A rapid systematic review of randomized controlled trials of chloroquine and hydroxychloroquine as antiviral prophylaxis for COVID-19

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Review question / Objective: There is a growing number of clinical trials launched recently to evaluate the potential of chloroquine (CQ) or hydroxychloroquine (HCQ) as prophylaxis against COVID-19. We seek to identify and comprehensively review the different approaches and methodologies of currently proposed trials in terms of target populations studied, different preventative dose schedules of CQ versus HCQ deployed and the various outcome measures used to assess efficacy of prophylaxis.

Rationale: As COVID-19 has been declared a pandemic, we urgently seek to establish effective pharmacologic prophylactics where currently there is none. We earlier proposed chloroquine as a chemoprophylaxis for COVID-19 and a number of clinical trials has since been announced. We seek to analyze the methodologies and parameters of such trials to assess their potential in providing the critical information on a potentially efficacious prophylaxis for COVID-19.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 17 April 2020 and was last updated on 17 April 2020 (registration number INPLASY202040101).

INTRODUCTION

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Condition being studied: SARS-CoV-2 infection and COVID-19 disease.

METHODS

Search strategy: Two independent researchers will search for relevant ongoing, recently completed and unpublished clinical trials using the 26 major regional, international and national clinical trial registries as listed by HHS's OHRP online: including ClinicalTrial.gov and WHO's ICTRP databases) in English (for all registries) and Chinese (for China's CHICTR registry) for all trials registered on or before Apr 15 2020* using search terms: SARS-CoV, 2019-nCoV, 2019nCoV, SARS-CoV-2, COVID19, COVID-19, chloroquine, hydroxychloroquine. This will be supplemented by PubMed, Embase, Cochrane Library, CINAHL and CNKI searches with no limit to the publication language. Citations of previous published Systematic Review and relevant reviews on related subject will be examined to identify related relevant studies. (*search date to be modified or updated as necessary).

Participant or population: Those who are healthy but at high risk of contracting the virus and disease: healthcare workers, and close contacts of diagnosed cases. Inclusion criteria is generally healthy adults over age of 16 or above able to consent, willing to participate, able to comply. EXCLUSION criteria include pre-existing sensitivity to treatment drugs, or pre-existing health conditions such as pregnancy, hypersensitivity to study drugs, and specific health issues such liver disease, kidney disease, prolonged-QT interval on EKG, and concomitant use of certain medications (e.g. abiraterone acetate, agalsidase, amodiaquine, conivaptan, dabrafenib, dacomitinib, dapsone, enalapril, fusidic acid, idealisib, lanthanum, lumefantrine, mefloquine, mifepristone, mitotane, pimozone, and QT-prolonging agents which may interact with the study drugs.

Intervention: Chloroquine or hydroxychloroquine independently or in combination with other agent as prophylaxis against SARS-CoV-2 infection or COVID-19 disease.

Comparator: Placebo, or other active antiviral as control.

Study designs to be included: Randomized controlled trials in human subjects.

Eligibility criteria: Randomized controlled trial which includes the use of chloroquine or hydroxychloroquine in human subjects intended as preventative against SARS-CoV-2 infection of COVID-19 disease.

Information sources: The 26 national, regional, international clinical trial registries including WHO's ICTRP portal, Pubmed, Embase, Cochrane library, CINAHL and CNKI searches.

Main outcome(s): The review intends to review differences amongst the trials as to target populations (e.g. front line health workers, vs. contacts of index cases), timing and intensity of interventions (CQ v. HCQ, different dosage regimens), outcome assessments (e.g. seroconversion, hospitalizations, loss of work, side-effects), as well as methodologic differences in masking/blinding, statistical power of the various trial studies.

Additional outcome(s): None.

Data management: The researchers will independently maintain and electronically store a searchable database of trials and references related to the systematic review and store all references selected for the systematic review using Mendeley when
 synthesizing and reporting the results of the systematic review.

Quality assessment / Risk of bias analysis: The two researchers will independently assess risk of bias for each RCT study using The Jadad scale (Oxford Quality Scoring System). This is composed of five points in total; two for randomization, two for blinding, and one for the drop out rate, and gives an output in reference to the quality of the trial. In case of discrepancy between the two researchers, a third party will be asked to apply the scale to independently address the discrepancy. Additionally, we intend to qualitatively summarize the risk of bias across different studies for each of six domains: (1) random sequence generation (2) allocation concealment (3) blinding methods (4) incomplete outcome data (5) selective outcome reporting (6) other biases) as referenced by the Cochrane collaboration network.

Strategy of data synthesis: An initial preliminary narrative synthesis of the key elements from the included studies will be presented according to the review questions with summary tables for study characteristics and methodological details to analyze for differences in inclusion and outcome criteria and methodology shortfalls. As results for the trials become available over time, outcomes will be included in a meta-analysis to provide summary estimates of proportions and errors, and likelihood of primary outcomes according to relevant clinical factors. Analysis will initially be univariate. Where appropriate and required, RevMan 5.3 will be used to calculate the relative risk (RR) or odds ratio (OR) and its 95% confidence interval (95% CI) will be used in the count data, and the mean squared error (MD) and its 95%CI in the measurement data. If P0.05, we will consider the difference to have statistical significance. Meta-regression will be performed to assess and define study heterogeneity, the I² test of heterogeneity will be used to assess heterogeneity in models with random effects. Where heterogeneity is high, sensitivity analyses will be performed using inverse variance heterogeneity models.

Subgroup analysis: Subgroup analysis can involve different risk groups (household contact v. healthcare worker), different drug (chloroquine v. hydroxychloroquine), different dosage schemes (e.g. 2 weeks, 8 weeks, 12 weeks), different dosage strengths (e.g. 200mg v. 400mg v. 800mg daily).

Sensibility analysis: Reporting of sensibility bias will be done in tabular form as per Cochrane Handbook. We expect that the issues suitable for sensitivity analysis may best be identified during the review process where the individual peculiarities of the studies under investigation are identified. When sensitivity analyses show that the overall result and conclusions are not affected by the different decisions that could be made during the review process, the results of the review can be regarded with a higher degree of certainty. Where sensitivity analyses identify particular decisions or missing information that greatly influence the findings of the review, greater resources can be deployed to try and resolve uncertainties and obtain extra information, possibly through contacting trial authors and obtained individual patient data.

Country(ies) involved: US, Taiwan.

Keywords: SARS-CoV-2, COVID-19, chloroquine, hydroxychloroquine, corona virus, chemoprophylaxis, antiviral.

Dissemination plans: Open access via relevant preprint servers and subsequent journal submissions

Contributions of each author: Author 1 - Search, data extraction, analysis, synthesis, discussion and manuscript drafting. Author 2 - Independent search, data extraction and validation, analysis confirmation, graphics, discussion and manuscript review.