



RESEARCH ARTICLE

Journal home page: www.jpadr.com

Safety of Hydroxychloroquine use for COVID-19 prophylaxis: A questionnaire-based pilot study in healthcare professionals

Pratibha Nadig^a, Vamsavardhan Reddy^b, Anupam Bhambhani^{c,*}, Ravikiran^d, Satyagama Suvarchala^a, Supriya Acharya^e

^a Department of Pharmacology, Vydehi Institute of Medical Sciences and Research Centre, Bangalore, Karnataka, India 560066.

^b Department of General Medicine, Vydehi Institute of Medical Sciences and Research Centre, Bangalore, Karnataka, India 560066.

^c Department of Cardiology, Vydehi Institute of Medical Sciences and Research Centre, Whitefield, Bangalore, Karnataka, India 560066.

^d Vydehi Institute of Medical Sciences and Research Centre, Whitefield, Bangalore, Karnataka, India 560066.

^e Department of Community medicine, Vydehi Institute of Medical Sciences and Research Centre, Bangalore, Karnataka, India 560066.

ARTICLE INFO ABSTRACT



Received 25 June 2021;
Revised 07 August 2021;
Accepted 21 August 2021.

Keywords:

Adverse drug reactions,
COVID-19
prophylaxis,
hydroxychloroquine,
SARS-COV-2

Introduction: Hydroxychloroquine (HCQ) was recommended for prophylaxis against SARS-COV-2 for the health care professionals by the Indian Council for Medical Research. **Objectives:** We conducted this study to explore the safety of Hydroxychloroquine in health care professionals.

Methods: A validated questionnaire was circulated electronically to the health care professionals, who were on HCQ as per ICMR recommended regimen. Questions on specific adverse drug reactions (ADRs) were asked along with other details. The participants were requested to upload the baseline and additional electrocardiograms (ECGs) taken during HCQ prophylaxis. Incidence, severity, causality (relatedness to the drug), expectedness, and seriousness of the ADRs were determined as per the standard guidelines. The ECGs were evaluated for the appearance of significant changes. The observations were analyzed through descriptive statistics. The ECG changes were compared using the Students t-test and the association of risk factors with the ADRs was evaluated using logistic regression analysis.

Results: ADRs were observed in 58 (46 %) of 126 participants. Gastrointestinal symptoms followed by headache and skin rashes were commonly observed. The ADRs were mostly mild to moderate in the category, non-serious, and possibly related to HCQ. Significant ECG changes were rare. Diabetes, hypertension, and the use of concomitant medication/s were the risk factors. Except for blurred vision, all the ADRs were unexpected in terms of frequency.

Conclusions: HCQ causes non-specific ADRs of mild to moderate degrees when used as prophylaxis. Though non-serious, almost all were unexpected. ECG changes are probably not frequent in the absence of a pre-existing disease.

An official publication of Global Pharmacovigilance Society.



* Corresponding Author

Anupam Bhambhani

E-mail: anupam.bhambhani@yahoo.in

Contact: +91 9986190006

* Copyright: 2582-7235 // © 2021 The Author(s).

Published by Global Pharmacovigilance Society.

This is an open-access article under the CC BY-NC-ND license.



Available online 1 September 2021

Introduction

The COVID-19 pandemic has resulted in several deaths across the globe. To bring about a rapid control of mortality and morbidity, several drugs were explored as repurposed drugs, Hydroxychloroquine (HCQ) being one of them. Its use is recommended for the moderate cases in the "Updated Clinical Management Protocol for COVID-19, version-5" that was published on July the 3rd 2020 by the Ministry of Health and Family Welfare, Government of India (MoHFW, 2020).

