Systematic review of registered trials of Hydroxychloroquine prophylaxis for COVID-19 healthcare workers at the first third of 2020

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ABSTRACT

In the absence of a vaccine the medical and scientific community is looking intensely at utilizing a pre or post exposure drug that could decrease viremia. The search for a medication that could reduce risk of serious disease, and ideally of any manifestation of disease from SARS-CoV2, and of asymptomatic shedding of SARS-CoV2 is of urgent interest. Repurposing existing pharmaceuticals is among the approaches to achieve these ends. We performed a systematic review of all interventional studies registered in ClinicalTrials.gov with a focus on one repurposed drug, Hydroxychloroquine (HCQ). The detailed analysis of these studies, some of them already recruiting, provide an overall picture of HCQ use as a COVID-19 prophylaxis around the world. Among the included studies, all but three were randomized and parallel and most of them (74%, 23/31) were double-blinded to quadruple-blinded studies. We found a great diversity in dosing and nearly all the possible scientifically reasonable regimens are under evaluation. This diversity offers benefits as well as challenges. Importantly, the final analysis of these trials should be done through an extensive reading of the results in regard to the clinical design, it will be crucial to carefully read and evaluate the results of each study in regards to the clinical design rather than quickly glancing a 140 characters-based social media message announcing the failure or success of a drug against a disease.

1. Introduction

In the absence of a vaccine the medical and scientific community is looking intensely at utilizing a pre or post exposure drug that could decrease viremia. The search for a medication that could reduce risk of serious disease, and ideally of any manifestation of disease from SARS-CoV2, and of asymptomatic shedding of SARS-CoV2 is of urgent interest, particularly to decrease the risk to health care workers, first responders, and others with high risk of exposure to patients with COVID19. The prospect of protecting healthcare workers against COVID-19 based on repurposing of existing pharmaceuticals is among one of the recent scientific debates [1,2]. The value of hydroxychloroquine (HCQ) as a prophylactic needs careful documented, empirical research in this context [3]. In order to obtain strong clinical evidence, a large number of scientists and teams have launched prospective studies that were registered on ClinicalTrials.gov over a short period of time. The detailed analysis of these studies, some of them already recruiting, will give an overall picture of HCQ use as a COVID-19 prophylaxis around the world. This will help to identify the gaps to be fulfilled with the idea of getting definitive evidence on the positioning of HCQ for COVID-19 prophylaxis in exposed health-care workers.

2. Material and methods

We performed a systematic review of all interventional studies registered in ClinicalTrials.gov on the 27th of April under the disease “COVID” and “hydroxychloroquine prophylaxis” as other terms [4]. No other filter was used. Studies using hydroxychloroquine (HCQ) as treatment, studies that did not record details about HCQ regimen, as well as those using HCQ in combination with other drugs, were not included. ClinicalTrials.gov is a Web-based resource maintained by the National Library of Medicine that provides patients, their family members, health care professionals, researchers, and the public with access to information on clinical studies. Information on ClinicalTrials.gov is provided and updated by the sponsor or principal investigator of the clinical study.

Two independent authors (ALB, SP) performed the screening of the study record detail to assess eligibility. Data were extracted by Information collected included ClinicalTrials.gov identifier, official title, recruitment status, starting and completion dates, estimated enrollment, allocation, location, intervention model, masking, and HCQ regimen. To ensure reproducibility and completeness of data extraction, an Excel spreadsheet (Microsoft Corp., Redmond, WA, USA) compiling all variables to be extracted was used. Disagreements over eligibility or data extraction were resolved by discussion. Data were centrally checked by an independent operator for completeness, plausibility, and integrity before synthesis.

3. Results

All interventional clinical trials that studied the use of HCQ for COVID-19 prophylaxis were included in the qualitative analysis. Forty-one (n = 41) studies were identified through ClinicalTrials.gov on the 27th of April (Fig. 1). After screening for eligibility record details of the selected studies, 31 studies were included in the qualitative analysis. Ten studies were not included: reasons for exclusion included the
absence of details about HCQ regimen \( (n = 1) \), the use of HCQ as indication other than prophylaxis \( (n = 3) \), and the combination of HCQ to other drugs or vitamins \( (n = 6) \). The qualitative analysis focussed on HCQ drug regimens of the 31 included studies as recorded in ClinicalTrials.gov from the 17th of March to the 24th of April. (See Table 1.)

