reactions in the 1 month beginning 27 March 2020. Of these, 103 (86%) were associated with HCQ alone or associated with AZM (60%). Among the 131 reported effects, there were 90 (68.7%) of QTc prolongation and 8 (6.1%) of ventricular arrhythmias as well as 8 (6.1%) of sudden or aborted deaths. Reports such as this and others led regulatory authorities to issue warnings concerning the proarrhythmic potential of these drugs when used without appropriate monitoring and outside hospital setting or clinical trials.[65,66]

In the efficacy studies summarized above, ECG monitoring was undertaken in 7 studies. When monitored, QTc interval

TABLE 2 Dosing schemes used in efficacy studies reviewed

Study	Hydroxychloroquine dose	Azithromycin dose	Ref
Chen et al	400 mg daily for 5 d		28
Gautret et al	600 mg daily for 10 d	500 mg on day 1 followed by 250 mg daily for the next 4 d	29
RECOVERY	2400 mg on day 1 followed by 800 mg daily for 9 d		35
Lee et al	400 mg daily for 14 d		37
Molina et al	600 mg daily for 10 d	500 mg on day 1 followed by 250 mg daily for the next 4 d	38
Chen et al	400 mg daily for 5 d		39
Gautret et al	600 mg daily for 10 d	500 mg on day 1 followed by 250 mg daily for the next 4 d	40
Million et al	600 mg daily for 10 d	500 mg on day 1 followed by 250 mg daily for the next 4 d	41
Mahévas et al	600 mg daily (duration not specified)		42
Tang et al	1200 mg for 3 d followed by 800 mg daily for 2-3 wk		43
Geleris et al	1200 mg for 1 d followed by 400 mg for 5 d		44
Boulware et al	1400 mg on day 1 followed by 600 mg for 4 d		45
Mitja et al	800 mg on day 1 followed by 400 mg for 6 d		46

prolongation, typically ≥60 ms increase over baseline, often led to discontinuations of the study drug[38,41,42]; however, only 1 patient exceeded the 500 ms proarrhythmic threshold but without developing an arrhythmia.[42] Patients with COVID-19 infection frequently have multiple risk factors for QT-related arrhythmias, including hypokalaemia, comedications with QT-prolonging potential and comorbidities.[67] Therefore, a number of investigators undertook studies specifically to examine the cardiac safety of CQ and HCQ in COVID-19 patients.

One Brazilian study, comparing two doses of CQ together with AZM, had to prematurely discontinue the high-dose arm because of cardiac safety concerns.[68] In this study, QTc interval > 500 ms was found in 11.1% of the low-dose cohort and 18.9% of the high-dose cohort; ventricular tachycardia in the two groups were 0 and 2, respectively. A more recent study, investigating the effect of lower doses of CQ in 95 hospitalized COVID-19 patients, reported CQ-induced QTc prolongation of ~35 ms,[69] with 22 patients (23%) who had normal baseline values developing QTc interval > 500 ms. A small but significant increase in the QRS duration in this study possibly led to slight overestimation of CQ-induced QTc prolongation but there were no cases of TdP.

QT-related findings from five studies, investigating the QT liability of HCQ, are summarized in Table 3. The dose of HCQ used was 800 mg on day 1 followed by 400 mg daily for 4 days in three studies [70,71,73] and 400 mg for 10 days in one[72]; the dosing scheme was not specified in the other.[74] Concomitant AZM (250-500 mg for 5 days) was variously administered in all the five studies. In the study by Mercuro et al,[73] one patient receiving the combination discontinued because of QTc prolongation (499 ms) but developed TdP 3 days later and went on develop other ventricular arrhythmias; however, this patient had other risk factors (bradycardia and use of propofol). The likelihood of prolonged QTc was reportedly greater in patients receiving concomitant loop diuretics or had a baseline QTc ≥ 450 ms.[73] In the study by Maraj et al,[74] one patient developed polymorphic ventricular tachycardia which degenerated into ventricular fibrillation and another developed self-terminating TdP. Collectively, these five studies suggest that although a significant proportion of patients develop marked prolongation of QTc interval at the doses studied, the risk of a proarrhythmia is very small.

