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PERSPECTIVES IN RHEUMATOLOGY

Hydroxychloroquine in the post-COVID-19 era: will this pandemic upset decades of clinical practice?

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Abstract
In the early stage of the COVID-19 pandemic, Belgian health authorities endorsed the interim guidelines for the treatment of COVID-19 pneumonia: hydroxychloroquine (HCQ) recommended for treatment of hospitalized patients with moderate to severe disease. As a growing number of patients were admitted, inevitably, our internal medicine team questioned the efficacy and safety of HCQ, especially with regard to cardiac side effects. In parallel with our concerns, data regarding the safety and efficacy of HCQ were published, with discordant results and debate in the medical community. Media coverage of the possible risks and benefits of HCQ use in COVID-19 also caused confusion amongst the public. In this *Perspectives in Rheumatology* article, we review the use and safety of HCQ in autoimmune disease and its putative efficacy and toxicity in COVID-19. Finally, we share our concern about the future of this widely used and inexpensive drug after the COVID-19 pandemic has passed.

Keywords Autoimmune disease · COVID-19 · Hydroxychloroquine · Systemic lupus erythematosus · Toxicity

Introduction

In the early stage of the COVID-19 pandemic, in March 2020, Belgian health authorities endorsed the interim guidelines for the treatment of pneumonia: hydroxychloroquine (HCQ) was recommended for COVID-19 hospitalized patients with moderate to severe disease. The regimen included HCQ at the dose of 400 mg twice on day 1 followed by 200 mg twice daily from day 2 to day 5. Our teaching hospital of 1000 beds set up dedicated COVID-19 wards, and a growing number of patients were admitted. Inevitably, questions arose within our teams of internal medicine and infectious disease specialists about the efficacy and safety of HCQ, especially of possible cardiac side effects. Two main questions were as follows: Does it work? And, at the dosage used, could it be toxic? These two issues prompted heated debate. The internal medicine group was confident that the drug was safe at the dosage they used, confidence that was probably based on their long experience of using it for the treatment of the common autoimmune disorders (systemic lupus erythematosus, primary Sjögren's syndrome, and sarcoidosis). However, infectious disease colleagues had reservations about the risk of prolonged corrected QT interval (QTc), mostly over HCQ used in association with antibiotics such as quinolones and macrolides (azithromycin). An electrocardiogram performed prior to the start of each treatment was made compulsory. Neither the internal medicine nor the infectious disease specialists, though, had witnessed a case of sudden death due to torsade de pointes linked to the use of HCQ.

Review of the literature on significant adverse effects linked to HCQ usage also was reassuring. For COVID-19, the use was off-label, having at heart the "Do no harm" principle. Nevertheless, we had to consider the context in which we were treating patients at the height of this new disease, with little known about how to prevent fatalities.

Now, with the flattening of the first wave of COVID-19, we have real-life data from our cohort of patients treated with HCQ, with or without azithromycin. Given at the recommended dose from a standard protocol (short, 5-day duration; baseline ECG prior to starting treatment; control ECG during combined treatment; and blood monitoring and correction of electrolyte disturbance), we have not noticed a concerning number

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of cardiac-related events directly attributed to the above-mentioned medications [1]. We remain confident about the safety of HCQ, but we were not able to answer the question of its efficacy.

HCQ and autoimmune diseases

For more than 50 years, HCQ has been the main treatment of the commonest autoimmune diseases: systemic lupus erythematosus (SLE), primary Sjogren's syndrome, rheumatoid arthritis, antiphospholipid syndrome, and sarcoidosis. Its immunomodulatory properties are the mainstay to prevent flare-ups and promote long-term survival.

The proposed mechanisms of HCQ's action are based on in vitro studies; their link with clinical efficacy has not been elucidated. In summary, HCQ increases the pH of lysosomes and other intracellular compartments, leading to interference in phagocytosis, change in antigen presentation, and interference with Toll-like receptor 7 and 9 signalling pathways. HCQ also blocks T cell response and reduces production of pro-inflammatory cytokines (INF-gamma, TNF, IL-1, and IL-6). Finally, it stimulates nitrite oxide production by endothelial cells to produce an anti-thrombotic effect by inhibiting platelet aggregation and acting on antiphospholipid antibodies [2, 3].