Among the included studies, all but three were randomized and parallel and most of them (74%, 23/31) were double-blinded to quadruple-blinded studies. On the 27th of April, 55% \( (17/31) \) of them were recruiting. Estimated enrolment in HCQ arm was from 45 to 20.000 participants, with a median of 380 participants and a total of 45.728 persons receiving HCQ.

Regarding HCQ regimen, 61% \( (19/31) \) of the included studies used an HCQ loading dose, followed by daily \( (14/19) \) or weekly \( (5/19) \) doses. The range of the loading doses was from 400 to 1400 mg on day 1. The most common daily doses were 400 mg \( (12/31 \text{ (39%)}) \) and 200 mg \( (9/31 \text{ (29%)}) \); a 600 mg daily dose was less common and was recorded for only 13% \( (4/31) \) of the studies. The remaining six studies used weekly doses of 400 mg. Regarding the duration of prophylaxis, it was highly variable, ranging from 5 to 180 days \( (\text{median} = 40 \text{ days}) \) for daily regimen, and 3 to 24 weeks for weekly regimen \( (\text{median} = 12 \text{ weeks}) \). Of note, the most frequent prophylactic regimen \( (6/31 \text{ (19%)}) \) was an HCQ loading dose of 800 mg on day 1, followed by HCQ 400 mg for four additional days. Among the studies \( (n = 5) \) that did not use a loading dose but a 400 mg daily dose, duration of prophylaxis was highly diverse from 4 to 180 days \( (\text{median} = 60) \). For the studies \( (n = 2) \) that reported a 200 mg daily dose, one study used a loading dose of 800 mg on day 1 and 2, followed by 90 days of 200 mg HCQ, and the other one used a loading dose of 400 mg from day 1 to 3, followed by 14 days of 200 mg HCQ.

4. Discussion

More than 40 randomized clinical trials have been registered in less than 2 months from 13 different countries to answer the same question: should we used HCQ to protect health-care workers from the COVID-19 consequences? This very active recording in ClinicalTrials.gov demonstrates the huge interest of the scientific community regarding this question. Indeed, the debate continues to rage regarding the use of HCQ for COVID-19 and we need to shed more light based on clinical evidence. At the present time, the debate is still a non-documented speculation that will be ended in the next few months.
Table 1
Description of interventional studies registered in ClinicalTrials.gov on the 27th of April under the disease "COVID" and "hydroxychloroquine prophylaxis".