3.3 | COVID-19 infection per se confers QT susceptibility

COVID-19 is a disease with high inflammatory component. IL-6 is one of the main mediators of inflammatory and immune response initiated by infection or injury. Increased levels of IL-6, found in more than half of patients with COVID-19, seem to be associated

TABLE 3 QT liability of hydroxychloroquine (HCQ) with or without azithromycin (AZM)

Study	Patients (n)	Drugs	Treatment group	Patients with		ECG-related discontinuations	Torsade de pointes (n)	Ref
				ΔQTc ≥ 60 ms	QTc > 500 ms			
Saleh et al	201[a]	CQ/HCQ	CQ/HCQ (n = 82)	14.9%	8.5%	2.4%	0	70
		CQ/HCQ ± AZM	CQ/HCQ + AZM (n = 119)	27.1%	9.2%	4.2%	0	
Chorin et al	251	HCQ + AZM	HCQ + AZM	20%	13%	2.8%	1	71
Bessière et al	40	HCQ ± AZM	HCQ (n = 22)	25%	5%	17.5%	0	72
			HCQ + AZM (n = 18)		33%			
Mercuro et al	90	HCQ ± AZM	HCQ alone (n = 37)	8%	19%	0%	0	73
			HCQ + AZM (=53)	13%	21%	1%	1	
Maraj et al	91	HCQ + AZM	HCQ + AZM	23%	14%	(Not reported)	1	74

Abbreviation: CQ, chloroquine.

[a]Only 10 patients received CQ.

with inflammatory response, respiratory failure, need for mechanical ventilation and/or intubation and increased mortality.[75-77] IL-6 reportedly inhibits IKr current via IL-6R and JAK pathway activation, resulting in QT interval prolongation observed in inflammatory diseases.[78] In patients with RA, inflammatory cytokines (TNF-alpha, IL-1b, IL-6, IL-10) have been shown to positively correlate with QTc interval duration.[79]

Administration of tocilizumab, an IL-6 inhibitor, results in marked reduction in QT interval duration in these patients.[80] In another study, 80% of the 40 patients with TdP showed elevated CRP levels with an identifiable inflammatory disease in 18 (45%) of these cases. In these subjects, IL-6 (but not TNF-alpha and IL-1) level was ~15-20 times higher than in controls. In the inflammatory cohort, where QTc prolongation was common, CRP reduction was associated with a decrease in IL-6 level and significant QTc shortening (−22.3 ms).[81] Thus, it may not be entirely coincidental that many patients with reported HCQ-induced QTc prolongation have higher systemic inflammatory response and be in intensive care units requiring intubation.[67,73]

4 | DISCUSSION

Under normal circumstances, drug development is an orderly process whereby, after appropriate clinical pharmacology and dose-ranging studies, pivotal clinical trials are undertaken with an identified optimal dose to characterize a drug for its efficacy and safety during clinical use. Important among the clinical pharmacology studies are the drug-drug interaction studies which could impact safety and efficacy during routine clinical use, whereas the pivotal trials are carefully designed with specific inclusion and exclusion criteria.

Clinical trials aimed at repurposing CQ and HCQ for COVID-19 have hitherto proceeded without prior determination of a safe and effective antiviral clinical dose.[82,83] In the pursuit of urgently finding an anti-COVID-19 agent, there appears to have been a lack of a systematic approach. The global scientific response, although highly collaborative in spirit, appears fragmented and disorganized. This is perhaps best illustrated by premature enthusiastic response to early studies from China and France[28,29] followed by the study reported by Mehra et al[50] In an effort to find a therapeutic agent to fight COVID-19, a large number of clinical trials have proliferated[84-88] but these trials vary widely in their design, target population and its stratification, indication, exclusion criteria, sample size, drugs and their dosing regimen, duration of therapy and study endpoints. An analysis of 201 trials registered before 26 March this year concluded that a third of these exclude clinical endpoints, almost half were designed to recruit 100 patients or less and more than 70% were open label, thus limiting their long-term usefulness.[89] Furthermore, the roles of potential drug interactions or inflammation per se which may impact the safety (including QT liability) or efficacy have not received the attention they deserve. It is questionable if a new drug can expect to be approved these days on the basis of the study designs used hitherto for repurposing CQ or HCQ, with or without AZM, and the

quality of evidence used to support dose selection; approval can only be expected if the evidence of efficacy in a life-threatening condition is consistent, even if preliminary.

Overall evaluation of the available evidence (Table 1) shows that at the doses used, CQ or HCQ (with or without AZM) is not effective in reduction of viral load, post-exposure prophylaxis, improving survival or reducing the need for respiratory support in hospitalized patients. However, these studies were undertaken in absence of reliable information on the effective therapeutic dose or concentration of HCQ in COVID-19 patients. As shown in Table 2, the dosing schedules of HCQ have varied widely. It is also likely that the effective doses and the level of efficacy are different in subgroups of patients with different viral loads and/or severity of disease.

