Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to Editors

Inhaled hydroxychloroquine to improve efficacy and reduce harm in the treatment of COVID-19

ABSTRACT

Current formulations and dose regimens of hydroxychloroquine (HCQ) put patients at risk of harm. An analysis of clinical trials registered on ClinicalTrials.gov revealed that this may continue as many studies combine HCQ with agents that prolong the QT interval. Further, almost all of the trials registered do not consider dosage adjustment in the elderly, a patient population most likely to require HCQ treatment. Here we describe an inhaled formulation of HCQ which has passed safety studies in clinical trials for the treatment of asthma and discuss how this approach may reduce side-effects and improve efficacy. As this simple formulation progressed to phase II studies, safety data can be used to immediately enable phase II trials in COVID-19.

The COVID-19 (SARS-CoV-2) pandemic has had devastating health consequences worldwide [1], and life has been brought to a standstill as the world awaits a vaccine. Meanwhile, many patients continue to fall critically ill and, in the absence of a vaccine, antivirals and other treatments to alleviate the effects of the disease are urgently sought.

In recent months, since the outbreak of COVID-19, a large number of clinical trials have been registered on ClinicalTrials.gov with the aim of repurposing medicines to reduce the severity of the disease [2]. Chloroquine and hydroxychloroquine (HCQ) were two of the earliest drugs to receive attention as possible repurposable treatment options for COVID-19 [3]. Indeed, a number of studies investigated their anti-SARS-CoV activity as early as 2003 [4–6]. However, the potential efficacy of HCQ must be balanced against its side-effects, particularly those associated with QT elongation, which is exacerbated by age, comorbidities and administration with other agents (such as azithromycin) that prolong the QT interval [7]. A recent analysis of NHS (UK) electronic health records revealed that the most striking risk factors for COVID-19 death were age and male gender [8], and those same risk factors have been identified previously in the context of drug induced QT elongation [9,10]. Concerns associated with severe side effects are such that the FDA and EMA now formally recommend against taking HCQ for COVID-19 infection unless it is being prescribed in the hospital or as part of a clinical trial [11,12].

Our analysis of the 185 trials registered with ClinicalTrials.gov (13th May 2020) using the search terms “COVID-19 and hydroxychloroquine” (Fig. 1) revealed that the most common dosage regimen in use in treatment trials (n = 50, 45%) is a loading dose of 800 mg (i.e. 400 mg twice daily), followed by 400 mg (i.e. 200 mg twice daily). This dosing regimen is consistent with a recent pharmacokinetic model [13], however due to the complex pharmacokinetics of HCQ coupled with the uncertainty of its antiviral mechanism, this *in silico* approach to dose selection is not perfect with some authors suggesting that in some cases HCQ may not achieve the intracellular concentrations to ensure 100% viral eliminiation [14,15]. Further, as HCQ is primarily cleared by the kidneys and as kidney function decreases with age [16], the drug dose should be adjusted to reduce side-effects in the elderly patient population (the population most at risk of severe disease). This may be further compounded by the fact that many trials combine HCQ alongside other agents that extend the QT interval (n = 43, 38% of treatment trials). Unfortunately, dosage modification is being addressed in only two of the 185 trials (ClinicalTrials.gov Identifier: NCT04334382); in one of these two studies dosage adjustments are based on weight (when $\leq$ 45 kg), while in the other study, the dose is halved when GFR $\leq$ 60 mL.min^{-1} (NCT04347512). The database search results are summarised in Fig. 1.

Targeted delivery of hydroxychloroquine to the lung via oral inhalation

COVID-19 is an acute respiratory tract infection, the severe presentation of which may result from the virus using a virus receptor that is expressed predominantly in the lung [17,18]. Viral particles lodge and proliferate in the respiratory tract, where they multiply and spread to other tissues. In this context, one option to potentially improve HCQ efficacy at a lower dose is to deliver the drug directly to the lung as an inhaled formulation. Based on lung versus whole body weight differences and *in vitro* levels of HCQ found to be effective as an antiviral in alveolar cells, Klimke *et al.* recently proposed, in a first dose estimation, substitution of 200–400 mg HCQ twice daily in oral form with 2–4 mg HCQ twice daily by inhalation [19].