| NCT     | Title                                                                 | Starting Date | Completion date | Recruiting | Location                                | Randomization | Masking | Placebo | Nb patients Nb in HCQ arm | Dose D1 mg | Dose per day | Nb days | Dose per week | Nb of weeks |
|---------|-----------------------------------------------------------------------|---------------|-----------------|------------|-----------------------------------------|---------------|---------|---------|--------------------------|------------|--------------|---------|---------------|-------------|
| 4,308,668 | Post-exposure Prophylaxis or Preemptive Therapy for SARS-CoV-2: A Pragmatic Randomized Clinical Trial | March 17, 2020 | April 21, 2020  | Yes        | Minneapolis, Minnesota, USA             | Yes           | Quadruple | Yes     | 3000 1500               | 1400 600    | 5 mg         | –       | –             | –           |
| 4,334,148 | Healthcare Worker Exposure Response and Outcomes of Hydroxychloroquine Trial         | April 2020    | July 2020       | No         | Duke University Durham, UK             | Yes           | Triple   | Yes     | 15,000 7500            | 1200 400    | 30 mg        | –       | –             | –           |
| 4,342,221 | Randomized Controlled Trial of Hydroxychloroquine Versus Placebo for the Treatment of Adult Patients With Acute Coronavirus Disease 2019 - COVID-19 | March 29, 2020 | March 2021     | Yes        | University Hospital Tuebingen, Germany | Yes           | Quadruple | Yes     | 220 110                | 800 600     | 7 mg         | –       | –             | –           |
| 4,329,923 | Prevention And Treatment of COVID-19 With Hydroxychloroquine PATCH 2 & 3 Prevention and Treatment of COVID-19 With Hydroxychloroquine | April 2020    | April 2021     | Yes        | University of Pennsylvania, USA        | Yes           | Triple   | Yes     | 400 200                | 600 600     | 60 mg        | mg      | –             | –           |
| 4,353,037 | Randomized Controlled Trial of Hydroxychloroquine in the Prevention and Treatment of COVID-19 | April 7, 2020 | April 2021     | Yes        | ProHealth New York, USA                | Yes           | Double   | Yes     | 850 210                | 600 600     | 60 mg        | mg      | –             | –           |
| 4,352,933 | ChemoPROphylaxis For covid-19 Infectious Disease (the PROLIFIC Trial) | April 2020    | October 31, 2020 | No         | Cambridge University Hospitals Trust, UK | Yes           | Quadruple | Yes     | 1000 330               | 800 200     | 90 or 400/ wk after loading | 12       | –             | –           |
| 4,330,144 | Hydroxychloroquine as Post Exposure Prophylaxis for SARS-CoV-2 Population | 01/04/2020 | 30/03/2021 | No          | Gangnam Severance Hospital, Seoul, South Korea | Yes           | Single   | No      | 2486 1243             | 800 400     | 5 mg         | –       | –             | –           |
| 4,318,444 | Hydroxychloroquine Post Exposure Prophylaxis (PEP) for Household Contacts of COVID-19 Patients: A NYC Community-Based Randomized Clinical Trial | March 2020 | March 2021 | No          | Columbia University Irving Medical Center New York, USA | Yes           | Quadruple | Yes     | 1600 800              | 800 400     | 5 mg         | –       | –             | –           |
| 4,342,156 | Safety And Efficacy Of Hydroxychloroquine As COVID-19 Prophylaxis For At-Risk Population | April 2020 | August 2020 | No          | Tan Tock Seng Hospital Singapore       | Yes           | None     | No      | 1200 600              | 800 400     | 5 mg         | –       | –             | –           |
| 4,304,053 | Treatment of Non-severe Confirmed Cases of COVID-19 and Chemoprophylaxis of Their Contacts as Prevention Strategy: a Cluster Randomized Clinical Trial (PEP CoV-2 Study) | March 18, 2020 | June 15, 2020 | Yes        | Departament de Salut, Barcelona, Spain | Yes           | None     | No      | 30 40 1520            | 800 400     | 5 mg         | –       | –             | –           |
| 4,329,611 | Prevention And Treatment of COVID-19 With Hydroxychloroquine PATCH 1 & 2 Prevention and Treatment of COVID-19 With Hydroxychloroquine | April 13 | August 31, 2020 | Yes        | ProHealth New York, USA                | Yes           | Triple   | Yes     | 1660 550              | 800 400     | 5 mg         | –       | –             | –           |

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| NCT   | Title                                                                                                                                  | Starting Date | Completion date | Recruiting | Location                                                                 | Randomization | Masking | Placebo | Nb patients | Nb in HCQ arm | Dose D1 mg | Dose per day mg | Nb days | Dose per week | Nb of weeks |
|-------|----------------------------------------------------------------------------------------------------------------------------------------|--------------|----------------|------------|--------------------------------------------------------------------------|---------------|---------|---------|-------------|---------------|-----------|----------------|---------|--------------|------------|
| 4,351,191 | A Randomized, Double-blind, Placebo-controlled Trial to Assess the Efficacy and Safety of Oral Hydroxychloroquine for the Treatment of SARS-CoV-2 Positive Patients for the Prevention of Severe COVID-19 Disease. | April 15, 2020 | April 30, 2020 | No         | Mayo Hospital Lahore, Pakistan                                           | Yes          | Quadruple | Yes     | 400         | 100           | 800       | 400             | 5       | mg           |            |
| 4,303,507 | Use and Dosage of Hydroxychloroquine and Chloroquine to Convert Symptomatic RT-PCR Positive Severe Acute Respiratory Syndrome Coronavirus 2 Coronavirus Infectious Disease 2019 Patients to RT-PCR Negative as a Means to Reduce Hospitalization Rate Chloroquine/ Hydroxychloroquine Prevention of Coronavirus Disease (COVID-19) in the Healthcare Setting | April 2020    | April 2021    | No         | University of Oxford, UK                                                | Yes          | Double   | Yes     | 40,000      | 20,000        | 600       | 200             | 90      | mg           |            |
| 4,354,870 | ff Label Study to Evaluate the Efficacy of HCQ for Pre-exposure Prophylaxis (PrEP) to Prevent Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection Among Health Care Workers (HCWs) Who Are at High Risk of Occupational Exposure to SARS-CoV-2 | April 3, 2020 | August 1, 2020 | Yes        | NYU Langone Health, New York, New York, USA                            | No           | None    | No      | 350         | 300           | 600       | 200             | 90      | mg           |            |
| 4,330,495 | Randomized, Controlled, Double-blind Clinical Trial Comparing the Efficacy and Safety of Chemoprophylaxis With Hydroxychloroquine in Patients Under Biological Treatment and/or JAK Inhibitors in the Prevention of SARS-CoV-2 Infection | April 6, 2020 | Nov 6, 2020   | No         | Instituto de Investigación Marqués de Valdecilla, Spain                  | Yes          | Double   | Yes     | 800         | 400           | 400       | 400             | 180     | mg           |            |
| 4,352,946 | Protecting Health Care Workers From COVID-19 With Hydroxychloroquine Pre-exposure Prophylaxis: A Randomized, Placebo-controlled Trial | April 24      | June 24, 2020 | No         | GeoSentinel Foundation                                                   | Yes          | Quadruple | Yes     | 374         | 187           | 400       | 400             | 60      | mg           |            |