If HCQ was effective against COVID-19 at the doses used, it would be expected that patients with SLE receiving long-term HCQ therapy (typically 200-400 mg daily for years) will be relatively protected from COVID-19 infection (pre-exposure prophylaxis). Although it is almost impossible to compute this risk prospectively, available evidence shows that HCQ therapy at these doses does not confer protection to these patients.[90-93]

Pharmacokinetic modelling studies aimed at determining an optimal dose have used different approaches and have concluded with different optimal doses.[81,94-96] Although their modelling study has a number of limitations, Garcia-Cremades et al[95] have suggested that the half-maximal effective concentration (EC_{50}) of HCQ was 4.7 μmol/L (~1.58 μg/mL), comparable to those reported in in vitro studies. Based on structure-activity considerations, Garcia-Cremades et al[95] assumed in their modelling that CQ and HCQ are equipotent in prolonging QT interval and predicted that HCQ doses >400 mg twice daily for ≥5 days were more likely than lower dose (≤400 mg daily) regimens to rapidly decrease viral loads, reduce the proportion of patients with detectable COVID-19 infection and shorten treatment courses. HCQ course of 400-600 mg twice daily for 10 days was unlikely to be associated with clinically significant cardiac toxicity in patients without a known risk factor for QTc prolongation, whereas HCQ daily doses (>600 or 800 mg twice daily), although efficacious, were predicted to increase the risk of QTc prolongation.[95] Their modelling did not permit prediction of the impact of concomitant AZM on risk of HCQ-induced QTc prolongation.

Importantly, therapeutic or cardiotoxic plasma concentrations of HCQ have not been established. If one accepts HCQ dose >400 mg twice daily for ≥5 days as the most optimal as suggested,[95] the HCQ dosing regimens used in most clinical studies, except the RECOVERY trial[35] and the one by Tang et al,[43] were likely subtherapeutic. Furthermore, pharmacokinetics of HCQ are so complex and variable that many patients do not achieve the presumed therapeutic concentrations of >1 and <2 μg/mL.[82] For example, mean HCQ concentrations following the same dosing regimen in the two French studies[29,38] with contradictory efficacy findings were lower as well as much different (0.46 and 0.68 μg/mL, respectively). In the study by Million et al,[41] mean (SD) concentration of HCQ on day 2 of treatment was 0.25 (0.16) μg/mL. The choice of doses was probably influenced not only by the results of various pharmacokinetic simulations but also possibly concerns on cardiotoxicity ("QT-phobia"). Interestingly, in the study by Perinel et al,[82] HCQ was withdrawn in two patients due to QT interval prolongation (381-510 ms and 432-550 ms) on days 2 and 3 with HCQ blood levels that varied widely (0.03 and 1.74 μg/mL, respectively) with no correlation to its QT effect. Nevertheless, in revoking the EUA for CQ and HCQ on 15 June 2020, the FDA determined that in light of ongoing serious cardiac adverse events and other potential serious side effects, the known and potential benefits of CQ and HCQ no longer outweigh the known and potential risks for the authorized use.[53]

The studies summarized in Table 3 show that at the doses used in QT-liability studies, typically HCQ 800 mg on day 1 followed by 400 mg daily for 4 days,[70,71,73] a substantial proportion of patients developed QTc interval prolongation, many with absolute QTc interval exceeding the 500 ms threshold for likely proarrhythmia risk. However, the number of patients developing TdP or serious ventricular arrhythmias was very small. Of the total cohort of 673 patients across these five studies, 92 (13.9%) developed an absolute QTc interval exceeding 500 ms and yet, despite the presence of risk factors such as comorbidities and other QT-prolonging drugs, only 3 progressed to develop TdP. The low prevalence of proarrhythmia is also supported by a meta-analysis of 14 studies involving 1515 patients, showing that approximately 10% of COVID-19 patients treated with CQ or HCQ developed QT prolongation but ventricular arrhythmias were found in only two COVID-19 patients, both from a group of 28 treated with high-dose CQ.[63] Jain et al[67] also reported that although 19.7% of the 524 patients they screened had QT prolongation, none developed TdP despite the presence of multiple risk factors for proarrhythmia. Another study in 105 ethnic minority COVID-19 patients also reported an increase in the rates of QTc interval duration ≥500 ms from 4.8% baseline to 16.2% post-treatment with CQ/HCQ with or without AZM and yet only one patient developed non-fatal ventricular tachycardia.[97] In this study, patients who had either QTc ≥ 500 ms or an increase in QTc of ≥60 ms had increased odds of mortality than those who did not, though no patients died from ventricular tachyarrhythmia; the high mortality is believed to be probably linked to the severity of viral disease requiring intubation in ICU.