The clinical benefit of HCQ has been largely demonstrated in SLE, with proven control on disease activity; decrease in flare-ups, particularly during pregnancy and breastfeeding; reduction in thrombotic events; and reduction in mortality [2, 3]. Use of HCQ in SLE has also been associated with reduction in the rate of cardiovascular complications, lowering of fasting glucose levels, and improvement in lipid profile [2, 3]. HCQ is, therefore, amongst the most recommended treatments for SLE worldwide [4]. In rheumatoid arthritis patients, HCQ has had a significant effect on controlling the disease in its early and mild forms [5]; as in SLE, improvement of lipid profile and insulin resistance have been demonstrated [3], alongside a reduction in cardiovascular events [6].

Several retrospective studies have reported HCQ to be protective against infections. It was associated with a 16-times decrease in major infection risk in the Lupus-Cruces cohort [7] and an odds ratio of 0.05 in favour of HCQ in a Dutch cohort of SLE patients [8]. This association has been observed also amongst rheumatoid arthritis patients [9]. One explanation for this protective effect could be that HCQ exerts in vitro properties against viral, bacterial, and even fungal pathogens by way of the aforementioned actions (increase in lysosomal and phagolysosomal pH and interference with antigen presentation) but also by protein glycosylation that prevents viral shedding [10]. Another explanation would correlate this protective effect to patients treated with HCQ having a mild form of the underlying autoimmune disease, thus not relying on other immunosuppressive treatment [8].

Hence, HCQ is strongly recommended in the management of the prominent autoimmune diseases, such as SLE, rheumatoid arthritis, antiphospholipid syndrome, and primary Sjogren's syndrome (articular manifestations), and as part of the management of sarcoidosis (pulmonary, articular, or cutaneous). The usual dose is 200 to 400 mg/day, with a maximum dose of 5 mg/kg/day.

Toxicity/safety of HCQ in autoimmune diseases

HCQ is considered mainly an immunomodulator rather than an immunosuppressive drug, and it has a good safety profile. The most common adverse effects are gastrointestinal symptoms (nausea, diarrhoea, and abdominal discomfort). To prevent these adverse effects, HCQ is best taken during meals [2, 3].

The most severe toxicity related to HCQ is retinopathy associated with long-term use (more than 12 months) and the cumulative dose effect. HCQ causes lipofuscin accumulation in retinal pigment epithelium due to lysosomal degradation of the external receptor [11]; the result is circular defects known as "bull's eye maculopathy." Unfortunately, the retinopathy can progress for several months, even after discontinuation of treatment. Appropriate dosage (< 5 mg/kg/day) alongside usage of advanced screening modalities of ocular toxicity can prevent the occurrence of this adverse effect.

Other less frequent adverse outcomes with HCQ, such as myopathy (with proximal muscle weakness or atrophy, but typically without myalgia or increased muscle enzymes), have been reported with HCQ use. Improvement can be achieved by discontinuing the drug [3, 12]. Cutaneous and neurological toxicity also have been reported [3]. Finally, cardiac toxicity has occurred, ranging from rhythm disorders to cardiomyopathy [2, 3]. Patient's age, duration of use, pre-existing heart conditions, use of high doses, and renal failure are aggravating risk factors for cardiotoxicity [3]. HCQ can cause long-QT syndrome due to blockade of the Kv11.1 (hERG) channel [13]. The clinical manifestation of the electrical disturbance of the heart (syncope and torsade de pointes) mostly occurs with long-term use; simultaneous use of other long-QTc medications (azithromycin, quinolones, and others); electrolyte disturbance; renal failure; or an acute overdose. Before the pandemic, one case of ventricular arrhythmia due to HCQ used alone had been reported [14]. McGhie et al. [15] reported 453 SLE patients with 0.7% cases of prolonged QTc with no ventricular arrhythmia. Unpublished post-marketing data from Sanofi (n = 21,446) related 137 adverse drug reactions (0.64%) of cardiac nature, with 19 torsade de pointes (0.09%) with 1 fatal outcome; this result is consistent with the US Food

and Drug Administration database (FAERS) analysis of 1968 to early 2020, in which 57 HCQ-linked adverse events were recorded, with 10 deaths attributed to cardiac arrhythmias (torsade de pointes and prolonged-QTc syndrome) [16].

