System for administering and monitoring hydroxychloroquine prophylaxis for COVID-19 in accordance with a national advisory: preliminary experience of a tertiary care institute in India

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ABSTRACT

**Background:** Hydroxychloroquine (HCQ) was one of the earliest drugs to be recommended for tackling the COVID-19 threat leading to its widespread usage. We provide preliminary findings of the system, established in a tertiary care academic center for the administration of HCQ prophylaxis to healthcare workers (HCW) based on Indian Council of Medical Research (ICMR) advisory.

**Methods:** A dedicated clinical pharmacology and internal medicine team screened for contraindications, administered informed consent, maintained compliance and monitored for adverse events.

**Results:** Among the 194 HCWs screened for ruling out contraindications for prophylaxis, 9 were excluded and 185 were initiated on HCQ. A total of 55 adverse events were seen in 38 (20.5%) HCWs out of which 70.9%, 29.1% were mild and moderate & none were severe. Before the completion of therapy, a total of 23 participants discontinued. Change in QTc interval on day 2 was 5 (IQR: −3.75, 11) ms and the end of week 1 was 15 ms (IQR: 2, 18). Out of the 5 HCW who turned positive for COVID-19, 2 were on HCQ.

**Conclusion:** HCQ prophylaxis was found to be safe and well tolerated in HCW when administered after appropriate screening and with monitoring for adverse events.

1. Introduction

Hydroxychloroquine/Chloroquine (HCQ) has been much in the news for the treatment as well as prophylaxis of COVID-19 [1–3]. In-vitro studies with these agents have shown a potential to decrease viral load by modulating the pH of early endosomes to basic pH thereby preventing further progression to late endolysosome [4,5]. However well-conducted clinical studies evaluating benefit when used for the purpose of prophylaxis are yet to be performed [6]. A randomized controlled trial evaluating postexposure prophylaxis role of HCQ was conducted by Boulware et al. which demonstrated no beneficial effect but the study had limitations in design and execution including use of symptomatic case definitions and reliance on participant reports [7]. Even in the clinical studies of HCQ evaluating treatment benefits, the results have been conflicting so far with some studies reporting benefit [8,9] and others reporting inefficacy [10,11]. Moreover, methodolgy of most of the available studies has been critiqued in terms of inadequate sample sizes, lack of control groups, observational designs amongst others [12,13]. India reported its first case of COVID-19 on 30 January 2020 and as on 28 September 2020, the number of active cases have crossed 6 million [14]. After the initial reports of potential benefit in COVID-19 patients with HCQ, combined with past usage of chloroquine as prophylaxis for influenza-like disease and emerging in-vitro evidence, the Indian Council of Medical Research (ICMR) issued an advisory for HCQ prophylaxis for a select group of population on 22 March 2020 [4,15,16]. The recommended dosage was loading dose of 400 mg twice daily on day 1 followed by 400 mg weekly for next 7 weeks for health care workers (HCWs) and 3 weeks for close contacts of patients.

Ease of over the counter availability of medications and improper/incorrect propagation of information led many people to self-medicate themselves with HCQ [17]. Seeing the situation Government had to undertake initiatives to prevent people from self-medicating HCQ such as issuing of circulars and informative online videos so that HCQ be dispensed only with a valid prescription [18,19]. RECOVERY trial suspended its HCQ arm on 5 June 2020, and emerging evidence exists against the efficacy of the drug to treat COVID-19, but still its role in prophylaxis against SARS-CoV–2 infection especially with no other strong contenders needs to be investigated. Of the several side effects, the risk of prolonging QT interval has been a major concern [20–22].
The main aim of this article is to outline the system which was set up to monitor the administration and adverse events of HCQ to HCWs at institute level following the ICMR advisory amidst the ongoing COVID-19 pandemic.

2. Methods

This study was designed as an observational registry (HCQ-HCW registry) and was initiated after obtaining due permission from the Institute’s Ethics Committee (IEC-03/2020- 1594).

2.1. Study setting and study team

The registry included details of the HCQ prescription and its associated follow-up that was maintained by collaboration between Department of Internal Medicine and Department of Pharmacology in one of the largest tertiary care academic center in North India. HCQ was administered at the institute level as hospital policy following the recommendation of ICMR. The pictorial representation of flow of activities in the registry are shown in Figure 1. A trained clinical pharmacology (CP) resident (PK-M) and nurse (DK) were posted in a designated area where the prospective participants were screened before initiating HCQ prophylaxis.

2.2. Study population

The HCWs working throughout the hospital which included doctors or, nursing staff, sanitary workers, laboratory attendants, security officials, and research team were enrolled in the study. The advertisement regarding the availability for HCQ for administration and the option to enroll in registry was made in the institution internal communication networks and a pre-circulated telephone number was used for contact. A telephonic conversation was initiated for briefing about the process, discussing the movement plan and the infection control procedure to be followed, before visiting the designated area.

