World Health Organization

WHO R&D Blueprint

COVID-19

Informal consultation on the dose of chloroquine and hydroxychloroquine for the SOLIDARITY Clinical Trial

Geneva, Switzerland, 8th April 2020

R&DBlueprint

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Appropriate WHO Confidentiality Undertakings were signed and submitted to WHO by all participating experts

INTRODUCTION

Chloroquine, a drug traditionally used to treat malaria for several decades, has recently attracted increased interest as a therapeutic agent for the management of COVID 19. There are now many countries that are offering chloroquine to COVID 19 patients either through clinical trials or through a compassionate access protocol. Also, studies are currently ongoing to assess the prophylactic efficacy of chloroquine in COVID 19 with these interventions utilizing different dose regimens.

The WHO has launched a multicountry clinical trial called 'the SOLIDARITY trial' to evaluate the efficacy of chloroquine and other therapeutic agents in a coordinated manner. The Chloroquine or Hydroxychloroquine schedule selected for the trial includes two oral loading doses (250 mg per tablet CQ or 200mg per tablet HCQ), then oral twice-daily maintenance doses for ten days. This meeting convened to discuss the appropriateness of the selected dose for the trial.

The activity of chloroquine and hydroxychloroquine against the SAR-CoV-2 virus is seen only at high concentrations, so if there is any benefit from the drug, it is likely to require high concentrations of free drug in plasma to produce high concentrations in the infected respiratory epithelium. It is assumed that the cytosolic concentrations of the drugs in the respiratory epithelium will be in dynamic equilibrium with the plasma.

Evidence from the treatment of life-threatening infections indicates that the earlier in the evolving disease process that pathogen multiplication is inhibited, the better is the outcome. This argues for achieving high plasma concentrations as soon as possible, but this must be balanced against toxicity. The selected doses are undoubtedly high, but the disease is serious.

The concentrations that will occur in the first few hours of treatment are similar to those which will appear after about one week's twice-daily treatment. Serious toxicity (hypotension, arrhythmias, convulsions) is unlikely at these doses. Relatively well, patients may well feel nauseated and dysphoric. Paradoxically by analogy with malaria, sicker bed-bound patients generally tolerate these drugs relatively well. It is hoped that COVID19 patients would respond in a similar way to malaria patients, but this will need to be determined.

This expert consultation convened experts in cardiology, pharmacology, internal medicine, tropical medicine, public health, and regulatory affairs.

Agenda items

- Introduction and roll-call.
- Discussions on the ideal dose of chloroquine for the SOLIDARITY trial.
- Next steps

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Participants

Name	Position	Institutional Affiliation
Marco Cavaleri(Chair)	Head of Anti-infectives and Vaccines	European Medicines Agency, Netherlands
Nicholas White	Professor of Tropical Medicine	Mahidol University, Thailand
Scott Miller	Senior Program officer	Bill and Melinda Gates Foundation, USA
Richard Peto	Professor of Medical Statistics and Epidemiology	Oxford University

Invited but absent: Josep Brugada (Head of Cardiology, Hospital Clínic de Barcelona, Spain)

WHO Secretariat: Ana Maria Henao Restrepo, Marie-Pierre Preziosi, Vasee Moorthy, Andrea Bosman, Alejandro Costa, and Kolawole Salami.

Overview of deliberations

- Chloroquine(CQ) has complex pharmacokinetic properties where most of the plasma concentration profile following administration is determined by distribution and not elimination. The terminal elimination half-life is about a month. Hydroxychloroquine(HCQ) differs only having a smaller total volume of distribution. The danger from a cardiovascular (CVS) point of view is that they do not have enough time to distribute out from a small central compartment, highlighting the danger when administered via the intravenous route. However, the distribution rate, when given orally, is sufficient to avoid this danger. Modelers have, however, oversimplified the multi-compartmental pharmacokinetic properties into 2 or 3 compartment models, which translates

to a too rapid elimination (12-20 days in different models), giving a different pattern of accumulation.

- These drugs are hypotensive in high concentrations and have a multichannel effect on the heart. Also, sometimes causing bradycardia without hypotension via the funny channel of the heart. They may also cause prolonged QT intervals. There is no evidence that therapeutic doses of CQ lead to torsade de pointes nor increases the risk of sudden death, even when given in high doses for a prolonged period in patients with rheumatoid arthritis. In the latter patients. Conversely, what is observed in these patients is an anti-arrhythmic effect.

- The dose of CQ or HCQ employed in the SOLIDARITY protocol was intended to exploit the maximum chance of therapeutic efficacy. Some participants noted that the SOLIDARITY protocol is using the highest dose of CQ of any recent COVID 19 study or expanded access protocol. Hence, it is crucial to proceed with caution and take safety concerns seriously. It was suggested that safety monitoring, especially cardiac monitoring, be considered in the SOLIDARITY protocol.

- It was, however, noted that other therapeutic agents used in the SOLIDARITY trial also have possible side effects that have not precluded their experimental use. Also, the main anticipated side-effect-QT prolongation- are considered not critical enough to foreclose the use of CQ at the specified dose in the trial. Cardiac arrhythmias are the primary cardiovascular concern, but it's unlikely that it would occur at the dose in the protocol. Also, the risk of hypotension and hypoglycaemia at the given dose may not be significant, especially given that study participant are hospitalized patients with anticipated access to blood glucose and cardiovascular function monitoring. Some participants, however, differed on the risk of hypoglycaemia, stating that evidence from mouse models and human observational studies in India indicate the risk may be significant. The SOLIDARITY trial is, however, currently not collecting extensive safety data on these. The protocol is only recording Suspected Unexpected Serious Adverse Reactions [SUSAR]

- Although the preponderance of opinion tilted towards a reasonable benefit-risk profile for the intervention, there was some scepticism about what was considered a 'minimalistic safety data collection' currently included in the protocol. However, it was stressed that the study is in hospitalized patients and is not a community study. Respective countries are free to include these additional safety monitoring clauses in their protocols, as already seen in some EU countries.

- The protocol is now approved in some countries. While WHO would share the outcome of the meeting with the cardiologist for his inputs, the study should continue in sites where the protocol is approved, especially where there is the clinical ability to ensure safety monitoring of patients

Proposed next steps

- WHO will share the meeting outcomes with the cardiologist, Dr. Joseph Brugada, (who was absent) to provide expert advice.

- WHO will document and consider experts' opinions and update the protocol- if necessary.

Cardiologist's input (22nd April)

- I agree with the document. In all trials and compassionate use of chloroquine, an ECG is recorded before and 48 hours after taking the drug to ensure that QTc is not above 500 ms basal and does not prolong more than 60 ms from basal after drug intake. In almost all centres, ECG is mandatory and different gadgets like Alive Cor or externally recorded systems to avoid contact with the patient are used to record the ECG.

Note that the above prioritization decisions are preliminary and may change as further information is provided to WHO.