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Literature Review

Revisiting cardiac safety of hydroxychloroquine in rheumatological diseases during COVID-19 era: Facts and myths

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Abstract

Severe acute respiratory syndrome coronavirus 2 has spread across the globe affecting more than 10 million people as of August 2020. With the pandemic spreading at such an alarming rate, a lot of efforts are in the process of identification of an effective treatment at it's earliest. Hydroxychloroquine (HCQ) is such a drug that is being studied as a repurposed agent, although the early results are still inconclusive. However, an important adverse effect that has raised concerns in the recent times is its possible cardiac toxicity, mainly the 'QT,' prolongation in electro-cardiogram, which has created a sense of apprehension for its use in traditional indications like rheumatological conditions. In decades of HCQ use by rheumatologists, this cardiac toxicity was rarely ever seen. So, what is different in the current coronavirus disease 2019 (COVID-19) era? This review outlines various studies on HCQ reporting cardiac adverse events in patients with rheumatic diseases as well as, in patients with COVID-19 infection. In addition, two important observations were noticed; first, the doses that have been used in the current COVID-19 scenario are much higher than what are used in rheumatology. Second, COVID-19 infection may by itself lead to intrinsic cardiac abnormalities, which is probably acting as a confounder. Most of the available and credible data suggest that HCQ is a safe drug, including the RECOVERY trial stating no cardiotoxicity by HCQ. This review reinforces the safety profile of HCQ in a data-driven manner and addresses the concerns of the physicians. However, its cautious use in those with pre-existing cardiac abnormalities cannot be overemphasized.

Keywords: Hydroxychloroquine, arrhythmias, coronavirus disease 2019, cardiotoxicity

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Introduction

Hydroxychloroquine (HCQ) and chloroquine (CQ), initially used as antimalarial agents, have now become the backbone drugs of many rheumatic diseases, such as systemic lupus erythematosus (SLE), for many years. HCQ is a 4-aminoquinole, which has an extra hydroxyl group in contrast to CQ. Although these drugs are generally safe, they have certain toxicities, of which the extremely rare cardiac toxicity can be life-threatening. This specific toxicity, which was not very commonly heard of, has now gained momentum in the current coronavirus disease 2019 (COVID-19) era. Much speculation in this regard has created a sense of fear among the patients and physicians alike in using HCQ and CQ for the routine rheumatological conditions. Does it warrant a renewed look at this drug, which has survived 4 decades of clinical practice, or is it a false alarm? These issues have been elucidated in this article after reviewing the currently available evidence.

Severe acute respiratory syndrome coronavirus 2

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes COVID-19 has spread across the globe with more than 30 million cases, claiming more than half a million lives so far and still counting (1).

COVID-19 was first identified in patients with severe respiratory disease in Wuhan, China (2). SARS-CoV-2 primarily infects the ciliated bronchial epithelial cells and type II pneumocytes, where it binds to the surface receptor, angiotensin-converting enzyme 2 (ACE2), through S glycoprotein found on its surface (3). The antiviral and anti-inflammatory mechanisms of actions of HCQ are elucidated in Figure 1. Currently, other than remdesivir (4), which has shown numerical reduction in time to clinical improvement in the treatment of COVID-19, there are no specific antiviral treatments or vaccines available for COVID-19. Treatment options are mainly focusing on symptomatic and respiratory support according to the protocols issued by the local health authority in each country. This highlights the need for rapid research into new therapies. Drug repurposing is one such quick fix in such situations. It basically utilizes the mechanism of action of the drug