2.3. Informed consent

The participants were asked to obtain an electrocardiogram if a recent report (within 4 weeks) was not available and present themselves for informing the study details followed by voluntary consent. The contents of the information sheet detailed the available evidence for efficacy and safety of HCQ, need for monitoring of adverse events, data confidentiality and right to refuse prophylaxis.

2.4. Eligibility criteria

All asymptomatic HCWs providing a written informed consent for HCQ administration and/or monitoring under the registry and working in areas devoted to suspected or confirmed COVID19 patients were considered eligible. The contraindications to HCQ prophylaxis that led to exclusion of participants were (1) Hypersensitivity to CQ/HCQ, 2) Cardiomyopathy, clinically relevant cardiac rhythm disturbance and, prolonged QTc (Males, >450 ms and Females >460 ms). For doubtful electrocardiogram, consultation was sought from cardiologist (AG). Electrocardiograms were evaluated for rate, rhythm, or any other abnormality. QTc interval was calculated from the automated 12 lead ECG or using Bazzett’s formula if the ECG conducted did not have this value. (2) History of Porphyria Cutanea Tarda, epilepsy, Myasthenia gravis, psoriasis or myopathy of any cause 3) Serious hepatic or renal disease. (4) History of Glucose-6-Phosphate (G6PD) deficiency. (5) Severe depression/psychosis. (6) On concomitant medication which could possibly lead to clinically significant drug interaction. Potential for drug interaction with an ongoing medication (for any chronic or acute illness) was evaluated with clinical pharmacologists (NS and SM) and Internal Medicine consultant (RM). In case of any queries, Lexicomp database through UpToDate was also queried [23].

2.5. Regimen of HCQ administered

We administered HCQ as per ICMR advisory (i.e.) loading dose of 400 mg separated by 12 hours on week one, followed by 400 mg weekly for the next seven weeks. It was required for the HCW to be asymptomatic at the time of enrollment. Regarding exposure to COVID-19, the HCW might have already been exposed to COVID-19 patients during duty, they were still eligible for enrollment, but we documented the time elapsed since exposure. The HCQ was administered as hospital policy and the aim of the registry was to enroll, dispense and followup the HCQ recipients among the HCWs. All those enrolled were given phone number for contacting in case of...

Figure 1. Pictorial representation of system for executing HCQ administration and monitoring.
any emergent adverse events. A provision was also made for delivery of HCQ dose for those who could not come in–person to the clinic due to isolation/quarantine. They were also asked to repeat ECG within 24–48 hours after the loading dose (day 1). The participants were asked to take ECG at week 1 and week 4 if possible, and in both these cases the ECGs were taken before the administration of the week’s dose. Follow-up was for the entire duration of HCQ administration as per the advisory guidelines.

2.6. Outcomes evaluated

The outcomes considered for evaluation were adverse events during administration. We also evaluated the efficacy outcomes of participant in terms of COVID-19 positivity. The hospital had the policy of keeping the HCWs posted for the COVID-19 duty to be kept in isolation during duty period and they had to undergo a mandatory 14-day quarantine in the immediate post-duty period. The HCW was checked for novel SARS-Coronavirus-2 positivity [using Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) analysis of throat swab] at the end of quarantine period. The information about the exposure, if any, to COVID-19 patients or suspects was noted down but the level of exposure was not documented. Adverse events were categorized as mild, moderate, or severe based on Hartwig’s Severity Assessment Scale [24]. Additionally, adverse events were also classified as serious or non-serious [25]. Causality assessment of adverse events to the HCQ prophylaxis was done using the WHO-Uppsala Causality Assessment Criteria [26].

2.7. Statistical analysis

Statistical analysis was performed using R version 3.6.1 [27]. Categorical variables were expressed as number along with percentages. The non-skewed continuous data were expressed as mean ± S.D. and skewed data were expressed as median with IQR. No missing data imputation was performed.

3. Results

The program for HCQ as prophylaxis was rolled out from 28 March 2020 at our institute. At the time of compilation of this data, 204 HCWs had approached for initiating HCQ prophylaxis. Five out of 204 (2.5%) HCWs refused consent. Out of 199 who gave consent, 9/199 (4.5%) had contraindications and 5/199 (2.5%) did not take a single dose in spite of collecting the drug and consenting. The reasons for exclusion and flow of participants are outlined in Figure 2. The remaining 185 received HCQ prophylaxis under observation of the study team. Out of the total recruited participants, 95 (51.4%) had previous possible exposure to COVID-19 patients and 90 (48.6%) did not have prior history of exposure. Among the 95 participant who had previous exposure to COVID-19 patients, 77 (81.1%) had a possible exposure to a proven case of COVID-19 within 15 days but were using Category III personal protective equipment (PPE) and rest 18 (19.9%) were exposed more than 15 days prior to starting the prophylaxis.