The HCQ use is approved by the Drug Controller General of India for various clinical conditions like Malaria, Rheumatoid Arthritis, and Systemic Lupus Erythematosus. Early in the pandemic, it was suggested as a possible preventive measure for Covid-19. This was based on its in-vitro antiviral activity against both 1 and 2 forms of the Severe-Acute-Respiratory-Syndrome Corona-Virus (SARS-CoV-1 and SARS-CoV-2). HCQ is known to impair the terminal glycosylation of the angiotensin-converting-enzyme-2 (ACE-2) receptor, which is the binding site for the spike glycoprotein present on virus envelope; and thus, has been shown to inhibit the endolysosome function (Vincent *et al.*, 2005; Yao *et al.*, 2020; Liu *et al.*, 2020). Based on some preliminary clinical evidence indicating the beneficial effect of this drug on the shortening of the time to recovery from COVID-19 (Gautret *et al.*, 2020; Chen *et al.*, 2020), USFDA issued an Emergency Use Authorization (EUA) of HCQ in March 2020 (ICMR, 2020). The Indian Council of Medical Research (ICMR) also recommended HCQ as a therapeutic and prophylactic agent, based on laboratory studies, in-vivo studies, and pre-clinical data (Chatterjee *et al.*, 2020). Following this advisory, many health care professionals (HCPs) across the world started using hydroxychloroquine for COVID-19 prophylaxis. A case-control study conducted by ICMR showed that consumption of four or more doses of HCQ brings about a significant decline in the odds of getting infected and that a dose-response relationship existed between the frequency of exposure to HCQ and such reductions (Borba *et al.*, 2020). However, soon after the initial enthusiasm, some safety concerns were raised concerning the use of HCQ. A Brazilian study stated that tested the safety and efficacy of two different Chloroquine (but not HCQ) dosages as adjunctive therapy in patients hospitalized for COVID-19, had to be halted due to severe cardiac complications and probable cardiac deaths; however, the dose used in this study was much higher than what is routinely recommended (Clinical trial registry India, 2020). In a cohort study of 90 hospitalized patients, the use of HCQ with or without azithromycin for the treatment of COVID-19 was associated with frequent QTc prolongation; and those taking HCQ and azithromycin together had greater QT prolongation than the ones taking HCQ alone. One patient in that series developed Torsades de pointes (Mercuro *et al.*, 2020).

Because of this background, we felt that there was a need to understand the incidence, seriousness, and severity of both cardiac and non-cardiac adverse drug reactions (ADRs) of HCQ among healthcare professionals in India, who were consuming HCQ as per the recommendations of ICMR. When we initiated the study, there were very few studies conducted in this regard especially, with safety as the primary endpoint. The objectives of the present study were to determine the incidence and profile of non-cardiac and cardiac ADRs of HCQ, based on clinical signs and symptoms as well as ECG changes; to analyze the ADRs for their severity and seriousness.

Methodology

Study design and setting

This was a cross-sectional, observational, questionnaire-based study conducted on HCPs, who were taking HCQ for COVID-19 prophylaxis. Before recruiting subjects, the questionnaire was sent to 5 physicians for content validation. The final version incorporated the inputs from these physicians. The study was approved by our Institutional Ethics Committee.

Study population

The source population comprised of colleagues from the academic groups of the investigators. Since the incidence of ADRs with a prophylactic dose of HCQ is not known, it was not possible to calculate the sample size; hence, we conducted this study as a pilot study. The sampling technique was convenient sampling. The study population included HCPs (doctors, nurses, and paramedics), aged 18-years and above, at high risk of exposure to SARS-COV-2. We approached 300 HCPs. The participants belonged to different parts of the country, and were consuming HCQ for COVID-19 prophylaxis as self-medication, in the ICMR recommended doses.

Data collection

The study was carried out from April 2020 to December 2020. The questionnaire was designed as a google form that had an inbuilt section for obtaining consent. The participants were free to refuse at any stage during the filling-up of the questionnaire. The link to the google forms was circulated electronically through telephonic messages and E-mails. The questionnaire included open-ended questions with options. It included personal data such as age, sex, occupation, co-morbidities such as hypertension, diabetes, or any other co-morbidity. There were questions on the use of drugs that were likely to interact with HCQ. The questionnaire had enlisted the expected ADRs as reported in the product information (Electronic medicines compendium) to enable the participants to recollect the symptoms. The details of specific ADRs were also enquired into. Apart from the presence or absence, the questions on each ADR included details such as severity on the visual analog scale, duration of symptom/s, how did they subside (spontaneously or had to be intervened with). In addition,

the participants were also requested to upload baseline ECGs and additional ECGs taken during the HCQ prophylaxis regimen, if available.

