Book Chapter

What is the Best We Can Do with Hydroxychloroquine for COVID-19?

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Foreword

The pandemic of coronavirus disease 2019 (COVID-19) has been raging and lingering for almost the last three years on this planet. Now it is a right moment to look back what happened and to learn meaningful lessons. Based on our own experiences in early 2020 when the first wave hit the Europe, we composed a proposal for easy control of COVID-19 and submitted it to different levels of healthcare authorities, though without any responses. Then, we expanded this proposal into a manuscript, which had been repeatedly rejected by numerous medical journals, and eventually it was accepted and published, provided lots of "hypothesis" wording throughout the text must be added [1]. Meanwhile, we purchased quantitative over-the-counter hydroxychloroquine (HCQ) for off-label treatment of the identified COVID-19 outpatients free of charge. So far, hundreds of early patients have been quickly cured by HCQ without any noticeable side effects, hospitalization, death, and sequelae. Such encouraging outcomes have been coincidentally supported by the real time online big data that show about 100% percent safety and efficacy once HCQ is used around 3 days of COVID-19 onset [2]. We believe if this approach had been widely adopted, the majority of the covid-19 mortality in the world could have been avoided, and in addition no subsequent healthcare overload, economic crisis and social turmoil would occur. Thus, we decide to publish a book chapter to document this important event in human history. Another reason for republishing this work is to compensate the second important author Prof. Dr. Miaojia Zhang here whose name was omitted somehow during the submitting procedure and not allowed by the journal [1] to be added at the proof-reading stage. The main contents of our published paper [1] are retained into this chapter, reflecting the knowledge two years ago, with only a little text rephrasing, reference adjustment and modification on figures for updated information.

Abstract

There are widespread anecdotal reports of seemingly successful treatment among the early (3-7 days from symptoms) stage coronavirus disease 2019 (COVID-19) patients with the drug hydroxychloroquine (HCQ), and randomized placebo-controlled trials of HCQ in outpatient settings are underway. In this chapter we (i) report observational evidence and present scientific reasoning as to why early treatment with HCQ may succeed while treatment later in the disease progression is likely to fail, and (ii) propose a public health regime under which HCQ may be used to mitigate the impact of the current pandemic.

Keywords

COVID-19; Pandemic; Early Treatment; Hydroxychloroquine; Lockdown

Introduction

The current coronavirus disease 2019 (COVID-19) outbreak caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has swept the world since late 2019 [3], with over 643.0 million confirmed patients and over 6.6 million deaths to date [4], leading to unprecedented societal costs and a global economic crisis. Now, countries are confronting the dilemma of how to resume normalcy after lockdowns while still containing the current COVID-19 pandemic and its possible subsequent resurgences [5,6].

Few medications for COVID-19 have been approved by the US Food and Drug Administration (FDA) and other authorities [7]. Clinical management relies mainly on spontaneous recovery by the patient, symptomatic treatment and implementation of supportive measures. Due to the urgent nature of this viral pandemic, physicians can, under emergency use authorizations (EUA) and emergency investigational new drug (EIND) rules, access and prescribe existing medicines approved or licensed for other indications to COVID-19 patients for compassionate, expanded or off-label use.

Currently, for the treatment of COVID-19, there are thousands of clinical trials around the globe on numerous new investigational agents or drugs approved already for other indications [8]; among these are chloroquine (CQ) and its derivative hydroxychloroquine (HCQ, widely marketed as Plaquenil®), used for decades as anti-malaria drugs and found to have broad- spectrum antiviral potential [9], with HCQ being preferred to CQ for its better efficacy and safety [10]. HCQ has also been approved as an immunomodulatory agent for the long-term treatment of chronic rheumatic diseases such as systemic lupus erythematosus and rheumatoid arthritis [11]. However, CQ and HCQ are controversial in terms of their efficacy and safety for clinical control of COVID-19 [12,13]. A large-scale registry analysis of data from 671 hospitals in 6 continents recently reported no observed benefit in patients, instead an increased risk in hospital mortality associated with treatment of COVID-19 patients with either HCQ and CQ (with or without a macrolide); however this study was subsequently withdrawn by three of its four authors [14]. Treatment with HCQ, azithromycin, or both, compared with neither treatment, was not significantly associated with differences in in-hospital mortality, on a basis of a retrospective study of 1438 hospitalized patients [15].