Various categories of HCWs were administered prophylaxis with predominant category being that of nursing personnel [63 (34.1%)] followed by the resident doctors [52 (28.1%)] (Table 1). Of those administered prophylaxis, 44 (23.8%) had comorbidities. Of the total HCQ recipients, 30 (16.2%) were on concomitant medications. Potential for possible drug interaction was noted in two individuals, who were asked to stop the medication (long-term oral antifungal therapy and azithromycin) after discussion. Table 1 describes the baseline characteristics of the study participants.

Baseline ECG was obtained in 142 (9.8) participants. The baseline ECG could not be obtained in remaining individuals because they had initiated HCQ on their own and reported for the registry after the first dose. A repeat ECG along with initial recorded baseline ECG for comparison could be obtained in 70 HCWs. Around 171 (92.4%) participants had at least one ECG performed within the first 4 weeks of treatment. The QTc findings in all ECG recordings at all time points were within normal limits for our study participants. The ECG findings of the study participants are detailed in Table 2.

Adverse events were noted in 38 (20.5%) HCWs. There were a total of 55 individual adverse events, out of which 39 were mild and 16 were moderate and none were deemed to be severe. No serious adverse events were reported during our study. Causality assessment for relatedness was certain (n = 13), probable (n = 36) and possible (n = 6) for the reported adverse events. The details of adverse events noted along with severity and relatedness are listed in Table 3.

Before the completion of therapy, a total of 23 participants discontinued HCQ prophylaxis. The reasons along with time of discontinuation are given in Table 4. Adverse event requiring discontinuation of prophylaxis were four, the reasons being gastritis (1), hot flushes (1), palpitation (1) and dizziness & fatigue (1). At the time of analysis, 93 (50.3%) of participants had completed 4 weeks of HCQ therapy and 17 (9.2%) have completed 6 weeks of HCQ administration. The duration of completion of all participants can be found in Figure 2. Till the date of present report, number of HCWs who tested positive for SARS-CoV-2 in the institute were five. Out of these, two were receiving HCQ prophylaxis. The percentage of HCWs turning positive for novel SARS-CoV–2 with HCQ prophylaxis was nearly 1%. First HCW, had completed six weeks while the second HCW had completed one week of HCQ prophylaxis. The second HCW was also a known case of ulcerative colitis and was receiving concomitant treatment with immunosuppressants.

4. Discussion

The present report highlights the functioning of a dedicated system that was established for meeting the requirements of HCQ prophylaxis for COVID-19 as per the ICMR advisory. The registry is ongoing, and this report represents an interim analysis. The system was established as an arrangement for preventing HCWs from taking HCQ prophylaxis indiscriminately and to report any adverse events, thereby ensuring that the benefits of this experimental regimen outweigh its potential risks.
A total of 185 HCW were administered HCQ in this registry and were followed up for any adverse event. This number represents around half of entire high-risk healthcare force of the institute. Several HCW had already indulged in self-administration and others were not involved in the care of COVID-19 patients. Importantly, we ensured that information regarding insufficient evidence for usefulness of HCQ as a prophylactic agent and that of potential to cause harm were provided to all the HCW approaching for HCQ prophylaxis. A written informed consent was obtained. It is very perplexing that despite providing this information, barring five HCW, rest wanted to be initiated on HCQ. The residents and consultants who comprised majority of the recipients are trained in the principles of evidence-based medicine and apply it routinely in their practice. On the contrary, some participants who opted out of therapy, cited the reason of failure of HCQ to demonstrate efficacy in treatment trials as the reason for stoppage of HCQ prophylaxis [28,29]. Exploring the reasons for disparity may be addressed by adopting behavioral sciences methods at a later date.
Table 1. Baseline characteristics of the participants of study.

| Characteristic | Data Summary (N = 185) |
|----------------|------------------------|
| Age (y), Mean ± S.D | 30.2 ± 6.9 |
| Gender: F/M, n (%) | 77 (41.6)/108 (58.4) |
| **Designation, n (%)** | |
| Resident Doctor | 52 (38.1) |
| Staff Nurse | 63 (43.1) |
| Consultant | 11 (5.9) |
| Hospital Attendant/Sanitation Worker | 27 (14.6) |
| Lab Technician | 28 (15.1) |
| Security Officer | 2 (1.1) |
| Others | 2 (1.1) |
| **Participants with Co-morbidity, n (%)** | |
| Hypertension | 12 (6.4) |
| Diabetes Mellitus | 4 (2.1) |
| Ischemic Heart Disease | 1 (0.5) |
| Immunosuppressed state | 1 (0.5) |
| Thyroid Disorder | 8 (4.3) |
| Respiratory Disorder | 5 (2.7) |
| Skin Disorder | 6 (3.2) |
| Others | 17 (9.1) |
| **Participants using Concomitant Medications, n (%)** | |
| Anti hypertensive | 30 (16.2) |
| Anti diabetic | 10 (5.3) |
| Immunosuppressant | 4 (2.1) |
| Thyroxine supplements | 1 (0.5) |
| Bronchodilators | 6 (3.2) |
| NSAIDs | 3 (1.6) |
| Others | 3 (1.6) |
| **ECG Findings (N = 142)** | |
| Ventricular Rate (per minute), Median (IQR) | 79.5 (71, 89) |
| PR interval (ms), Median (IQR) | 141.5 (128.2, 152) |
| QRS duration (ms), Median (IQR) | 88.0 (82.0, 97.8) |
| QT interval (ms), Median (IQR) | 341.5 (329.0, 360.0) |
| QTc interval (ms), Median (IQR) | 379.0 (369.0, 388.8) |