HCQ in the treatment of autoimmune diseases is considered one of the safest uses of the drug. Ordinarily, patients are followed clinically and biologically on a regular basis, e.g., every 3 to 6 months, and educated on their disease and treatment. Common recommendations for HCQ treatment include regular screening for retinal toxicity (every 6 months) and physical examination with attention to muscle strength and reflexes. HCQ should be avoided in patients who have congenital long-QT syndrome or persistently corrected QT measurements > 500 ms, and who are taking other drugs that prolong the QT interval; consideration should be given to discontinuing these drugs [3].

HCQ in COVID-19 disease

As reported [10], HCQ has in vitro activity against pathogens, either bacterial, fungal, or viral, including in vitro activity against SARS-CoV-2 [17]. However, HCQ's antiviral effects were not evident in life-like models of infection with human respiratory cells. Also, no therapeutic benefit was derived in a SARS-CoV-2 infection model in hamsters and non-human primates [18]. Through other mechanisms of action, though, HCQ may be effective in treating the second phase of COVID-19, that is, a syndrome characterized by a "cytokine storm" involving an IL-6 and interferon response, thrombotic events, and endothelial dysfunction [19].

HCQ was used for the first time in China at an early stage of the pandemic in a small randomized controlled trial of 62 patients to improve pneumonia regression and reduce the recovery time [20]. HCQ then was included in national recommendations in many countries as part of the strategy to fight the pandemic. Table 1 lists the main studies where HCQ was used in the treatment of COVID-19, e.g., retrospective studies of more than 1000 patients and randomized controlled studies [21–40]. Whilst most retrospective studies reported clinical improvement with HCQ, randomized controlled studies were stopped because of inefficacy and, eventually, a tendency towards increased overall mortality. The discrepancies between the retrospective studies and the randomized controlled studies have not been explained. HCQ doses were higher, particularly in the Recovery and Solidarity HCQ arms [36, 38], than in retrospective studies, but this was not the case in the Orchid or Cavalcanti trial [37, 39]. Another possible explanation could be differences in the time of initiation of HCQ treatment; in the Recovery trial, the median time between symptom onset and randomization was 9 days, with 16.7% of patients already on mechanical ventilation at randomization. In contrast, HCQ was initiated within the first day after admission in the Catteau and Lammers studies [25, 30].

On July 4, 2020, the World Health Organization announced that it had stopped HCQ and lopinavir/ritonavir arms in their clinical trials, Solidarity and Discovery, respectively. The conclusion was that both drugs added little or no benefit in reducing mortality. HCQ now is not being used in the treatment of COVID-19, but it remains a subject of debate [41].

Cardiac toxicity of HCQ in COVID-19 disease

Published safety data on HCQ use in COVID-19 have also revealed discordant results: Mercuro et al. [42], without comment regarding efficacy, found that 19% of 90 patients had prolonged QTc, and "one torsade de pointes" occurred. Gerard et al. [43] reviewed the French Drug Agency reports of adverse drug reaction at an early stage of the pandemic and found 103 of 120 cases of cardiac adverse drug effect linked to HCQ; within the 131 reported effects, 3.0% were sudden or unexplained deaths, 6.1% were ventricular arrhythmias, and 68.7% were prolonged QTc. In contrast, most retrospective studies reported no adverse effect of HCQ, although QTc prolongation was present in some subjects (Table 1). In particular, the Rosenberg cohort [32] had an increase in arrhythmias (16% vs 10%) and almost 2 times more cardiac arrests in the HCQ arm (13% vs 6.8%). In the large-scale cohort study by Mehra et al. [35], published in *The Lancet* (retracted), an increase in arrhythmia risk was also described, with 6.1% of patients with de novo ventricular arrhythmia.