Potential Efficacy and Its Possible Mechanisms

Despite controversies, accumulating evidences have been demonstrating the potential anti- COVID-19 activity of both CQ and HCQ, on the basis of observational studies, randomized controlled clinical trials and basic studies [7,10-14,16-18]. Risch reviews in detail the experiences in the USA and other countries of administering HCQ, with or without an antibiotic, to early stage COVID-19 patients, concluding that the observational evidence of efficacy is very strong [19]. Formal clinical trials in outpatient setting have now begun, with the first results expected in

September, 2020. They may exert antiviral activities in the following possible ways [11,20]: 1) reduce the terminal glycosylation of angiotensin- converting enzyme 2 (ACE2) receptor on the surface of cells, thus interfering the binding of SARS-COV-2 to the ACE2 receptor; 2) increase the pH of lysosomes and endosomes to prevent the fusion process of the virus with host cells and subsequent virus replication; 3) prevent antigen processing and major histocompatibility complex class II-mediated autoantigen presentation to T cells, which reduces T cell activation, differentiation and expression of co- stimulatory proteins and cytokines (e.g. IL-1, IL-6 and TNF-α) produced by T cells and B cells; and 4) disrupt the interaction of DNA/RNA with toll-like receptors (TLRs) and the nucleic acid sensor cyclic GMP-AMP (cGAMP) synthase (cGAS) and therefore the transcription of pro- inflammatory genes cannot be stimulated [21]. Now, it is known that COVID-19 is primarily a respiratory disease but also an illness that can affect multiple organs [22,23]. When the SARS- CoV-2 virus enters the human body, it breaks into cells with the help of two proteins, ACE2 and transmembrane protease serine 2 (TMPRSS2), which are expressed on the cell. There are enriched ACE2 and TMPRSS2 at olfactory epithelium of nasal mucosa that presents the first frontline per SARS-CoV-2 invasion [24]. In this sense, HCQ should be administered early to COVID-19 patients within the first week of symptoms onset to prevent the virus from infecting the deeper type 2 lung cells through the ACE2 receptors and thus to stop disease progression.

According to current COVID-19 guidelines, CQ and HCQ should only be used in clinical trials or emergency use programmes [25,26]. Now, most clinical trials on CQ and HCQ are found in two extreme cohorts: either “too late”, in severe stage hospitalized patients [12,13], or “too early”, among people at risk for possibly contracting SARS-CoV-2 [27]. The reported unsatisfactory outcomes in the first

scenario [12-14,28] are understandable, because the disease has advanced to the deeper airway with the characteristic X-ray ground glass opacity and multiple other organs, even without remaining SARS-CoV-2; and all severe pulmonary, renal, cardiovascular and cerebral complications come from late stage of disease pathologies with a high death rate. On the other hand, the prophylactic effects of HCQ was reported to be uncertain [27]. However, the current study has several limitations, such as lack of consistent diagnosis for COVID-19 and long duration between exposure and administration of HCQ [29]. The SARS-CoV-2 load is low during early onset before massive viral replications in the body, hence only low dose of HCQ is needed, thus better safety, without additional need for Azithromycin that is known to be synergistic with CQ or HCQ for cardiac toxicity [7,30,31]. Therefore, both timing and dose appear crucial for the optimal use of HCQ in COVID-19 treatment. More recently, sequela such as fatigue, shortness of breath and headache are reported among patients 3 months after their recovery, even those with "mild" symptoms can suffer from Covid-19 for a long time [32,33]. However, among our own over 200 cumulated early outpatient cases successfully managed with small doses of HCQ, none of them complained of similar longed sequela months after their recovery.