Outcomes

The ADRs were evaluated for the incidence as percentages of the reactions. The severity and causality (relatedness to the drug) assessments, the expectedness of the ADR, and whether they were serious or non-serious, were defined as per the WHO guidelines ([WHO-UMC Scale](#)). The reaction was considered mild if the symptoms did not interfere with the day-to-day activities; while severe if it affected the routine activities and/or had to be intervened with for the management of symptoms or signs. Anything intermediate between these two extremes was classified as moderate. An ADR was considered serious if it caused prolonged hospitalization, was life-threatening, or resulted in a disability. Causality assessment was based on WHO criteria ([WHO-UMC Scale](#)), which depends upon, whether the ADR appeared after the drug was administered, could it be explained by any alternative cause, and whether similar reactions were known in the past with the culprit drug or the same drug class.

Electrocardiographic evaluation

The participants were inquired if their 12-lead ECGs had been recorded before (baseline), during, or immediately after the HCQ prophylaxis and were requested to upload all such available graphs. All the ECGs were qualitatively evaluated for the appearance of new changes while the subject was on HCQ. The standard intervals in each ECG were measured by a single cardiac technologist, under the guidance of a cardiologist. Manual calipers were used for these measurements. QT interval was calculated in the lead with the sharpest and most clear onset of QRS complex and the end of T wave and corrected according to Bazett's formula. QTc interval durations beyond 450 ms for men and 460 ms for women were deemed abnormal ([Rautaharju et al., 2009](#)). A QTc ≥ 500 ms or prolongation thereof (delta QTc) from "baseline" ≥ 60 ms, after treatment introduction, were deemed "serious". Similar to Q-Tc, P-R interval, QRS duration, and heart rate (HR) were also determined using

standard methods ([Nagaraja et al., 2020](#)). All these intervals were measured in ECGs (wherever available) after successive doses of HCQ and evaluated for the development of significant changes.

Statistical analysis

The results were analyzed through descriptive statistics as means and proportions. The objective cardiac parameters of toxicity (ECG changes) were analyzed before and after receiving the medication through Student's t-test. The results were analyzed through SPSS software version-21.

Results

A total of 132 responses were obtained after reaching out to 300 HCPs, out of which 6 refused to participate. Hence the analysis was done on 126 patients. Twenty-five participants had got their ECGs done before and during/after taking HCQ prophylaxis; one of them had prolonged QTc (>500 ms) at baseline but still consumed HCQ as he was not aware of the consequences of the ECG abnormality.

Demographic data

As seen from Table 1, there were slightly more male participants than females and the mean age was 39.6 years. The majority of them were doctors and hence self-medication was observed in most of them. The most common co-morbidity was hypertension, followed by diabetes mellitus, thyroid dysfunction, and polycystic ovarian disease. Metformin and glimepiride were the common concomitant medications used for type-2 diabetes mellitus. The antihypertensives used were mainly Telmisartan, Cilnidipine, and Amlodipine.

The duration of use of HCQ ranged from one week to 8 weeks. The cumulative dose at the time of answering the questionnaire varied and ranged from less than 1 gram to 4 grams. Almost all of them followed the ICMR advisory as far as the dosage schedule was concerned.

Table 1. Demographic data

Variable (n=126)	Frequency (percentage) or Mean $\pm$ SD
Age (years)	39.66 $\pm$ 13.66
Men* (n=77)	44 (57.14)
Doctor	114 (90.47)
Nurse	2 (1.58)
Pharmacist	1 (0.79)
Paramedic	3 (2.38)
Other	6 (4.76)

Hypertension	18 (14.28)
Diabetes mellitus	12 (9.52)
Thyroid dysfunction	9 (28.56)
HCQ prophylaxis taken as self-medication	84 (66.66)
Duration of HCQ use	
< 1 week	26
1-2 weeks	36
2-4 weeks	26
4-6 week	24
6-8 weeks	14
Cumulative HCQ dose consumed by the time of participation in the study	
< 1 gram	38
1-2 grams	46
2- 3 grams	19
3-4 gram	23

*Calculation is based on the number of responses to the particular question.

