Peer-reviewed version available at *Medical Hypotheses* **2020**; doi:10.1016/j.mehy.2020.109815

Does zinc supplementation enhance the clinical efficacy of chloroquine/hydroxychloroquine to win todays battle against COVID-19?

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Abstract

Currently, drug repurposing is an alternative to novel drug development for the treatment of COVID-19 patients. The antimalarial drug chloroquine (CQ) and its metabolite hydroxychloroquine (HCQ) are currently being tested in several clinical studies as potential candidates to limit SARS-CoV-2-mediated morbidity and mortality. CQ and HCQ (CQ/HCQ) inhibit pH-dependent steps of SARS-CoV-2 replication by increasing pH in intracellular vesicles and interfere with virus particle delivery into host cells. Besides direct antiviral effects, CQ/HCQ specifically target extracellular zinc to intracellular lysosomes where it interferes with RNA-dependent RNA polymerase activity and coronavirus replication. As zinc deficiency frequently occurs in elderly patients and in those with cardiovascular disease, chronic pulmonary disease, or diabetes, we hypothesize that CQ/HCQ plus zinc supplementation may be more effective in reducing COVID-19 morbidity and mortality than CQ or HCQ in monotherapy. Therefore, CQ/HCQ in combination with zinc should be considered as additional study arm for COVID-19 clinical trials.

Keywords: COVID-19; SARS-CoV-2; Therapy; Chloroquine; Hydroxychloroquine; Zinc

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Background to hypothesis

Since December 2019, the new severe acute respiratory syndrome coronavirus 2, designated SARS-CoV-2, has spread rapidly to almost every country causing coronavirus disease–19 (COVID-19) pneumonia. According to the Johns Hopkins CSSE website https://coronavirus.jhu.edu/map.html as of 22-04-2020, there were globally more than 2.500,000 documented cases, 178,371 deaths with country specific mortality of more than 10% in Spain, Italy, France, and the UK [1]. It has been observed that morbidity and mortality increase with age and comorbidities like hypertension, diabetes, coronary heart disease, or chronic obstructive lung disease [2].

Currently, there are no approved vaccines or pharmaceutical therapies available for prevention of SARS-CoV-2 infection or treatment of COVID-19. Extensive global research efforts are underway to identify specific vaccination strategies and pharmaceutical targets. However, the development of a specific vaccine is not expected for at least 12-18 months due to required time for research, evaluation, and regulatory approval. Worldwide, social distancing and self-quarantine are currently the only protective measures to slow the rate of SARS-CoV-2 infections and help to keep the novel coronavirus from overwhelming the healthcare systems. Nevertheless, every day COVID-19 related deaths are still increasing and so the repurposing of available and approved drugs has emerged as a feasible strategy for treatment near term [3]. In this regard, potentially suitable antiviral and immunomodulatory candidates have been identified and selected [4].

One promising opportunity might be the clinical use of the oral prescription drugs chloroquine (CQ) and hydroxychloroquine (HCQ) used for the treatment of malaria and certain inflammatory conditions [4]. *In vitro* activity against SARS-CoV-2 has been demonstrated for both [5]. In a recent clinical study in China, it was demonstrated that CQ treatment of COVID-19 patients had a clinical benefit versus control treatment [6].

Results of an open label non-randomized clinical trial with hydroxychloroquine and azithromycin in France support these findings [7]. Based on these limited *in vitro* and clinical data, CQ and HCQ are now recommended for treatment of hospitalized COVID-19 patients in a growing number of countries and FDA just granted emergency authorisation for both.

A larger number of clinical trials to further investigate the benefit of CQ and HCQ in COVID-19 are already initiated in China and elsewhere [8]. Although the World Health Organization (WHO) and other organizations recommend CQ/HCQ for testing to fight COVID-19 pandemic, many questions remain regarding the design of conducted or ongoing clinical studies with CQ/HCQ and the conclusions drawn from the respective results [9].