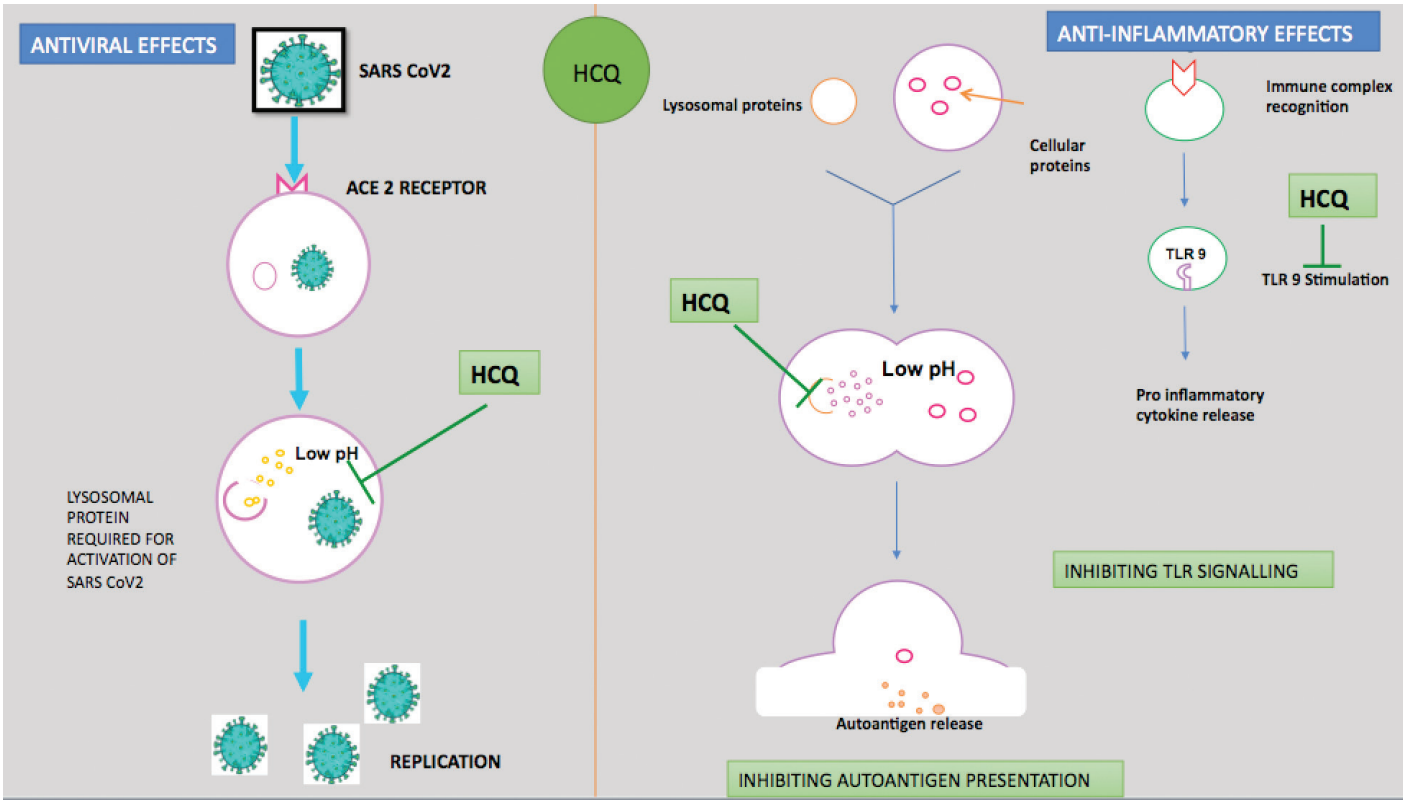

Figure 1. Mechanisms of action of HCQ.

to treat diseases with similar pathological basis. Although drug repurposing is a viable option, this process is actually complicated, involving a careful assessment into its adverse effects in the newly indicated condition. Antimalarials (HCQ and CQ) are one such group of drugs that has gained widespread attention in this COVID-19 era.

How does HCQ act in immune-mediated pathologies and COVID-19?