Incidence and expectedness of Adverse drug reactions

Out of 126 participants who completed the questionnaire, 58 (46 %) developed ADRs. A total of 108 ADRs were seen in these 58 patients (Table 2) and only one subject (0.79%) developed potentially serious ADR right bundle branch block (RBBB), although it spontaneously reversed. This participant was a doctor and was aware of the potential of ECG changes with HCQ; hence he repeated the ECG. Most of the reactions were expected as far as the symptoms were concerned; however, they were unexpected in terms of frequency. The expected frequency versus the observed frequency is shown in table 2. Except for the blurred vision, almost all the ADRs came under the unexpected category.

Severity and seriousness of ADRs

As seen from Table 2, the most common ADR were gastrointestinal symptoms namely nausea and vomiting, followed by abdominal pain and loss of appetite. Participants took pantoprazole, omeprazole, ranitidine, esomeprazole, and antacids for their gastrointestinal symptoms. Headache was the next common ADR. While most of the ADRs were mild to moderate in intensity, headaches and skin rashes were severe in many patients. Levocetirizine was used for the relief of skin rashes and paracetamol was used for headaches. No serious ADR was observed in any subject.

Table 2. Non-cardiac adverse drug reactions were observed with HCQ prophylaxis

Adverse events N=126	Frequency (%)		Severity score in mean $\pm$ SD or *median (Q1, Q3)	Frequency of spontaneous ADR remission (%)	Cumulative HCQ dose (grams) received before the ADR (Mean $\pm$ SD)	Causality assessment**	ADR frequency was as expected [#]
	Observed	Reported [22]					
Headache	6 (4.7)	1%	5 (3.8,7.3)*	50	2.4 $\pm$ 1.0	Possible -6	No
Dizziness	3 (2.3)	0.10%	2 (1,NA)*	66.7	2.0 $\pm$ 1.0	Possible -3	No
Ring sensation in ear	1 (0.7)	0.10%	NA	100	NA	Possible -1	No

Nausea/vomiting	25 (19.8)	10%	4.6±2.8	52	1.7±1.0	Probable -5, Possible -20	No
Pain abdomen	20 (15.8)	10%	4.5±1.6	61.5	1.4±0.9	Probable -6, Possible -14	No
Loss of appetite	13 (10.3)	1%	6 (2.8,8.5)*	50	1.3±0.8	Probable -3, Possible -10	No
Skin rash &/or itching in the throat	6 (6.3)	1%	5 (3.5,5.5)*	100	1.4±0.5	Probable -3, Possible -3	No
Hair loss	5 (3.9)	0.10%	3 (2,NA)*	66.7	1.6±1.0	Probable -1, Possible -4	No
Mood changes / irritability	5 (3.9)	1%	4 (3,NA)*	100	1.5±0.6	Possible -5	No
Dark urine	4 (3.1)	not reported	4 (3.2,5.5)*	100	1.9±1.1	Probable -1, Possible -3	No
Hypoglycemia like symptoms (sweating, tremors, blurred vision)	3 (2.3)	not reported	8 (4,NA)*	100	2.2±0.6	Possible -3	No
Chest pain	2 (1.4)	not reported	NA	NA	1.3±0.4	Possible -2	No
Palpitation	8(6.3)	not reported	8	NA	1.8±0.7	Probable -1, Possible -7	No
Field of vision disturbances	1 (0.7)	1%	NA	NA	NA	Possible -1	Yes
Muscle weakness/twitching	3 (2.3)	not reported	NA	NA	1.5±0.5 g	Possible -3	No
Loose stools	1 (0.7)	1%	NA	NA	NA	Probable -1	No

ADR, adverse drug reaction; HCQ, hydroxychloroquine

*Median (IQR); **causality assessment as per WHO criteria; # Concerning frequency reported earlier.