Protocol for implementing a Strategy to contain the COVID-19 Pandemic based on Administering HCQ Early in the Disease Onset

Self-evidently, observational evidences such as those referenced in this paper is an insufficient basis on which to implement nationwide strategies and protocols for administration of HCQ to early stage COVID-19 patients, the success of the treatment remains anecdotal. However, given the strong observational signals, it is not too early to

start work on the design and planning of such strategies and protocols, in anticipation of possible (or likely in the authors' view) positive outcomes of the randomized controlled clinical trials. It is accepted by public health authorities and medical regulatory bodies that the very high number of continuing fatalities in the current pandemic calls for a speeding up of the normal time-scales and processes for drug development and approval [19]. Absence of evidence does not necessarily imply evidence of absence. Additionally, given the urgency of the pandemic, some flaws in the published studies may be acceptable, such as lack of randomization or blinding, retrospective design and adoption of an unvalidated surrogate of end point, etc.

It is known that infection-control strategies focused solely on symptomatic residents are not sufficient to prevent transmission [34], and conventional infection-control and public health strategies rely heavily on early detection of the disease to contain spread [35]. In both cases, identification of laboratory-confirmed individuals is essential. Given the presence of asymptomatic SARS-COV-2 carriers and presymptomatic COVID-19 patients at incubation stage, containment of SARS-COV-2 transmission would anyway be challenging [34-36] despite the extremely high costs for all preventive measures. Given the considerably cost-effective, safe and excellent outcomes from our own experiences and positive observational reports with HCQ [10,11,13,16,18,30], we would propose, prepare, and implement promptly the following outlined protocol in this and possibly subsequent outbreaks of COVID-19 (Figure 1).

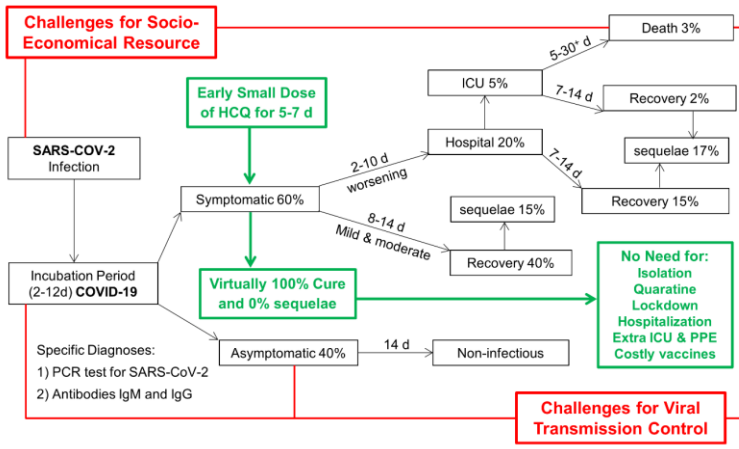

Figure 1: A schematic regime for COVID-19 pandemic control: estimated clinical scenarios (black), socioeconomic and epidemiological challenges (red), and a potentially simple solution (green). Note: SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; COVID-19: coronavirus disease 2019; PCR: polymerase chain reaction; IgM: Immunoglobulin M; IgG: Immunoglobulin G; HCQ: hydroxychloroquine; d: days; ICU: intensive care unit; PPE: personal protective equipment; +: or more.

1) By way of preparation, ensure the availability of sufficient quantities of the (easily prepared, small molecule) drug in oral doses, together with guidelines for prescription and use consistent with the regime outlined in this protocol. Proper provision, allocation and distribution of HCQ or CQ may help balance treatment between COVID-19 patients and dermatological or rheumatic patients who are previously prescribed with these drugs [36].

2) Additionally, make tests for the pathogens such as SARS-CoV-2 and their variants as well as their relevant serum antibodies ready as early and as widely available as possible.

3) In positively tested patients or in suspected cases without tests, administer HCQ at a dose to be finalized in light of the clinical trial results, but which we envision will be in

the range 100-200 mg, twice or thrice per day, for 5-10 days, a level which is likely to be highly efficacious because of patients' low viral load at this early stage and which can prevent patients from advancing to more severe stages.

4) Start interventions as quickly as possible, and ideally within 3-7 days of symptom onset, well before the disease advances to the patients' lungs (pneumonia) or other visceral organs, which otherwise would be too late to achieve optimal medical and societal outcomes.