HCQ is an alkalinizer of the cytosol preventing antigen presentation to T cells, thereby restricting the immune-mediated inflammatory mechanisms. HCQ and CQ are also potent inhibitors of autophagy and cell death (5). They also interfere with the glycosylation process of ACE2 and can interrupt the binding of SARS-CoV-2 virus to its receptor ACE2 (6). The initial *in vitro* studies from China suggested a potential role of HCQ in preventing the viral replication (7). Apart from direct antiviral actions, HCQ increases the intracellular pH, as mentioned earlier, and inhibits lysosomal activity in the antigen-presenting cells, including plasmacytoid dendritic cells. This causes an anti-interferon effect crucial in containing the immune-mediated pathologies. A French nonrandomized trial showed that nasopharyngeal clearance of the virus in patients receiving HCQ plus azithromycin, HCQ alone, and the control group were 100%, 57.1%, and 12.5%, respectively, on day 6 (8). Multiple studies have been reported subsequently, and many randomized clinical trials (RCTs) are still in progress, yet the claim of effectiveness is far from being conclusive. Over and above, an important concern that has come into the news is the suspected cardiac toxicity of HCQ when a man in Arizona self-medicated with high-dose CQ, fearing of catching COVID, and died after ingesting it (9). Similar cases of CQ poisoning have been reported in Nigeria as well (10). This has created a sense of apprehension amongst the healthcare workers regarding prescribing HCQ for rheumatological conditions. This aspect of potential cardiac toxicity attributable to HCQ is discussed in the following sections.

Main Points

- The risk of cardiac toxicity from HCQ in rheumatological diseases is low as per currently available evidence.
- Risk stratification needs to be done, and caution needs to be exercised only in high-risk populations.
- As per published data, HCQ was prescribed amongst patients with COVID-19 at much higher dosage than what is recommended for rheumatic diseases; this factor as well as cardiac injury due to the disease per se might be responsible for reports of higher cardiovascular events.

Is HCQ cardiotoxic?

A literature search in the electronic databases of PubMed, Scopus was performed using the terms "hydroxychloroquine," "Chloroquine," "COVID-19," "rheumatic diseases," "rheumatoid arthritis," "systemic lupus erythematosus," and "connective tissue disorders," over the last 20 years, to identify relevant publications of patients with rheumatic diseases and cardiac safety while on antimalarials. Studies that addressed the concerns of cardiac safety were selected for this review. The implicated cardiac effects range from simple conduction abnormalities to cardiomyopathy (11), life-threatening ventricular arrhythmias, and torsades de pointes (TdT). It has been reported from previous studies that long-term use of CQ may increase depolarization length duration and Purkinje fiber refractory period, leading to malfunction of the atrioventricular (AV) node and Bundle of His (12). CQ blocks the open channel of the human ether-a-go-go related gene (hERG) 1A and 1A/1B potassium channel and thereby, it prolongs QT interval. CQ also binds to cardiac sodium, calcium, and inward rectifier potassium channels to potentially cause QRS widening and conduction abnormalities (13).

In 4 decades of experience with these drugs, rheumatologists rarely encountered such complications. Moreover, these drugs have survival advantage in lupus and have actually been reported to be cardioprotective in lupus (14).

Table 1. Studies on cardiac complications and HCQ in rheumatological conditions.

Study	Type	Number of participants	Dosing	Conclusion
Wozniacka et al. (27)	Prospective	28	250 mg, CQ	No abnormality
Teixeira et al. (14)	Prospective	317	NA	Protective
Costedoat-Chalumeau et al. (30)	Observational	85	400 mg, HCQ	No abnormality
Costedoat-Chalumeau et al. (31)	Case control	133	400 mg, HCQ	No abnormality
Eljaaly et al. (32)	Meta-analysis	9 RCTs, 916	200-400 mg, HCQ	No cardiac AE
Chatre et al. (33)	Systematic review	127 patients	Cumulative dose 1,235 g for HCQ, 803 g for CQ	85% had conduction abnormalities*

*These are preselected case series of cardiac abnormalities from data of 127 patients belonging to 86 case reports and few small series.
RCT: randomized controlled trial; CQ: chloroquine; HCQ: hydroxychloroquine; NA: not applicable; AE: adverse event.

We discuss the available data on these drugs in relation to their actions in rheumatological diseases and COVID-19, and we try to address these controversies with biological and data-based facts.