A large retrospective study on the QT liability of HCQ in rheumatology patients treated with median dose of 400 mg daily for a median duration of 1006 days revealed that the mean QTc increased by a mean of only 8 ms from 424.4 ± 29.7 to 432.0 ± 32.3 ms during HCQ treatment.[98] Therefore, this report suggests that HCQ doses >400 mg twice daily for just 5-10 days may be safe. In the study by Tang et al[43] using high dose for 2-3 weeks, prolongation of the QT interval was not observed. The data on safety of HCQ from the RECOVERY trial,[35] which used HCQ doses of 2400 mg on day 1 followed by 800 mg daily for 9 days, are not yet available but will be of interest in considering whether any beneficial effect on survival may have been offset by any fatal cardiotoxic effects.

The observed high prevalence of marked prolongation of QT interval, despite low doses of HCQ, suggests presence of multiple factors that delay cardiac repolarization. Electrolyte imbalance and

comedication with QT-prolonging drugs (eg AZM) are obvious but it is also worth considering the extent to which HCQ-induced small increases in QTc interval are potentiated by increased levels of IL-6. Furthermore, there are also a number of explanations to account for low prevalence of proarrhythmia despite high frequency of proarrhythmic prolongation of QT interval. The data emphasize not only an imperfect correlation between the two but also raises the possibility of other poorly understood proarrhythmia-mitigating mechanisms in COVID-19 patients. The observed low frequency of ventricular tachyarrhythmias or TdP in COVID-19 patients receiving HCQ ± AZM, also reflects the success of monitoring strategies and timely discontinuation of therapy in patients who develop QT interval prolongation.

Completed clinical trials investigating HCQ efficacy have such limitations that it is by no means given that the risk outweighs the potential benefit of higher more appropriate doses of HCQ. The potential role of IL-6 in modifying cardiac repolarization also suggests that the risk in mild-to-moderate cases of COVID-19 may be small, if at all, and possibly greater in those with severe disease.[67,73] Importantly, the risk can be well managed by careful monitoring of ECGs and other proarrhythmia risk factors and a number of authors have proposed monitoring strategies for COVID-19 patients during the clinical use of HCQ/AZM.[67,99-103] Important factors to bear in mind when computing QT-related risk are the way QT interval is measured and then corrected for heart rate. All the five studies in Table 3 used Bazett's correction. Following their study of the QT liability of HCQ/AZM in COVID patients, Bun et al[104] reported an average −20 ms difference between average baseline automated QTc and manual QT measurements (Bazett's correction). The agreement was perfect when using Fridericia's correction. One study in COVID-19 patients treated with CQ reported that CQ induced a mean prolongation of 75 ms for the computerized interpretation and 43 ms for the manually calculated QTc interval and that 19 of the 30 patients unnecessarily had their treatment prematurely discontinued or had their dose adjusted due to a prolonged QTc interval based on the computerized interpretation of the ECG.[105] Thus, manually measured QT interval, corrected by Fridericia correction, may be the most appropriate to compute the potential risk of a proarrhythmia.

Davis et al[9] identified 31 large registered randomized trials with a target sample size of at least 1000 participants, grouped into four categories (prophylaxis and treatment of outpatients with mild COVID-19 and treatments of hospitalized patients with moderate and moderate-to-severe COVID-19 disease). HCQ was the most common therapeutic agent studied in 24 of these 31 trials, with potential total sample size of over 25 000 participants. In the wake of the results from the RECOVERY trial, the current status on the use of HCQ in these and other ongoing trials is unknown.

5 | WHAT IS NEW AND CONCLUSIONS

It is questionable whether the ongoing clinical trials will shed any further helpful light on the safety, efficacy and risk/benefit of CQ and HCQ in combating COVID-19 infection. At the doses used, the findings from the therapeutic RECOVERY trial[35] and the prophylaxis study by Boulware et al[45] are not encouraging. On the balance of probability, unless higher doses are tested in ongoing trials, there appears little cause for optimism in repurposing either CQ or HCQ, with or without AZM, to fight COVID-19 pandemic. The resulting discontinuation of HCQ from major large studies effectively marks the end of repurposing CQ or HCQ for combating COVID-19 infection but doubts will linger as to whether the doses used hitherto had an optimal risk/benefit balance. Failure to determine an optimal therapeutic dose and risk/benefit balance has frustrated numerous previous attempts at repurposing old drugs.[1]

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