Patent literature (WO1998017231A2, US6572858B1 and US7183112B2) reveals that HCQ (sulfate salt) can be formulated as a simple aqueous solution (100 mg.mL^{-1} HCQ in water, adjusted to pH 3.8 using sulfuric acid) [20] which can be delivered via nebulisation into the deep lung in animals (sheep) [21].

This HCQ formulation was developed by Aradigm Corporation for delivery of 50 µL dosage volumes (i.e. 5 mg/dose) via their AERx® handheld nebuliser system and progressed through phase I clinical studies to assess safety for use in asthma. The clinical study report of the phase 1 trial which was made available to us [22], entitled “A two-part, randomized, double-blind, placebo-controlled, ascending-dose study to evaluate the safety, tolerance and pharmacokinetics of orally inhaled hydroxychloroquine sulfate via the AERx system in healthy adult volunteers”, concluded that that inhaled hydroxychloroquine sulfate appears safe and well tolerated in healthy adult males and females in doses of up to 20 mg daily for 7 days. The two part study was carried out with 31 healthy subjects aged 18–55 (9 female, 22 male) [22]. The trial was preformed independently at the clinical facilities of CMAX, in 2004 at the Royal Adelaide Hospital, Australia with Dr Andrew Scroop as the principal investigator. For part A 15 participants were

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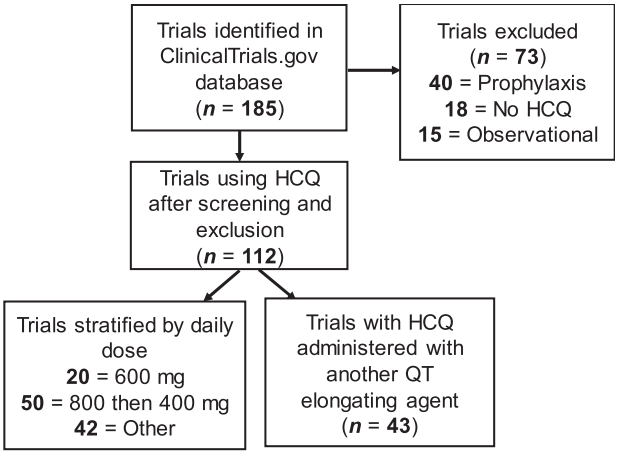

Fig. 1. Summary of search results from ClinicalTrials.gov database.

Table 1
Key pharmacokinetic parameters from part a of the phase I clinical trial data.

	Cmax (ng/mL)		Tmax (h)		AUCt (ng*h/mL)	
Dose	Mean	SD	Mean	SD	Mean	SD
5 mg	21.7	13.5	0.04	0.01	6.72	4.04
10 mg	44.8	37.7	0.03	0	15.10	10.24
20 mg	68.7	24.8	0.03	0	53.81	8.76

Cmax: maximum serum concentration achieved after administration.
Tmax: time taken to reach Cmax.
AUCt: area under the concentration vs. time curve from time 0 to t.
SD: standard deviation.

randomised into three groups to receive a single exposure of 5, 10 or 20 mg and the results were used to inform the second part of the study. Part B involved 16 (new) subjects who were administered multiple doses of 10 or 20 mg daily for 7 days. In both parts vital signs, including ECG and spirometry were recorded prior to and post administration and 7 days following treatment. Subjects also conducted a bitter taste test and were also questioned regarding the flavour and characteristics of the formulation after administration [22]. Pharmacokinetic data is summarised in Table 1.