Once again, an increase in cardiac events was not substantiated in randomized controlled studies (Table 1). Similarly, the prospective study of Gasperetti et al. [44] of 649 COVID-19 patients treated with HCQ, either at home, in hospital, or in ICU, found no increase in arrhythmia-related cases or deaths despite a relative increase in prolonged QTc. Interestingly, in that study, baseline QTc length and fever at admission were the most important determinants of QT/QTc prolongation [44].

What could contribute to higher risks of cardiac events with HCQ treatment of COVID-19 than with autoimmune disease? First, SARS-CoV-2 infection itself can injure cardiac myocytes, leading to arrhythmic events. Indeed, the results of early studies suggested that COVID-19 is associated with a high incidence of cardiac arrhythmias. Bhatla et al. [45] reported that amongst 700 patients (11% received ICU care), 9 cardiac arrests, 25 incident atrial fibrillation events, 9 clinically significant bradyarrhythmias, and 10 non-sustained ventricular tachycardia events occurred. Second, electrolyte disturbances, e.g., hyperkalemia or acute kidney injury, frequently occur during the disease [46]. These abnormalities directly increase the risk of arrhythmia by potentializing the QTc

Table 1 Main studies of HCQ in COVID-19 (retrospective observational studies of > 1000 patients, or randomized controlled trial) regarding efficacy

Authors/journal/date	Study type	*N* patients (*N* HCQ)	Severity	HCQ dosage	Outcome	Toxicity	Comment
Bernaola et al. MedRxiv Jul 2020 [21]	Retrosp. multic. (Madrid)	1645 (1498)	Hospit.	Unspecified	Decrease in mortality before and after propensity matching	Not reported	
Million et al.Travel Med Infect Dis May–Jun 2020 [22]	Retrosp. monoc.	1061 (1061)	Hospit. and "day-care"	600 mg/day 10 days	4.6% poor clinical outcome (ICU transfer, death, hosp > 10 days)	25 mild AE, not serious	+ AZM
Sbidian et al. MedRxiv Jun 2020 [23]	Retrosp. multic.	2738 (623)	Hospit.	Unspecified	Discharge rates higher in HCQ group but no difference in mortality after regression analysis	Not reported	
Yu et al.Sci Ch Life Sci Aug 2020 [24]	Retrosp. monoc.	2882 (278)	Hospit.	400 mg/day 7–10 days	Biological improvement (IL6, troponin), decreased mortality in patient with cardiac injury	Not reported	
Catteau et al.Int J Antimicrob Ag Aug 2020 [25]	Retrosp. multic. nationwide	8075 (4542)	Hospit.	2400 mg over 5 days	Lower mortality in HCQ group	Not reported	
Di Castelnuovo et al. CORIST study Europ J Int Med Aug 2020 [26]	Retrosp. multic. observ.	3451 (2634)	Hospit.	400 mg/days 5–15 days	30% reduction in the risk of death in patient HCQ	Not reported	
Arshad et al. Int J of Inf Dis Jun 2020 [27]	Retrosp. multic. observ.	2541 (1202)	Hospit.	2800 mg (400 mg ×2 d1, 200 mg ×2 d2–d5)	13.5% mortality HCQ group vs 26% usual care	No torsade de pointes, but QTc prolonged	
Lagier et al.Travel Med Infect Dis Jun 2020 [28]	Retrosp. monoc.	3737 (3119)	Hospit. and "day-care"	600 mg/day 10 days	Association decreased risk of ICU transfer, risk of extended hospitalization and risk of death	No torsade de pointes, no sudden death, 25 patients QTc prolongation, 12 discontinuation (3 patients > 500 ms)	+ AZM
Ayerbe et al.Int and Emerg Medicine Sept 2020 [29]	Retrosp. multic. observ.	2075 (1857)	Hospit.	400 mg ×2 d1, 200 mg ×2 d2–d6	Decreased mortality after adjustment for confounding values	Not reported	
Lammers et al.Int J Inf Diseases Sept 2020 [30]	Retrosp. multic. observ.	1046 (189)	Hospit.	Mean cumulative 1800 mg	No effect on mortality, significant decreased risk of ICU (− 53%)	Not reported	
Ip et al.Plos One Aug 2020 [31]	Retrosp. observ. cohort study	2512 (1914)	Hospit.	Majority 400 mg ×2 d1, 200 mg ×2 d2–d5	No significant difference in survival between groups	Prolonged QTc leading to discontinuation of HCQ in 4%, arrhythmias leading to discontinuation in 2%, but arrhythmia reported in 5% HCQ vs 4% non HCQ; 1% cardiomyopathy in both groups	
Rosenberg et al. JAMA May 2020 [32]	Retrosp. multic. cohort study	1438 (271)	Hospit.	Unspecified	No significant difference in mortality between groups	14.4% prolonged QTc vs 5.9% neither drug, 16.2% arrhythmias vs 10.4%, more cardiac arrest in HCQ + AZM (15.5%) and in HCQ group (13.7%) vs 6.8%	
Singh et al. Medrxiv May 2020 [33]	Retrosp. multic. cohort study	3372 (1125)	Hospit.	Unspecified	No significant differences after propensity score matching	Not reported	+AZM in 799
Geleris et al. NEJM Jun 2020 [34]	Retrosp. monoc. observ.	1376 (811)	Hospit.	600 mg ×2 d1, 400 mg ×2 d2–d5	No differences in terms of death and intubation	Not reported	
		2186 (538)	Hospit.	Unspecified		Not reported	+AZM