ECG evaluation

On ECG evaluation, one out of 25 patients was discovered to have developed asymptomatic QRS widening with RBBB, but it resolved after discontinuation of HCQ. No

significant changes were seen in other ECG parameters (Table 3). Although palpitations were a common symptom, none of these patients had any objective evidence of rate or rhythm abnormalities appearing in response to HCQ.

Table 3. Changes in ECG parameters observed during HCQ prophylaxis

ECG parameters	Baseline Median (IQR)	First ECG during HCQ prophylaxis		Second ECG during HCQ prophylaxis		P (baseline vs first ECG)	P (baseline vs second ECG)
		The median duration from beginning HCQ (days)	ECG variable Median (IQR)	The median duration from beginning HCQ (days)	ECG variable Median (IQR)		
Heart Rate (beats per minute)	85 (25)		79 (25)		77 (23)	0.68	0.69
PR interval (msec)	140 (40)		140 (10)		140 (30)	0.54	0.67
QRS duration (msec)	80 (20)	1	80 (10)	56	80 (0)	0.44	0.52
QTc interval (msec)	428 (46)		431 (45)		423 (44)	0.72	0.38

ECG, electrocardiogram; HCQ, hydroxychloroquine; IQR, interquartile range

Relatedness of the ADRs to hydroxychloroquine (Causality assessment)

None of the participants discontinued the medication due to the ADR and hence it was not possible to evaluate the

effects of de-challenge. Thus, no re-challenge or de-challenge was possible and hence almost all of them fell under the category of either “possibly related” or “probably related” (Table-2).

Discussion

In the present cross-sectional, questionnaire-based study, we observed that at least one ADR was seen in 58 participants out of 126 resulting in an incidence of 46%. This was higher than the earlier publications on HCQ safety. Nagaraja et al conducted a similar cross-sectional questionnaire-based study on HCPs in India and found an incidence of 37.9% (Abella et al., 2021). A randomized clinical trial on the efficacy and safety of HCQ on pre-exposure SARS-COV-2 prophylaxis among health care workers, by Abella et al., revealed an ADR incidence of 45% in the HCQ group, versus 26 % in the placebo group accounting for a net incidence of 19% attributable to the drug (Kulkarni et al., 2020).

The most common ADRs in our study were gastrointestinal symptoms. This was similar to the observations by Abella et al and Nagaraja et al where nausea, vomiting, and pain abdomen were observed in a maximum number of participants (36%) (Abella et al., 2021; Kulkarni et al., 2020). However, Kulkarni et al in a similar study observed headache as the most commonly occurring ADR (22%) (Keating et al., 2005).

Most of the ADRs in our study were of mild to moderate intensity and were self-limiting; however, a few participants had to take antacids, Ranitidine, or proton pump inhibitors for their gastrointestinal symptoms. Skin rashes were severe in some of the patients and were managed by oral Levocetirizine. Apart from this, among one-third of the patients with nausea, the symptom was severe.

The HCQ is known to affect electrophysiologic properties of the heart, which may result in QT prolongation, fatal ventricular arrhythmias, and sinus node suppression (Yilmazer et al., 2015; Gerard et al., 2020). Because of these effects, the drug has the potential to cause serious cardiac effects. These have been reported in pharmacovigilance surveys conducted in COVID-19 patients (FDA, 2020). But same effects may not replicate with prophylactic use of HCQ in healthy individuals who are different from patients infected with SARS-COV-2, as the latter frequently develop myocarditis, which itself can cause ventricular arrhythmias and conduction disturbances. Based on anecdotal reports of deaths that probably occurred with self-medication of HCQ, cautions have been raised against its use, but data is grossly deficient on its potential cardiac risks in normal individuals (Ponticelli et al., 2017). In our survey, we analyzed the available ECGs for changes appearing after HCQ intake in healthy volunteers. One subject in our study developed an asymptomatic isolated right bundle branch block (RBBB), which reversed after

stopping HCQ. In patients on HCQ developing RBBB, one has to be overly cautious, because HCQ causes first RBBB, then LAHB, and eventually CHB (Montastruc et al., 2020). No other severe cardiac effects were noted in our study. In contrast, the French survey studying ADRs in COVID-19 patients reported sudden, or aborted deaths in 6% of patients, and ventricular arrhythmias in another 6% of patients. The same group observed conduction defects in 15% of cases. We did not find HCQ induced significant changes in any of the ECG intervals, including QTc (Table 3). These observations suggest that cardiac ADRs, including ECG changes, are probably more frequent when HCQ is administered in presence of potential substrate for conduction abnormality, including COVID-19. Since some subjects ignorantly consumed HCQ despite having baseline prolongation of QTc, we suggest that a physician's advice should be taken before starting intake of this drug.