The WHO recently announced the initiation of the so called “Solidarity Trial” which physicians from all over the world can easily join without many bureaucratic barriers [9]. Four drugs have been initially recommended to be evaluated in this trial as monotherapy or in combination:

- CQ, previously used for treatment of malaria
- Remdesivir, developed for treatment of Ebola
- Lopinavir and ritonavir used in combination for treatment of HIV
- Lopinavir and ritonavir with interferon beta

The antiviral nucleoside analogue, remdesivir has been administered to patients with confirmed, severe SARS-CoV-2 infections in the United States, Europe, and Japan [4].

Other therapies have been evaluated in human clinical trials during previous coronavirus outbreaks (SARS-CoV in 2002/2003 and MERS-CoV in 2012) and include lopinavir and ritonavir with or without interferon beta [4].

However, it is not known whether these proposed strategies are effective in the treatment of SARS-CoV-2 infected COVID-19 patients. For example, lopinavir and ritonavir already failed to show beneficial clinical effects versus standard of care in a recently published clinical study with COVID-19 patients conducted in China [10].

It is expected that the WHO list of drugs and compounds will continue to be amended with other candidates planned to be researched in the Solidarity Trial [9].

Statement of hypothesis

CQ and the metabolite HCQ are well known drugs concerning pharmacology, approved indications, dosing, appropriate patient populations, as well as clinical efficacy and safety. Both drugs act as weak bases and are known to accumulate within endosomes, lysosomes, or Golgi vesicles within cells resulting in increase of pH within these compartments [11]. The increase in pH, especially in lysosomes,

could interfere with pH-dependent steps of SARS-CoV-2 replication like fusion and uncoating [12]. As coronavirus requires acidification of endosomes for proper functioning [12], it is speculated that a pH increase in intracellular compartments might be one important inhibiting effect of CQ and probably of HCQ in the treatment of SARS-CoV-2 infected patients [8].

An interesting new finding demonstrated that CQ has characteristics of a zinc ionophore and specifically targets the extracellular trace element zinc to intracellular lysosomes [13]. Zinc is an essential micronutrient, with strictly regulated systemic and intracellular concentrations, and it is physiologically needed for an effective antiviral response [14].

From *in vitro* and some clinical studies, it is well known that zinc elicits activity against several viruses [14]. Indeed, it was demonstrated that zinc inhibits the activity of RdRp of Hepatitis E virus [15]. It was further shown *in vitro* that zinc inhibited coronavirus RdRp activity and that zinc ionophores blocked coronavirus replication [16]. Despite the well-known antiviral effects of zinc and possible properties of CQ/HCQ as zinc ionophore, the combination of zinc with one of these established drugs to achieve additive or even synergistic antiviral effects ought to be still confirmed.

Zinc is a general stimulant of antiviral immunity [14]. In the context of COVID-19 morbidity and mortality, zinc deficiency may be relevant for the outcome of patient populations with severe clinical courses of COVID-19 including elderly patients, patients with hypertension, diabetes, coronary heart disease, or chronic obstructive lung disease. In addition, hypertensive and cardiovascular disease patients are frequently treated with hydrochlorothiazide, angiotensin-converting-enzyme inhibitors, and angiotensin 2 receptor antagonists which can result in an increased urinary excretion of zinc with subsequent systemic zinc deficiency [17]. Zinc deficiency was also demonstrated in diabetic patients [18]. Decreased zinc plasma levels are even present in a large number of healthy elderly patients [19]. The NHANES III study demonstrated that 35%–45% of adults aged 60 years or older had zinc intakes below the estimated average requirement of 6·8 mg/day for elderly females and 9·4 mg/day for elderly males. 20%–25% of older adults still had inadequate zinc intakes even when intakes from both food and dietary supplements were considered [20]. It may be speculated that also younger adults or even infants and adolescents with present

zinc deficiency could be at higher risk for severe courses of SARS-CoV-2 infections. Therefore, we hypothesize that effective zinc supplementation during treatment of COVID-19 with CQ and HCQ, which have zinc ionophore characteristics, may result in increased intracellular zinc levels in general and in lysosomes specifically. Higher intracellular zinc levels might result in a more efficient RdRp inhibition and consequently a more effective inhibition of intracellular SARS-CoV-2 replication, potentially improving clinical outcomes of COVID-19 patients treated with CQ or HCQ. Whether this accumulation and treatment effect may sufficiently occur in relevant pulmonary tissue of COVID-19 patients has to be confirmed.