Table 1 (continued)

Authors/journal/date	Study type	*N* patients (*N* HCQ)	Severity	HCQ dosage	Outcome	Toxicity	Comment
Rivera et al. (CCC19) Cancer DiscJul 20 [35]	Retrosp. multic. observ. cohort study				No difference in mortality after multivariable logistic regression; in combination with other drugs, associated with increased mortality		cancer
Mehra et al. LancetMay 2020 [35]	Retrosp. multic. observ.	90,032 (3016)	Hospit.	Unspecified	Increased mortality (HR 1,335)	Independently associated with increased de novo ventricular arrhythmia during hospitalization	*Retracted*
Horby et al. (RECOVERY) Oct 2020 [36]	Prosp. RCT blinded	4716 (1430)	Hospit.	800 mg h0, 800 mg h + 6, 400 mg h + 12, 400 mg ×2 until d9	No difference in mortality, worse discharge and ventilation rates for HCQ group; stop enrolment in HCQ arm	1 case of torsade de pointes, no differences in supraventricular tachycardia frequency, ventricular fibrillation or AV block requiring intervention	
Cavalcanti et al. NEJMJul 2020 [37]	Prosp. RCT open label	504 (221)	Hospit.	400 mg ×2 d1–d7	No effect on mortality, or clinical status at day 15	33.7% AE reported in HCQ vs 22% neither group, serious AE in 1% HCQ vs 1.1% in neither group, 14.7% QTc prolonged in HCQ	
Hongchao et al. (SOLIDARITY) MedRixvOct 2020 [38]	Prosp. RCT blinded	954 (11,266)	Hospit.	800 mg h0, 800 mg h + 6, 400 mg h + 12, 400 mg ×2 until d10	No difference in mortality, initiation of ventilation, and duration of stay	Not reported	
Self et al. ORCHID JAMA Nov 2020 [39]	Prosp. RCT blinded	242 (433)	Hospit.	400 mg ×2 d1, 200 mg d2–d5	No difference in survival, or time to discharge, stopped for futility	No significant difference in SAE	

Abbreviation: *AZM* azithromycin, *AV* atrioventricular, *d* day, *hospit*. hospitalized, *ICU* intensive care unit, *multic.* multicentric, *monoc*. monocentric, *observ.* observational, *prosp*. prospective, *RCT* randomized controlled trial, *(S)AE* (serious) adverse effect

prolongation induced by HCQ. Third, a cumulative effect of additional drug with the potential to prolong QTc may be another explanation (association of HCQ/azithromycin/lopinavir + ritonavir). This hypothesis is reinforced by the reported increase in cardiac arrest in the HCQ + azithromycin arm of the Rosenberg cohort [32].