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| NCT     | Title                                                                 | Starting Date | Completion Date | Recruiting | Location                                    | Randomization | Masking | Placebo | Nb patients | Nb in HQ arm | Dose D1 mg | Dose per day mg | Nb days | Dose per week mg | Nb of weeks |
|---------|-----------------------------------------------------------------------|---------------|----------------|------------|---------------------------------------------|---------------|---------|---------|-------------|-------------|-----------|-----------------|----------|-----------------|-------------|
| 4,328,285 | Chemoprophylaxis of SARS-CoV-2 Infection (COVID-19) in Exposed Healthcare Workers: A Randomized Double-blind Placebo-controlled Clinical Trial | April 14, 2020 | Nov 30, 2020 | Yes        | CHU de Saint-Etienne Institut Pasteur, France | Yes           | Triple  | Yes     | 1200        | 300         | 400       | 400 60 mg        |          |                 |             |
| 4,344,379 | Prevention of SARS-CoV-2 in Hospital Workers Exposed to the Virus | April 15, 2020 | July 31, 2020 | Yes        | Assistance Publique - Hôpitaux de Paris, France | Yes           | Double | Yes     | 900         | 300         | 400       | 400 40 mg        |          |                 |             |
| 4,331,834 | Pre-Exposure Prophylaxis With Hydroxychloroquine for High-Risk Healthcare Workers During the COVID-19 Pandemic: A Unicentric, Double-Blinded Randomized Controlled Trial | April 3, 2020 | Oct 3, 2020 | Yes        | Barcelona Institute for Global Health, Spain | Yes           | Quadruple | Yes     | 440         | 220         | 400       | 400 400 24        |          |                 |             |
| 4,328,961 | Efficacy of Hydroxychloroquine for Post-exposure Prophylaxis (PEP) to Prevent Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection Among Adults Exposed to Coronavirus Disease (COVID-19): a Blinded, Randomized Study | March 2020 | Sept 30, 2020 | Yes        | University of Washington, New York University, USA | Yes           | Double  | Ascorbic acid | 2000        | 1000        | 400 200 14        |          |                 |             |
| 4,341,441 | Will Hydroxychloroquine Impede or Prevent COVID-19?: WHIP COVID-19 Study | April 7, 2020 | June 30, 2020 | Yes        | Detroit, Michigan, USA | Yes           | Triple  | Yes     | 3000        | 1500        | 400       | 200 56 Or 6 8 6.5 mg/week/week |          |                 |             |
| 4,336,674 | Low-dose Hydroxychloroquine for Primary Prophylaxis Against SARS-CoV-2 in Health-care Workers - a Randomized, Double-blind, Controlled Trial | April 2020 | July 2020 | No         | Medical University of Vienna, Austria | Yes           | Triple  | Yes     | 440         | 220         | 200       | 200 28          |          |                 |             |
| 4,318,015 | Chemoprophylaxis With Hydroxychloroquine in Healthcare Personnel in Contact With COVID-19 Patients: A Randomized Controlled Trial | April 14, 2020 | Dec 31, 2020 | Yes        | National Institute of Respiratory Diseases, Mexico | Yes           | Quadruple | Yes     | 400         | 200         | 200       | 200 60 mg        |          |                 |             |
| 4,334,928 | Prevention of SARS-CoV-2 (COVID-19) Through Pre-Exposure Prophylaxis With Tenofovir Disoproxil Fumarate/Emtricitabine and Hydroxychloroquine in | April 15, 2020 | June 30, 2020 | No         | Hospital Universitario Ramón y Cajal, Madrid, Spain, | Yes           | Double  | Yes     | 4000        | 1000        | 200       | 200 84 mg        |          |                 |             |