Hence, in our study, none of the ADRs were serious except one potentially serious transient RBBB.

A previously conducted pharmacovigilance study, which surveyed HCQ related ADRs for ten years through Vigibase (individual safety case reports), has hypersensitivity, arthralgia, gastrointestinal symptoms, edema, effusions, and cardiomyopathy as serious adverse reactions that were either life-threatening or needed hospitalization (Electronic medicine compendium, 2012). These reports were obtained from dermatologists or rheumatologists and occurred in patients. However, none of these were observed in our study. Similarly, such serious ADRs were not reported in other studies conducted on subjects using HCQ for prophylactic purposes (Abella et al., 2021; Kulkarni et al., 2020). Therefore, it appears that HCQ, when used in healthy individuals for COVID-19 prophylaxis at a lesser dose and a shorter duration, is less likely to cause serious ADRs. This may be explained by lower cumulative doses of the drug achieved with its prophylactic use. In another study investigating cardiac adverse effects resulting from long-term HCQ use, the authors observed that ECG effects appeared with much higher cumulative doses of the drug compared to those achievable with ICMR recommended doses for COVID-19 prophylaxis (Costedoat-Chalumeau et al., 2007).

An ADR, which is unanticipated in nature and severity according to the available product information, is considered as an unexpected ADR. We tried to explore whether any of the ADRs observed were unexpected. Identification of such data would help the pharmaceutical manufacturers and the regulatory agencies to update the product information. Since this was a focused study, the findings would be of great value. Our study showed that all the ADRs were expected in terms of their nature; however, except for the blurring of vision, they were unexpected in terms of frequency. They appear to be much more common than what is reported in the product information (Yun et al., 2012). This discrepancy can be explained in two ways: one, the source of the data generated here is from a retrospective

interrogation which can have a potential for recall bias from the participants' end; and second, this is active surveillance-based data. ADRs are usually more in number and are generally better detected in the active surveillance with a pre-specified set of safety questions than the spontaneous ADR reporting of adverse drug reactions (Costedoat-Chalumeau *et al.*, 2007).

During treatment, the appearance of any new signs and symptoms after consumption of any drug is generally suspected as an adverse event. However, these could be coincidental and there may be other reasons for these signs and symptoms. Therefore, WHO has given certain algorithms to determine the causality (association or relatedness of the ADRs to the drug). According to these guidelines, there are four categories to determine the strength of association or relatedness-unlikely, possible, probable, and definite. Our analysis showed that most of them were "possible" and few were "probable". Since none of the participants stopped taking the medications, we could not categorize them as definitely related to the drug.

Conclusions

HCQ, when used as prophylaxis for COVID-19, does cause non-specific ADRs that are mild to moderate and mostly tolerable. They occur at a higher incidence than previously reported; however, serious non-cardiac or cardiac effects may not be observable at this dose and duration. Cardiac ADRs, including ECG changes, are probably much less frequent when HCQ is administered in absence of cardiac disease, including any systemic disease-related myocardial damage. ECG monitoring, or at least a baseline evaluation, is strongly suggested before beginning the drug.

Limitations

The study has a limited sample size as not all of the contacted HCPs were willing to participate. The questionnaire was sent across to HCPs living in different geographic regions in India; hence, selection bias was avoided to some extent. Secondly, only a few participants had recorded ECGs; ECG parameters would have objectively added more clarity on the cardiac effect/s of the drug. Thirdly, since it's a questionnaire-based study, the element of recall bias cannot be ruled out. Hence the study can be considered only a preliminary observation. Prospective cohort studies would give more conclusive data in this regard.

Disclosure statement

The author(s) declare that they have no competing interests.