Data on cardiac adverse events of HCQ in patients with COVID-19 infection

The initial concern of this adverse event was reported from the study published in Lancet, which showed that HCQ alone or in combination with macrolides was associated with increased frequency of ventricular arrhythmias, when used for treatment of COVID-19 (15). The article was, however, later retracted, because the authors were unable to comply with the audit of the data from an independent body. The retraction notice in The Lancet reads: "As a result, they have concluded that they can no longer vouch for the veracity of the primary data sources." (16). In an observational study conducted on 19 patients by Hor et al. (17), it was seen that QTc interval prolongation occurred even in patients with COVID-19 infection prescribed with short-term (5 days) course of HCQ and azithromycin in combination. However, more than one-third of the patients in that study had pre-existing comorbidities. A systematic review and metaregression analysis, which was yet to be peer reviewed at the time of writing this article, showed that among 13 studies of 4,334 patients, the pooled incidence of discontinuation of CQ or HCQ due to prolonged QTc and QTc 500 ms were 5% (95% confidence interval [CI], 1-11) and 6% (95% CI, 2-12), respectively (18). An observational, retrospective study used VigiBase®, the World Health Organization pharmacovigilance database, which compared the adverse drug events in patients who received HCQ, azithromycin, or their combination (19). HCQ was reported to be associated with conduction disorders (AV and bundle branch blocks) and heart failure in patients with severe COVID-19 infection. The proportion that resulted in death for Torsades de pointes/Ventricular Tachycardia (TdP/VT) cases was 8.4% (7/83) with HCQ. However, because the data on the total population could not be obtained in Vigibase, the exact incidence could not be found. A randomized, phase IIb clinical trial conducted by Borba et al. (20) evaluated the effect of high doses (600 mg/day twice daily for 10 days) versus relatively lower doses (450 mg twice daily on first day and then once daily for 4 days) of CQ diphosphate in patients with SARS-CoV-2 infection. They observed that 7 out of 37 patients in the high-dosage group had QTc interval greater than 500 ms than that in 4 out of 36 patients in the low-dosage group. This highlights a significant role of dose-dependent cardiotoxicity. Chorin et al. (21) conducted a retrospective study in 84 patients with COVID-19 infection treated with a combination of HCQ and azithromycin; 11% of these patients had their QTc increased to >500 ms (baseline average of 447±30 ms to 527±17 ms [$p<0.01$]).

Most recently, RECOVERY study has proven that HCQ did not increase cardiac complications in COVID-19 cases despite using 4 times higher dosage than that used by rheumatologists.

Data on cardiac adverse effects of HCQ in rheumatic diseases

CQ and HCQ have been a part of treatment in many rheumatic diseases. They constitute a part of treatment regimens for rheumatoid arthritis (22), SLE (23), antiphospholipid syndrome (24), and primary Sjögren syndrome (25). In SLE, HCQ is known to prevent flares and promote the long-term survival (26). A study performed on 28 patients with SLE (27), which assessed the cardiotoxicity after 7 months of daily CQ intake, found no conduction abnormalities. All the patients had tendency to tachycardia, but no significant differences in the mean heart rate were found before and after CQ administration. Some studies, in fact, have described the protective role of CQ from cardiac arrhythmias by an unknown immunomodulatory mechanism of action (14, 28). Cardiac complications, including arrhythmias, are not rare in lupus (29), and improvement in disease activity by treatment regimen, including immunosuppressants along with CQ, contributes to containing these arrhythmias. Although it is not certain if this cardioprotective effect was due to other immunosuppressants or CQ, it is certain that controlling disease activity clearly contributes to containing these arrhythmias, rather than causing or worsening them. Similarly, in a study of 85 patients with connective tissue diseases treated with HCQ for 1 year, only 3 patients had features of conduction blockade, the prevalence of which was similar to general population (30). An RCT conducted in pregnant patients also did not show significant differences in the QTc interval among the patients in the HCQ group when compared with controls (31). The only published recent meta-analysis on 9 RCTs also did not show any significant adverse cardiac outcomes owing to treatment with HCQ (32). However, a systematic review of literature (33) involving 127 patients' data from 86 case reports and few small case series reported some cardiac conduction abnormalities in 85% of the patients, with 12.5% of them having irreversible damage. That review, however, included preselected, small, skewed, and potentially biased case reports, presenting with cardiac complications in both rheumatological and nonrheumatological settings, and the patients had a median time to follow-up of 7 years. It was also not certain, however, if these complications were inherently due to the underlying disease itself. Therefore, the quality of that review of case reports places it in the lowest level of evidence and should be interpreted with caution. In another study performed by Tselios et al. (34), it was seen that about 10% of patients with SLE had elevated levels of myocardial biomarkers in the absence of previous cardiac disease; however, they were older

(mean age, 54.7 years) patients with longer disease duration (in years, mean±standard deviation [SD], 22.54±10.44), and they received high cumulative dose of HCQ (in grams, mean±SD, 1251±883). In the absence of well-powered, well-designed randomized controlled trials, the exact attribution of CQ and HCQ to conduction anomalies is difficult to be established. Table 1 summarizes few studies in relation to HCQ-related cardiac toxicities.