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Table 1 (continued)

| NCT   | Title                                                                 | Starting Date | Completion date | Recruiting | Location                                      | Randomization | Masking | Placebo | Nb patients | Nb in HCQ arm | Dose D1 mg | Dose per day mg | Nb days | Dose per week | Nb of weeks |
|-------|-----------------------------------------------------------------------|---------------|-----------------|------------|-----------------------------------------------|---------------|---------|----------|-------------|--------------|------------|-----------------|----------|---------------|-------------|
| 4,349,228 | Healthcare Personnel: Randomized Clinical Trial Controlled With Placebo Assessment of the Efficacy and Safety of (HCQ) as a Prophylaxis for COVID19 for Health Professionals | April 15, 2020 | July 15, 2020 | No         | Hôpital Abderrahmane Mami-Ariana Tunis, Tunisia | Yes           | Single | Yes      | 530         | 265          | 200        | 200              | 60       | mg            | -           |
| 4,328,467 | Pre-exposure Prophylaxis for SARS-CoV-2: A Pragmatic Randomized Clinical Trial | April 6, 2020 | August 2020 | Yes        | Minneapolis, Minnesota, USA                   | Yes           | Quadruple | Yes     | 3500        | 1166         | 800        | –                | 1        | 400           | 12          |
| 4,333,225 | A Prospective Clinical Study of Hydroxychloroquine in the Prevention of SARS-CoV-2 (COVID-19) Infection in Healthcare Workers After High-risk Exposures | April 3, 2020 | July 30, 2020 | invitation | Baylor University Medical Center Dallas, Texas, USA | No            | None    | No       | 360         | 360          | 800        | –                | 1        | 400           | 7           |
| 4,347,389 | Prophylactic Hydroxychloroquine vs Vitamin C in Healthcare Workers at Risk of COVID-19: A RCT | April 20 | Dec 30, 2020 | No         | Stony Brook University, New York USA | Yes           | Single | Vitamin C | 1212        | 606          | 800        | –                | 1        | 400           | 12          |
| 4,352,933 | ChemoPROphylax For covid-19 Infectious Disease (the PROLIFIC Trial) | April 2020 | Oct 31, 2020 | No         | Cambridge University Hospitals NHS Foundation Trust, UK | Yes           | Quadruple | Yes     | 330         | 800          | 200        | 90              | or 400/ wk after loading | 12          |
| 4,341,441 | Will Hydroxychloroquine Impede or Prevent COVID-19: WHIP COVID-19 Study | April 7, 2020 | June 30, 2020 | Yes       | Detroit, Michigan, USA | Yes           | Triple | Yes     | 3000        | 1500         | 400        | 200              | 56       | or 6.5 mg/kg/week | 8           |
| 4,345,653 | Hydroxychloroquine as Chemoprevention for COVID-19 for High Risk Healthcare Workers | April 14, 2020 | April 8, 2021 | Yes       | Hackensack Meridian Health - JFK Medical Center Edison, New Jersey, USA | No            | None    | No       | 45          | 45           | 400        | –                | 1        | 400           | 3           |
The positive point regarding the high diversity of HCQ regimen among recorded clinical studies is that nearly all the possible regimens are under evaluation. The negative point of the high diversity in HCQ dosage and duration of prophylaxis could be that the conclusion of these different studies may be conflicting. Indeed, it would be surprising that a 200 mg daily dose during one month would have the same efficacy and the same ratio benefit/risk than a 600 mg daily dose during three months. As a consequence, the final analysis of these trials should be done through an extensive reading of the results in regards to the clinical design, rather than quickly glancing a 140 characters-based social media message announcing the failure or success of a drug against a disease.

The authors declare no conflict of interest.

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