References

Abella, B. S., Jolkovsky, E. L., Biney, B. T., Uspal, J. E., Hyman, M. C., Frank, I., Hensley, S. E., Gill, S., Vogl, D. T., Maillard, I., Babushok, D. V., Huang, A. C., Nasta, S. D., Walsh, J. C., Wiletyo, E. P., Gimotty, P. A., Milone, M. C., Amaravadi, R. K., & Prevention and Treatment of

COVID-19 With Hydroxychloroquine (PATCH) Investigators (2021). Efficacy and Safety of Hydroxychloroquine vs Placebo for Pre-exposure SARS-CoV-2 Prophylaxis Among Health Care Workers: A Randomized Clinical Trial. *JAMA internal medicine*, 181(2), 195–202.

Borba, M., Val, F., Sampaio, V. S., Alexandre, M., Melo, G. C., Brito, M., Mourão, M., Brito-Sousa, J. D., Baia-da-Silva, D., Guerra, M., Hajjar, L. A., Pinto, R. C., Balieiro, A., Pacheco, A., Santos, J., Jr, Naveca, F. G., Xavier, M. S., Siqueira, A. M., Schwarzbold, A., Croda, J., ... CloroCovid-19 Team (2020). Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection: A Randomized Clinical Trial. *JAMA network open*, 3(4), e208857.

Chatterjee, P., Anand, T., Singh, K. J., Rasaily, R., Singh, R., Das, S., Singh, H., Praharaj, I., Gangakhedkar, R. R., Bhargava, B., & Panda, S. (2020). Healthcare workers & SARS-CoV-2 infection in India: A case-control investigation in the time of COVID-19. *The Indian journal of medical research*, 151(5), 459–467.

Chen, Z., Hu, J., Zhang, Z., et al. (2020). Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. *MedRxiv*, 2020.

Clinical Trial Registry India. Effect of hydroxychloroquine on QTc interval. Retrieved from : www.ctri.nic.in; accessed on 30/09/2020

Costedoat-Chalumeau, N., Hulot, J. S., Amoura, Z., Leroux, G., Lechat, P., Funck-Brentano, C., & Piette, J. C. (2007). Heart conduction disorders related to antimalarials toxicity: an analysis of electrocardiograms in 85 patients treated with hydroxychloroquine for connective tissue diseases. *Rheumatology (Oxford, England)*, 46(5), 808–810.

Electronic Medicine Compendium. Hydroxychloroquine Sulfate 200 MG film-coated tablets –Summary of product characteristics (SmPC)-(emc) downloaded from <https://www.medicines.org.uk/emc/product/11540> #UNDESIRABLE_EFFECTS accessed on 20/08/2020

FDA. (2020). Hydroxychloroquine or chloroquine for COVID-19: drug safety communication – FDA cautions against use outside of the hospital setting or a clinical trial due to risk of heart rhythm problems. Accessed July 9, 2020.

Gautret, P., Lagier, J. C., Parola, P., Hoang, V. T., Meddeb, L., Mailhe, M., Doudier, B., Courjon, J., Giordanengo, V., Vieira, V. E., Tissot Dupont, H., Honoré, S., Colson, P., Chabrière, E., La Scola, B., Rolain, J. M., Brouqui, P., & Raoult, D. (2020). Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-