5) Antibiotics such as azithromycin can be combined especially when bacterial infections are observed; however in the absence of such observations, administration of HCQ would not be accompanied by azithromycin that may complicate the therapeutic regime with a known synergy for cardiac toxicity [7,28]. When the patient is dosed with HCQ or CQ and azithromycin, electric cardiograph (ECG) is recommended to use for monitoring potential cardiac adverse effects such as QT prolongation [38,39]. In addition, both basic researches and a retrospective clinical study implied the possible benefit of supplemental Zinc to hydroxychloroquine and azithromycin [40-42]. Nevertheless, perfectly designed and carefully preformed clinical trials may help address the necessity of such combinatory regimes.

6) Repeat or perform the nucleic acid tests, antibody test and/or T cell tests to follow up the therapeutic efficacy and to monitor potential post-infection herd immunity [43]. Concerning immunity of convalescent patients, the adopted immunity is likely mediated by SARS-CoV-2- specific T cells, rather than antibody [44,45]. More interestingly, people with mild or asymptomatic COVID-19 demonstrate T-cell-mediated immunity, even if they have not tested positively for antibodies [46]. Herd immunity thus achieved actively (i.e. through therapy- mediation) would avoid the heavy mortality in the population, which would be required to achieve herd immunity passively in the current and possible future outbreaks of COVID-19 [47].

7) Societal regimes for protecting individuals against infection transmission, such quarantines, social distancing, city lockdowns, should not generally be needed under this protocol, but should continue to be applied mainly to those population cohorts, such as the elderly or those with certain pre-existing health conditions, who are particularly susceptible for SARS-CoV-2 infection. Such a principle would also applies to the use of costly vaccines.

In line with the above proposals, our own encouraging outcomes during the last 2.5 years have been coincidentally supported by the real time online big data that show nearly 100% percent safety and efficacy once HCQ is used around 3 days of COVID-19 onset [2], as illustrated by Figure 2.

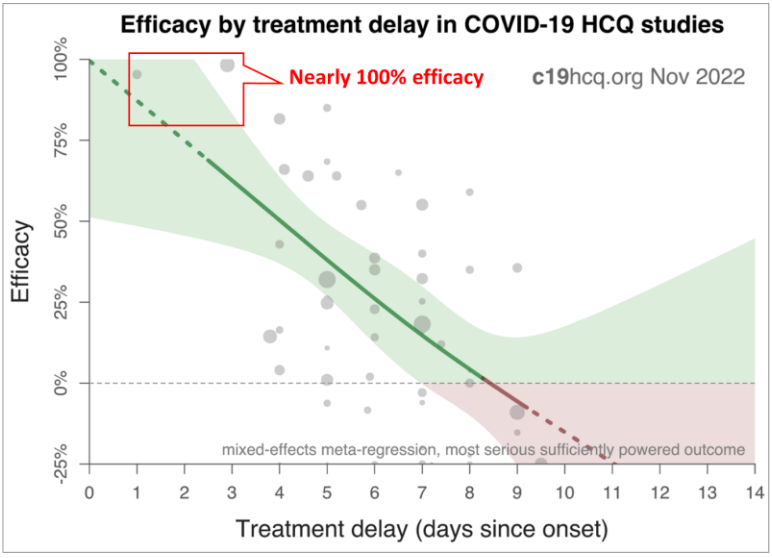

Figure 2: Meta-regression showing efficacy as a function of treatment delay in COVID-19 HCQ studies. Early treatment is critical. (Adapted from Ref 2. https://c19hcq.org/meta.html).

In summary, we believe that, following confirmatory clinical studies, the early administration of HCQ, with an antibiotic or zinc where indicated, could become the front line of the global strategic response to this and later outbreaks of COVID-19, allowing a great reduction in the need for measures such as quarantines, isolations, social distancing, city lockdown and in the need for hospitalizations. We have proposed a protocol for implementing this strategy, which should be refined and prepared in parallel with, rather than delayed until the definitive outcomes of placebo controlled randomized clinical trials on early (<7 days) onset COVID-19 patients.

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