‘Others’ category under comorbidities comprises of depression, dystonia, fatty liver, hemoglobin E disease, hyperuricemia, iron deficiency anemia, low visual acuity, migraine/sinus, pathological myopia, PCOD, past history of epilepsy and typhoid. ‘Others’ category under co-medications comprises of anti-histaminic, Oral contraceptive pills, iron supplements, folic acid supplements, antibiotic, anti-vertigo. The count of overall co-morbidity and concomitant medications may not match with individual participant count of co-morbidities and concomitant medications as each participant may have more than one of these.

Table 2. ECG parameters reported.

| Parameter | Values |
|-----------|--------|
| Difference between day 2 QTc and baseline QTc (n = 70) ms, Median (IQR) | 5 (-3.75, 11) |
| Difference between end of week 1 QTc and baseline QTc (n = 9) ms, Median (IQR) | 15 (2, 18) |
| Difference between end of week 4 or week 5 QTc and baseline QTc (n = 6) ms, Median (IQR) | 3.5 (~9.75, 10) |
| Increase of 10 ms of QTc between day 2 and baseline (n = 70) ms, n (%) | 19 (27.1) |
| Increase of 60 ms of QTc between day 2 and baseline (n = 70) ms, Median (IQR) | Nil |

Importantly, nine HCWs were not administered HCQ as part of our registry on account of contraindications to HCQ administration. Given the panic situation prevailing during the initial stages of the pandemic and the worldwide media and political statements supporting HCQ, there was a high probability that these HCWs would have self-medicated themselves with the drug had the registry not been in place. Out of these HCWs, two had absolute contraindications namely first-order family history of severe chloroquine hypersensitivity and another had single eye precious vision. Other seven had relative contraindications, out of which one had history of drug-induced hypoglycemia which can rarely even become fatal [30]. Consultations were made with the specialist for solving queries arising during the drug administration. A retrospective, cross-sectional study conducted in India for assessing HCQ prophylaxis-related adverse events' analysis among HCWs reported a higher rate of adverse events (38%) than our study (20%) and they too have recommended monitored dispensation among HCWs [31].

The registry identified, 55 adverse events which were of mild to moderate severity. The adverse effects like gastritis, dizziness, hot flushes, palpitation, headaches are known side effects of HCQ [23]. These adverse effects are most likely related to higher levels of HCQ which peaks at 2–4 h and remain high for 48–72 hours after drug administration and then begins to gradually decline with a half-life of 1–4 weeks [32,33]. No serious adverse event was noted and only four HCWs discontinued HCQ prophylaxis due to adverse events which were mild or moderate. The relatedness term of ‘certain’ which is seldom described in causality assessment, was noted for 13 adverse events. This could be the case because the adverse event abated two days after drug administration and then re-appeared after the next week’s dose indicating a positive rechallenge test. Though an increase in QTc interval
Table 3. Profile of adverse events.

| Name of the event, n (%) | Severity(n) | Relatedness (n) |
|--------------------------|-------------|-----------------|
| Abdominal discomfort, 2 (1.1) | Mild (2) | Probable (2) |
| Acne, 1 (0.5) | Mild (1) | Possible (1) |
| Cough, 1 (0.5) | Mild (1) | Possible (1) |
| Cramping, 2 (1.1) | Mild (2) | Probable (2) |
| Dizziness, 12 (6.5) | Mild (11), Moderate (1) | Certain (6), Probable (6) |
| Drug induced hypoglycemia, 2 (1.1) | Moderate (2) | Probable (2) |
| Flu like symptoms, 7 (3.8) | Mild (6), Moderate (1) | Certain (2), Probable (4), Possible (1) |
| Gastritis, 1 (0.5) | Moderate (1) | Possible (1) |
| Headache, 7 (3.8) | Moderate (7) | Certain (1), Probable (3), Possible (1) |
| High blood pressure, 1 (0.5) | Mild (1) | Possible (1) |
| Hot flushes, 1 (0.5) | Mild (1) | Probable (1) |
| Insomnia, 2 (1.1) | Mild (1), Moderate (1) | Certain (1), Probable (1) |
| Maculopapular rash, 1 (0.5) | Mild (1) | Probable (1) |
| Metallic taste, 2 (1.1) | Mild (2) | Probable (2) |
| Myalgia/Fatigue, 4 (2.2) | Mild (3), Moderate (1) | Certain (1), Probable (3) |
| Nausea and Vomiting, 2 (1.1) | Mild (1), Moderate (1) | Certain (1), Probable (1) |
| Palpitation, 4 (2.2) | Mild (4) | Probable (4) |
| Peeling of skin and blistering, 1 (0.5) | Mild (1) | Possible (1) |
| Periodoral pain, 1 (0.5) | Moderate (1) | Certain (1) |
| Throat irritation, 1 (0.5) | Mild (1) | Possible (1) |