i3 Research managed and administered the 2006 phase II clinical study entitled "A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose Study to Evaluate the Safety, Tolerance, and Efficacy of Orally Inhaled Hydroxychloroquine Sulfate (HCQ) via The AERx® System in Asthmatic Subjects" which confirmed that a dose of 20 mg daily delivered via oral inhalation of an aqueous solution by the AERx® (50 μL dosage volumes with 5 mg per dose as before) can be tolerated for up to 21 days [23]. However, the formulation failed to meet either its primary or secondary clinical endpoints for asthma treatment. The phase II study was carried out across 6 centres in Poland with Professor Piotr Kuna acting as principal investigator. In the study, 110 patients were randomised in a 3:2 ratio to receive active or placebo (34 female and 32 male patients received HCQ and 18 female and 26 male patients received placebo). Subjects using inhaled corticosteroids discontinued this treatment for a fortnight prior to the beginning of the study. Throughout the study the subjects were asked to record their morning and afternoon peak expiratory flow rate (PEFR), the asthma symptom scores, nocturnal awakenings, use of rescue medication, and concomitant medications on a daily basis. The primary efficacy variable was the relative change in FEV_1 compared to that patient's baseline which was measured daily (and for which there was no statistically significant difference after treatment compared to placebo). Notably, and importantly with respect to HCQ treatment of COVID-19, no participant experienced statistically or clinically significant ECG changes, and side-effects were minor (headache, nausea) concluding that, "…*the overall safety profile of HCQ was good and that the drug was well tolerated.*" [23].

It should be noted that, at a concentration of 100 $mg.mL^{-1}$, the solution used in Aradigm's phase I and phase II clinical studies was hypertonic and, while no adverse effects associated with solution hypertonicity were observed due to the very small dosage volume (50 μL) administered, HCQ should be formulated as an isotonic solution if used with standard nebuliser equipment whereby larger volumes are delivered.

Like other quinoline derivatives [24], HCQ has an extremely unpleasant and bitter taste [25] and Aradigm previously filed a patent of a liposomal formulation to mask the taste of hydroxychloroquine (US20080138397A1). Although taste masking was not problematic in the phase I or II trials, where a dosage volume of only 50 μL was delivered using the AERx® device, use of a standard nebuliser is likely to result in greater drug deposition in the oropharynx, and intolerability may arise via the cough reflex, as described in the patent. As reformulation to mask the taste of HCQ would "reset" this formulation and thereby necessitate additional pre-clinical/clinical studies, other options must be explored. Further, as pharmacological treatments to supress the cough reflex may not be appropriate in this application, treatments such as simple linctus or honey and lemon could be employed. These have shown efficacy in viral respiratory tract infections [26] and have been demonstrated to increase the cough threshold against a single-inhalation capsaicin challenge [27,28]. In addition, peanut butter or fruit concentrate have been demonstrated to improve the tolerability of other bitter agents such as ritonavir suspension [29]. Pre-administration of such treatments/food substances prior to HCQ administration by nebulisation is therefore recommended, where possible.

Recommendation

Therefore, we advocate for early treatment or prophylaxis of COVID-19, using HCQ as an inhaled aerosol, to deliver the drug directly to the lungs at a lower dose (up to 20 mg daily) than that required for oral systemic delivery. This may improve efficacy and potentially improve the risk/benefit ratio associated with HCQ therapy particularly in the elderly population.

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Declaration of Competing Interest

The authors declare that they have no competing financial interest. The HCQ formulation was developed and IP filed by APT Corporation. The clinical and regulatory work was done by Aradigm under contract to, and paid for by APT. While both corporations no longer exist, the rights to the data have since been licensed to Pulmoquine and development is progressing for COVID-19. Appropriate intellectual property has been filed.

Authorship statement

JF conceptualised this project. OK and AMH drafted the manuscript and OK preformed the analysis of the ClinicalTrials.gov data. FD provided the phase I and II clinical data and described the formulation. Discussions with SR, JF, NO'R and BM helped develop the idea. GW and AMH acquired funding to support the project. AA was responsible for logistical arrangements. All authors reviewed and agreed to the final manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.110110.

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