- randomized clinical trial. *International journal of antimicrobial agents*, 56(1), 105949.
- Gerard, A., Romani, S., Fresse, A., Viard, D., Parassol, N., Granvullemin, A., Chouchana, L., Rocher, F., Drici, M. D., & French Network of Pharmacovigilance Centers (2020). "Off-label" use of hydroxychloroquine, azithromycin, lopinavir-ritonavir and chloroquine in COVID-19: A survey of cardiac adverse drug reactions by the French Network of Pharmacovigilance Centers. *Therapie*, 75(4), 371–379.
- Indian Council of Medical Research. (2020). Advisory on the use of Hydroxy-Chloroquine as prophylaxis for SARS-CoV-2 infection. *MoHFW*.
- Keating, R. J., Bhatia, S., Amin, S., Williams, A., Sinak, L. J., & Edwards, W. D. (2005). Hydroxychloroquine-induced cardiotoxicity in a 39-year-old woman with systemic lupus erythematosus and systolic dysfunction. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography*, 18(9), 981.
- Kulkarni, R., Kinikar, A., Jadhav, T. (2020). Adverse drug reaction profile of prophylactic hydroxychloroquine for COVID 19 among doctors. *Medical journal of Dr. D. Y. patil vidyapeeth*, 13(3), 204-207.
- Liu, J., Cao, R., Xu, M., Wang, X., Zhang, H., Hu, H., Li, Y., Hu, Z., Zhong, W., & Wang, M. (2020). Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell discovery*, 6, 16.
- Mercuro, N. J., Yen, C. F., Shim, D. J., Maher, T. R., McCoy, C. M., Zimetbaum, P. J., & Gold, H. S. (2020). Risk of QT Interval Prolongation Associated with Use of Hydroxychloroquine with or Without Concomitant Azithromycin Among Hospitalized Patients Testing Positive for Coronavirus Disease 2019 (COVID-19). *JAMA cardiology*, 5(9), 1036–1041.
- MoHFW. Updated Clinical Management Protocol for COVID-19, version-5" published on July 3, 2020 by the Ministry of Health and Family Welfare, Government of India. Retrieved from: www.mohfw.gov.in
- Montastruc, J. L., Rousseau, V., Durrieu, G., & Bagheri, H. (2020). Serious adverse drug reactions with hydroxychloroquine: a pharmacovigilance study in Vigibase®. *European journal of clinical pharmacology*, 76(10), 1479–1480.
- Nagaraja, B. S., Ramesh, K. N., Dhar, D., Mondal, M. S., Dey, T., Saha, S., Khan, M. A., Rutul, S. D., Pratik, K., Manjula, J., Sangeeth, T. A., & Singh, V. (2020). HyPE study: hydroxychloroquine prophylaxis-related adverse events' analysis among healthcare workers during COVID-19 pandemic: a rising public health concern. *Journal of public health (Oxford, England)*, 42(3), 493–503.
- Ponticelli, C., & Moroni, G. (2017). Hydroxychloroquine in systemic lupus erythematosus (SLE). *Expert opinion on drug safety*, 16(3), 411-419.
- Rautaharju, P. M., Surawicz, B., Gettes, L. S., Bailey, J. J., Childers, R., Deal, B. J., Gorgels, A., Hancock, E. W., Josephson, M., Kligfield, P., Kors, J. A., Macfarlane, P., Mason, J. W., Mirvis, D. M., Okin, P., Pahlm, O., van Herpen, G., Wagner, G. S., Wellens, H., American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology, ... Heart Rhythm Society (2009). AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part IV: the ST segment, T and U waves, and the QT interval: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Endorsed by the International Society for Computerized Electrocardiology. *Journal of the American College of Cardiology*, 53(11), 982–991.
- Vincent, M. J., Bergeron, E., Benjannet, S., Erickson, B. R., Rollin, P. E., Ksiazek, T. G., Seidah, N. G., Nichol, S. T. (2005). Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. *Virology journal*, 2(69), 1-10.
- WH-UMC Scale. The use of WHO-UMC system for standardised case-causality assessment. Accessed on 05/05/2020
- Yao, X., Ye, F., Zhang, M., Cui, C., Huang, B., Niu, P., Liu, X., Zhao, L., Dong, E., Song, C., Zhan, S., Lu, R., Li, H., Tan, W., & Liu, D. (2020). In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, 71(15), 732–739.
- Yilmazer, B., Sali, M., Cosan, F., Cefle, A. (2015). Sinus node dysfunction in adult systemic lupus erythematosus flare: A case report. *Modern rheumatology*, 25(3), 472-475.
- Yun, I. S., Koo, M. J., Park, E. H., Kim, S. E., Lee, J. H., Park, J. W., & Hong, C. S. (2012). A comparison of active surveillance programs including a spontaneous reporting model for pharmacovigilance of adverse drug events in a hospital. *The Korean journal of internal medicine*, 27(4), 443–450.