was noted, they were never greater than 450 ms and the increase was never more than 60 ms on any occasion [34,35].

Two of the HCWs receiving HCQ prophylaxis became COVID-19 positive. They were tested positive 1 week and 7 weeks after HCQ administration. Around 3 HCWs who were not enrolled in the HCQ registry turned positive. Since the aim of the registry was to administer and follow the consequences of HCQ administration, the finding cannot be considered as an evidence against or for usefulness of HCQ for COVID-19 prophylaxis. Such evidence can be best generated by well-designed and adequately powered randomized control trials. One such trial is currently underway and will be able to address the utility of HCQ for preventing COVID-19 [36]. In the said trial, the investigators are also exploring different doses of HCQ for prophylaxis.

Consultations were made with the specialist for queries arising during the administration. The major consultation was with the cardiologist. The consultations were mainly for ECG abnormalities such as T wave inversion, ST-segment changes and Left Ventricular hypertrophy changes. These changes were graded as non-clinically significant in the context of HCQ prophylaxis, and the cardiologist opined us to initiate the HCQ therapy. One of the participants had pathological myopia with retinal detachment for whom we obtained an ophthalmologist consultation and did a baseline retinal recording for future follow-up. Though we were aware of the American academy of ophthalmology guidelines stating that retinal damage with HCQ is seldom possible (<2%) before 5–10 years at doses less than 5 mg/kg, we did the recording for future causality assessment, which essentially requires baseline recording [37,38]. We obtained a gastroenterologist opinion for a participant with ulcerative colitis who was on active immunosuppressive therapy, for whom clearance for giving concomitant HCQ was obtained. The intent for obtaining clearance in this case was not because HCQ would be harmful in ulcerative colitis, but to make sure that the treating gastroenterologist was aware that the disease activity may be changed due to the co-prescription of HCQ [39–41]. Based on an endocrinologist opinion for a participant who had history of drug-induced hypoglycemia, we deferred from initiating the HCQ therapy. This was essential as HCQ has shown to previously cause hypoglycemia in non-diabetic individuals although its significance with once weekly regimen was not known [30,42,43].

Around 51.4% participant had possible exposure to proven case of COVID-19. The reasons behind these participants taking dose post-exposure were: Evolving confidence among HCW to take HCQ on seeing their peers administering the drug; unexpected posting schedules due to quarantine of the prior healthcare team who would have got exposed to COVID-19; time lag in dissemination of information that HCQ is being administered in spite of repeated dissipation made in institute’s social groups. Though we cannot possibly prove that post-exposure prophylaxis effect of HCQ is there, invitro studies had shown that HCQ might provide post-exposure benefit up to 72 hours [4].

We followed a series of measures to ensure that the participants were compliant to the study drug. These include

Table 4. Reason along with time of discontinuation.

| Time point of discontinuation (in days) | Total, n (%) (N = 185) |
|----------------------------------------|------------------------|
| [0–7] | (7–14] | (14–21] | (21–28] | (28–35] | (35–42] | (42–49] | (49–56] | Total, n (%) (N = 185) |
| Reasons for discontinuation | | | | | | | | |
| Adverse event | 2 | 1 | 1 | - | - | 1 | - | - | 4 (2.2) |
| Turing COVID +ve | 1 | - | - | - | 1 | - | - | - | 2 (1.1) |
| Stopped therapy out of their choice | 6 | 2 | 2 | - | - | - | - | - | 10 (5.4) |
| Not responding to call | 2 | 1 | 3 | 1 | - | - | - | - | 7 (3.8) |
| Total, n (%) (N = 185) | 11 (5.9) | 3 (1.6) | 4 (2.2) | 3 (1.6) | - | 1 (0.5) | 1 (0.5) | - | 23 (12.4) |
administration of therapy as observed therapy; mailing of schedule of dosing regimen following registration; telephonic reminders on scheduled dates; delivery of medicine to place of quarantine; clarification of queries arising due to continuous emergence of evidence related to or unrelated to HCQ. The hospital had the policy of placing the HCW working in the COVID-19 ward in containment during the duty period and 2-weeks following duty period with 1 week leave after that. The delivery at the place of quarantine helped the participants to get the drugs at timely interval. The institute’s quarantine policy got updated around 1st week of May and we have made the required changes in our dispensing policies. An earlier population-based survey recommended extra attention on people with psychological distress and anxiety to improve adherence [44]. The emerging evidence may also be one of the reasons for 17 participants (leaving behind 2 COVID-19 positives and 4 who dropped out of adverse events) to drop out of the study before completion of the regimen proposed by advisory. The format of observed therapy helped us to clarify their queries at a swifter and timely fashion.