Dosing differences of HCQ in patients with COVID-19 infection

Logical explanation for discrepant data in COVID-19 scenario includes the higher dosages of HCQ used in COVID-19 trials in contrast to what has been used in rheumatological settings (maximum of 5 mg/kg of real body weight/day); and the basis for these higher doses used in COVID-19 scenario is not known. As discussed earlier, dose-dependent cardiac toxicity is known in antimalarials, such as CQ. Studies have also demonstrated some reduction in the resting heart rate with increasing cumulative dose of HCQ (35).

COVID-19-induced cardiac injury is common, and HCQ may not be solely responsible for it

Multiple mechanisms cause cardiac complications in patients with COVID-19 infection. Most important of them include the cytokine surge, which causes a proinflammatory state and direct injury to the myocytes (36). Direct myocardial injury by the virus, altered myocardial demand-supply ratio, plaque rupture, and coronary thrombosis due to hypercoagulabity are the other mechanisms described in COVID-19, leading to serious cardiac complications (37). In a single-center study on 417 patients, 17% of the patients had elevated troponin I levels at the time of admission (38). Guo et al. (39) in another study reported elevated troponin I levels in 27.8% of 187 patients. A study performed in Wuhan revealed cardiac injury, shock, and arrhythmia in 7.2%, 8.7%, and 16.7% patients, respectively, in their cohort of 139 patients with COVID-19 (40). There was also a study on significantly higher incidence of acute cardiac injury among patients with severe COVID-19 infection admitted in the intensive care unit (ICU) than those not admitted to the ICU (severe patients: RR=13.48; 95% CI=3.60–50.47; Z= 3.86; and p=0.0001) (41). Myocardial damage and cardiac failure contributed to 40% of deaths in the Wuhan cohort, either exclusively or in combination with respiratory failure (42). Patients with cardiac complications in COVID-19 can present with arrhythmias, ranging from sinus tachycardia and bradycardia to asystole. Palpitations are reported in 7.3% of patients, more in the critically ill patients (43). Acute coronary syndromes can also occur in COVID-19 as evidenced by elevated D-dimer levels, similar to such reports in the past after viral epidemics, such as influenza (44). There are also no credible data on the prevalence of prolonged QTc in patients with COVID-19. Safety of HCQ, thereby, may be reassured by assessing the baseline risk of QT prolongation. A risk score has been derived and validated by Joyce et al. (11), for prediction of drug-associated QT prolongation among hospitalized patients in a cardiac care unit. The risk factors that may predispose the patients to conduction abnormalities are older age, longer duration of medications use, cumulative dose, use of CQ instead of HCQ, pre-existing heart disease, and renal failure. Therefore, this may not be much of a concern in a young healthy patient with no comorbidities, although caution may be applied while using HCQ in elderly patients with underlying heart condition. A small study conducted by Yetkin et al. (45) suggested that it may be a reasonable approach to administer mexiletine and lidocaine in patients with COVID-19 infection with a QT interval exceeding 500 ms to complete the course of HCQ plus azithromycin treatment.

Conclusion

Risk of cardiac toxicity of HCQ according to four decades of data from rheumatology literature and real-life experience is extremely low as per the currently available evidence. However, it should be always in the back of the mind, mainly for the high-risk population considering the recently documented risks. Patients need to be reassured by the healthcare providers regarding the risk versus benefit ratio of HCQ in rheumatological diseases; however, under the current scenario, physicians can use the risk stratification strategy to render objective strength to their prescription habit. This may be achieved by a detailed history, clinical examination, and screening of high-risk individuals with an electrocardiogram and avoiding HCQ in those with risk or underlying cardiac rhythm abnormality.

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