Testing the hypothesis

Due to the existing substantial evidence, we propose to amend current clinical trial designs to test this hypothesis in the treatment of COVID-19 patients by including at least one treatment arm with oral CQ or HCQ in combination with zinc. However, because of the better clinical safety profile HCQ should be preferred. To avoid interindividual differences of oral absorption rates and because of possible gastrointestinal side effects of oral zinc supplementation, it is especially for inpatients proposed to use parenteral zinc preparations which are approved and clinically already used. For outpatients at expected high risk to develop severe COVID-19, oral administration of sufficient doses of zinc should be considered. Supplementation of zinc is known to be clinically relatively safe if dosing ranges and upper limits of dosing are based on recommended dietary allowances [20]. In a randomized, double-blind, placebo-controlled trial oral zinc supplementation with 45 mg zinc per day for 12 months demonstrated a significant lower incidence of infections in the elderly and was very well tolerated [21].

In the first clinical study arm, e.g. of an open-label randomized clinical trial, we recommend using preferably HCQ in daily doses and treatment durations as recently studied [7]. In the comparator arm, similar daily doses of HCQ should be combined with parenteral or oral zinc. As comprehensive zinc dose findings studies may currently not be feasible but as sufficient clinical safety needs to be ensured, we recommend administering zinc in the range of the upper limit of dosing based on recommended dietary allowances [20]. So, for a male or female adult patient with normal renal function and no contraindications a parenteral daily dose of 40 mg zinc could be implemented. Dependent on observed tolerability, safety, and growing

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clinical experience the total daily dose of zinc could be further increased or decreased at the discretion of the physician.

Based on real world dialogue the combination of HCQ with oral zinc, often in a triple combination with the antibiotic azithromycin, is obviously already used by some clinical practitioners. In accordance to his own statement and available press reports the medical practitioner Dr. Vladimir Zelenko form Monroe, New York, USA has already treated hundreds of patients with coronavirus-like symptoms with the described triple combination claiming favourable clinical outcome. Based on personal communication the following experimental treatment regimen has been used so far: HCQ 200 mg twice daily, zinc sulfate 220 mg once-daily, and azithromycin 500 mg once-daily, each for 5 days. Detailed analysis of patient outcome is currently ongoing and might support guidance for clinical practice and the design of needed randomized clinical trials.

Conclusion

More effective COVID-19 treatment protocols to ensure shorter hospital stays, less need for prolonged mechanical ventilation, and to reduce death are still missing. Based on the evidence of therapeutic effects of CQ/HCQ, their possible pharmacological effect as zinc ionophores and possibly underestimated specific and unspecific antiviral effects of zinc, we hypothesize that the combination of CQ/HCQ with zinc in the treatment of COVID-19 patients, in an out- or inpatients setting, may help to improve clinical outcomes and to limit the COVID-19 fatality rates [1,2].

The safety, tolerability and efficacy of a combination of CQ/HCQ with zinc, possibly in triple combination with an antibiotic like azithromycin, still represents an additional option to win todays battle against COVID-19. This hypothesis can be rapidly evaluated by amendment of a suitable WHO-supported Solidarity Trial or other studies. Important advantages of using CQ or preferably HCQ in combination with zinc are the broad availability, affordability, and demonstrated efficacy and safety in approved and clinically established indications. The European Medicines Agency recommends using CQ or HCQ only in clinical trials or emergency use programs [22]. Whether zinc supplementation in combination with CQ/HCQ should be recommended for high risk or also younger patients outside of clinical trials, as a prevention or treatment approach during SARS-CoV-2 pandemic, should be currently considered only on a case-by-case basis.

Conflict of interest

The author Roland Derwand is/was at the time of writing an employee of Alexion Pharma Germany GmbH. The author Martin Scholz is/was at the time of writing External Senior Advisor for the company LEUKOCARE in Munich, Germany.

The authors confirm that this article content has no conflict of interest.

Peer-reviewed version available at Medical Hypotheses 2020; doi:10.1016/j.mehy.2020.109815

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