The non-documentation of the level of exposure of the enrolled HCWs, observational study design, lack of comparator group, the selection bias potentially coming from the voluntarily enrollment of participants, and high number of non-exposed participants can be considered as potential limitations of our study. But the situation prevailing at the time of study initiation needs to be considered as also the fact that the registry was initiated almost immediately after the recommendation of the ICMR. Therefore, our study is in understanding to the methodologies to be adopted for safe administration of experimental therapeutics in emergency public health situations especially in lower- and middle-income country settings.

4.1 Expert Opinion

The initial evidence for therapies effective against COVID-19 are arising such as improvement of survival and outcome with Interleukin-6 receptor antagonist (Tocilizumab and Sarilumab) in critically ill COVID-19 patients requiring ventilator support [45]; lowering of 28-day mortality with dexamethasone on COVID-19 patients who were on additional invasive mechanical ventilation or oxygen support [46]. Simultaneously, some very promising therapies like remdesivir have failed to show survival benefit in large multicentric trials [47,48]. This puts the onus on the prophylaxis using vaccines or medicines. There had been radical therapies such as mesenchymal stem cells (MSC) & adipocyte-secreted exosomal miRNA explored to treat COVID-19 [49–51]. The rationality behind the exploration of MSC was due to immune modulation and repairing property, which it possesses. As per the experience from past histories, these radicalities employed with scientific rationality sows the seed for big discoveries. But the radicality component is missing in the case of prophylaxis using drugs. Probably the reason is due to the greater thrust the scientists place on vaccination over drug molecules given the long-term immunity imparted by former with few minor adverse events.

5. Conclusion

We suggest careful selection and adequate monitoring of participants in healthcare settings while administering drugs with potential for toxicity especially if consumed in unsupervised settings. This will ensure that benefits of such experimental therapies outweigh their harms. Serious adverse events were absent with HCQ prophylaxis and adverse events were seen in ~20% of HCWs. A system for administration of prophylactic medication to HCWs has been set and could be easily adopted by other centers.

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Author contributions

PK-M participated in the design, conduct, analysis, interpretation of data, drafting of paper, critically reviewed for intellectual content and final approval of the paper. RM participated in the conduct, critically reviewed for intellectual content and final approval of the paper. AB participated in the concept and design, conduct, critically reviewed for intellectual content and final approval of the paper. NS participated in the conception and design, conduct, analysis, drafting of paper, critically reviewed for intellectual content and final approval of the paper. VS participated in the conduct, critically reviewed for intellectual content and final approval of the paper. DK participated in the conduct, interpretation of data, critically reviewed for intellectual content and final approval of the paper. AKP participated in the conduct and final approval of the paper. AG participated in the conduct and final approval of the paper. PCG participated in the conduct and final approval of the paper. AP participated in the conduct and final approval of the paper. SM participated in the conception and design, conduct, analysis, interpretation of data, drafting of paper, critically reviewed for intellectual content and final approval of the paper.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Mathies D, Rauschning D, Wagner U, et al. A case of SARS-CoV-2-pneumonia with successful antiviral therapy in a 77-year-old male with heart transplant. Am J Transplant. 2020 Apr;20(7):1925–1929.

2. Gautret P, Lagier JC, Parola P, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: a pilot observational study. Travel Med Infect Dis. 2020 Mar - Apr;34:101663.

3. Gao J, Tian Z, Yang X. Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends. 2020;14(1):72–73.

4. Liu J, Cao R, Xu M, et al., Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov. 2020;6(1):16.

• Interest: In vitro evidence demonstrating that hydroxychloroquine is efficacious in inhibiting the SARS-CoV-2 infection in vitro as evaluated in standard CCK8 assay as a dose-response curve.

5. Yao X, Ye F, Zhang M, et al. 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). Clin Infect Dis. 2020;71(15):732–739.

6. Shah S, Das S, Jain A, et al. A systematic review of the prophylactic role of chloroquine and hydroxychloroquine in coronavirus disease-19 (COVID-19). Int J Rheum Dis. 2020 Apr;13(5):613–619.