HCQ, COVID-19, and autoimmune patients

In parallel with evaluations of the effect of HCQ in active COVID-19 disease, its use to prevent SARS-CoV-2 infection, as post-exposure prophylaxis or pre-exposure prophylaxis, has been studied. In studies of post-exposure prophylaxis, HCQ has not had a significant preventive effect: in a small, randomized trial of 821 high-risk contacts, asymptomatic patients, an absolute difference of only 2.4% of clinical infection between controls and HCQ-treated subjects was found [47]. Similar results were found in a cluster, randomized trial in Spain, with 2314 healthy contacts of 672 COVID-19 index cases [48].

Regarding pre-exposure prophylaxis, in a small double-blind placebo-controlled randomized clinical trial of 132 hospital health workers in the USA (terminated early), there was not a significant difference in incidence of SARS-CoV-2 between HCQ-treated subjects and placebo cohorts [49]. As the World Health Organization stopped recruitment into the HCQ arm in their major randomized controlled trial, the UK regulators authorized HCQ and CQ-related drugs to be given to healthcare workers in a clinical trial, the COPCOV. This trial would see chloroquine, hydroxychloroquine, or a placebo given preventively to more than 40,000 healthcare workers from Europe, Africa, Asia, and South America.

Evaluation of HCQ for prevention of COVID-19 in patients with autoimmune disease patients is an interesting approach, particularly in a supposed at-risk group. Gentry et al. [50] evaluated this potential preventive effect in a retrospective, 3-month study on 10,703 US veterans: compared with 21,406 propensity-matched patients, the HCQ group of patients had no significant decrease in SARS-CoV-2 infection risk (0.3% vs 0.4% rate of infection), with a nonsignificant OR of 0.79 (CI 0.51–1.20). There were also no differences in hospital admission, ICU requirement, or mortality associated with SARS-CoV-2 infection. But, without explanation, overall mortality during this 3-month period was significantly lower in the HCQ group [50]. Another retrospective observational study, of 6228 patients with autoimmune rheumatic diseases in China [51], found an overall rate of COVID-19 (0.43%) like that in the US study; the risk of COVID-19 was increased by age and rheumatic disease. After adjustment for age, sex, smoking, contact cases in the family, comorbidities, and SLE (as HCQ is more often prescribed in SLE patients), patients with rheumatic disease taking HCQ had a lower risk of COVID-19 than did those who were taking other disease-modifying anti-rheumatic drugs. By contrast, the rate of corticosteroid use in patients with COVID-19 was like that in patients free of COVID-19, around 50%. Finally, in a retrospective analysis of the Portuguese National Health System, including 26,815 SARS-CoV-2-confirmed patients, after adjustment for age, sex, and chronic treatment with corticosteroids and/or immunosuppressants, the odds ratio of SARS-CoV-2 infection for chronic treatment with HCQ was 0.51, also suggesting a protective effect of this drug [52]. Although there is suggestive evidence that autoimmune patients have benefited from the prophylactic use of HCQ during this pandemic, proper randomized clinical studies are needed.

Conclusion

During the COVID-19 pandemic, HCQ suffers the vagaries of fame. Almost adulated as promising treatment initially, the drug was eventually dismissed as controversial and toxic for patients. The media coverage of this subject has caused confusion amongst the public and within the medical community. In this context, what will be the use of HCQ after the COVID-19 pandemic? Will its use in other medical conditions, especially in autoimmune diseases, be affected? What should we expect when SLE patients or patients with other common autoimmune diseases are offered HCQ as a candidate drug? Will it be a negative answer, given the recent misleading publicity about its potential but still unproven toxicity? To correlate the above, we recall a recent encounter where a young male with a history of cutaneous sarcoidosis declined to be treated with HCQ because of the recent emphasis on its cardiac toxicity. As the place of HCQ in the prevention of treatment of COVID-19 is still inconclusive, in this *Perspectives in Rheumatology* article, we wanted to review the efficacy of HCQ in managing the main autoimmune diseases, HCQ's well-known safety profile, and monitoring recommendation in these conditions. We hope to restore the trusted relationship between patients and their practitioners regarding HCQ use for the management of the commonest autoimmune diseases.

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Compliance with ethical standards

Disclosures None.

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