7. Boulware DR, Pullen MF, Bangdiwala AS, et al. A randomized trial of Hydroxychloroquine as postexposure prophylaxis for Covid-19. N Engl J Med. 2020;383(6):517–525.

•• Considerable interest: First randomized control trial evidence assessed hydroxychloroquine’s role for post-exposure prophylaxis in adults who had household or occupational exposure to COVID-19.

8. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020 Mar;56(1):105949.

9. Million M, Lagier JC, Gautret P, et al. Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin: a retrospective analysis of 1061 cases in Marseille, France. Travel Med Infect Dis. 2020 May;35:101738.

•• Considerable interest: Early retrospective evidence showed that HCQ + Azithromycin administration was safe and associated with a low fatality rate in COVID-19 patients.

10. Cavalcanti AB, Zampieri FG, Rosa RG, et al. Hydroxychloroquine with or without Azithromycin in mild-to-moderate Covid-19. N Engl J Med. 2020 Jul 23;383(21):2041–2052.

11. Hernandez AV, Roman YM, Pasupuleti V, et al. Hydroxychloroquine or Chloroquine for treatment or prophylaxis of COVID-19: a living systematic review. Ann Intern Med. 2020;173(4):287–296.

12. Alexander PE, Debono VB, Mammen MJ, et al. COVID-19 coronavirus research has overall low methodological quality thus far: case in point for chloroquine/hydroxychloroquine. J Clin Epidemiol. 2020;123:120–126.

• Interest: A report highlighting that adequate powered, well-conducted clinical research was absent in the field of COVID-19.

13. Cortegiani A, Ippolito M, Inoglia G, et al. Update I. A systematic review on the efficacy and safety of chloroquine/hydroxychloroquine for COVID-19. J Crit Care. 2020 Oct;59:176–190.

14. MOHFW. MOHFW | home. 2020 [2020 May 19]. Available from: https://www.mohfw.gov.in/

15. National-Task-Force-for-Covid-19. Advisory on the use of Hydroxychloroquine as prophylaxis for SARS-CoV-2 infection. New Delhi: ICMR. 2020 [2020 May 22]Available from: https://www.mohfw.gov.in/pdf/AdvisoryontheuseofHydroxychloroquinasyprophylaxisforSARSCOVIDinfection.pdf

•• Considerable interest: The recommendation to administer HCQ for healthcare workers was based on this taskforce report from India’s Government.

16. Paton NI, Lee L, Xu Y, et al. Chloroquine for influenza prevention: a randomised, doubleblind, placebo controlled trial. Lancet Infect Dis. 2011;11(9):677–683.

17. Tripathy JP. Does pandemic justify the use of Hydroxychloroquine for treatment and prevention of COVID-19 in India? J Med Virol. 2020;92(9):1391–1393.

18. MOHFW. Information for general public: availability and use of necessary medicines in India 2020 [2020 May 19]. Available from: https://www.mohfw.gov.in/pdf/HICoserPosterFinal.pdf

19. MOHFW. Information for general public on use of necessary medicines for COVID 19. [cited 2020 Apr 18] Available from: https://www.youtube.com/watch?v=cQBo6Bbk0_A.

20. Mercuro NJ, Yen CF, Shim DJ, et al. 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 Cardiol. 2020;5(9):1036.

21. Chorin E, Wadhwani L, Magnani S, et al. QT interval prolongation and Torres De Pointes in patients with COVID-19 treated with Hydroxychloroquine/Azithromycin. Heart Rhythm. 2020;17(9):1425–1433.

22. Agstam S, Yadav A, Kumar MP, et al. Hydroxychloroquine and QTc prolongation in patients with COVID-19: a systematic review and meta-analysis. Indian Pacing Electrophysiol J. 2020 Oct 16;21(1):36–43.

•• Considerable interest: A metaanalysis focusing exclusively on the QT prolongation risk with HCQ in the context of COVID-19.

23. Lexicomp. Hydroxychloroquine: drug information - Lexicomp-upToDate 2020 [2020 May 19]. Available from: https://www.upodate.com/contents/hydroxychloroquine-drug-information

24. Hartwig SC, Denger SD, Schneider PJ. Severity-indexed, incident report-based medication error-reporting program. Am J Hosp Pharm. 1991;48(12):2611–2616.

25. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet. 2000;356(9237):1255–1259.

26. WHO-UMC. The use of WHO-UMC system for standardised case causality assessment: the Uppsala monitoring center. [cited 2020 May 5]. Available from: https://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOCausality_assessment.pdf.

27. Team R. R: a language and environment for statistical computing (Version 3.6.1). R Foundation for Statistical Computing. Vienna, Austria, 2019.

28. Magagnoli J, Narendran S, Pereira F, Cummings TH, Hardin JW, Sutton SS, Ambati J. Outcomes of Hydroxychloroquine Usage in United States Veterans Hospitalized with COVID-19. Med (N Y). 2020 Dec 18;1(1):114–127.e3.

29. Tribune T. Covid-19: FDA warns against side-effects of hydroxychloroquine. The Tribune. April 25 2020 [cited 2020 May 19]. Available from: https://www.tribunedia.com/news/coronavirus/covid-19-fda-warns-against-side-effectsof-hydroxychloroquine-76119

30. Ben Salem C, Fatallah N, Hmouda H, et al. Drug-induced hypoglycaemia: an update. Drug Saf. 2011;34(1):21–45.

31. Nagaraja BS, Ramesh KN, Dhar D, et al. HyPE study: hydroxychloroquine prophylaxis-related adverse events’ analysis among healthcare workers during COVID-19 pandemic: a rising public health concern. J Public Health. Oxf 2020 Aug 18;42(3):493–503.

•• Considerable interest: A questionnaire based study assessing the incidence of adverse events among the healthcare worker taking HCQ prophylaxis.

32. Lim HS, Im JS, Cho JY, et al. Pharmacokinetics of hydroxychloroquine and its clinical implications in chloroquine prophylaxis against malaria caused by Plasmodium vivax. Antimicrob Agents Chemother. 2009;53(4):1468–1475.

33. Ducharme J, Fieger H, Ducharme MP, et al. Enantioselective disposition of hydroxychloroquine after a single oral dose of
the racemate to healthy subjects. Br J Clin Pharmacol. 1995;40 (2):127–133.

34. Simpson TF, Stecker EC. Ventricular Arrhythmia risk due to Hydroxychloroquine Azithromycin treatment for COVID-19 - American college of cardiology 2020 [cited 2020 May 19]. Available from: http://www.acc.org/latest-in-cardiology/articles/2020/03/27/14/00/ventricular-arrhythmia-risk-due-tohydroxychloroquine-azithromycin-treatment-for-covid–19

35. Kapoor A, Pandurangi U, Arora V, et al. Cardiovascular risks of hydroxychloroquine in treatment and prophylaxis of COVID-19 patients: a scientific statement from the Indian heart rhythm society. Indian Pacing Electrophysiol J. 2020;20(3):117–120.

36. ClinicalTrials.gov. CROWN CORONATION: chloroquine Repurposing to healthWorkers for Novel CORONavirus mitigation - ClinicalTrials.gov clinicaltrials.gov 2020 [2020 May 19]. Available from: https://clinicaltrials.gov/ct2/show/NCT04333732

37. Marmor MF, Kellner U, Lai TY, et al. Recommendations on screening for Chloroquine and Hydroxychloroquine Retinopathy (2016 revision). Ophthalmology. 2016 Jun;123(6):1386–1394.

38. Gupta PC, Kumar MP, Ram J. COVID-19 pandemic from an ophthalmology point of view. Indian J Med Res. 2020 May;151(5):411–418.

39. Goenka MK, Kochhar R, Tandia B, et al. Chloroquine for mild to moderately active ulcerative colitis: comparison with sulfasalazine. Am J Gastroenterol. 1996;91(5):917–921.

40. Kanvinde S, Chhonker YS, Ahmad R, et al. Pharmacokinetics and efficacy of orally administered polymeric chloroquine as macromolecular drug in the treatment of inflammatory bowel disease. Acta Biomater. 2018 Dec;82:158–170.

41. Singh AK, Jena A, Kumar MP, et al. Risk and outcomes of coronavirus disease (COVID-19) in patients with inflammatory bowel disease: a systematic review and meta-analysis. United Eur Gastroenterol J. 2020;19:2050640620972602.

42. El-Solia A, Al-Otaibi K, Ai-Hwiesh AK. Hydroxychloroquine-induced hypoglycaemia in nondiabetic renal patient on peritoneal dialysis. BMJ Case Rep. 2018;2017:223639.

43. Cansu DU, Korkmaz C. Hypoglycaemia induced by hydroxychloroquine in a non-diabetic patient treated for RA. Rheumatology (Oxford). 2007;47(3):378–379.

44. Sundbom LT, Bingefors K. The influence of symptoms of anxiety and depression on medication nonadherence and its causes: a population based survey of prescription drug users in Sweden. Patient Preference and Adherence. 2013;7:805–811.

45. Gordon AC, Mouncey PR, Al-Beidh F, et al. Interleukin-6 receptor Antagonists in critically ill patients with Covid-19: preliminary report. medRxiv. 2021;2021(1):07.21249390.

46. Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with Covid-19 - preliminary report. N Engl J Med. 2020. Jul 17;20(3):117–120.

47. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 - final report. N Engl J Med. 2020;383(19):1813–1826.

48. Pan H, Peto R, Henao-Restrepo AM, et al. Repurposed antiviral drugs for Covid-19 - Interim WHO solidarity trial results. N Engl J Med. 2021;384(6):497–511.