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Short Communication

Problems of Not-Using Hydroxychloroquine (HCQ) for COVID-19 Patients

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DEAR COLLEAGUES,

We recognize that recently the Coronavirus Task Force and Vice President Michael Pence do not talk about Hydroxychloroquine in press briefings. I think this dramatic change occurred after the Dr. Boulware's report [1]. But the report can't be an absolute reference to recommend against the use of Hydroxychloroquine for COVID-19 patients and there was a withdrawal of the report that denounced the Hydroxychloroquine use for the COVID-19 treatment [2]. Recently there is a report recommending the use of Hydroxychloroquine + Azithromycin for COVID-19 patients [3].

Dr. Boulware's study cannot be a standard reference to recommend against the use Hydroxychloroquine for prevention for COVID-19 because it has problems in methods: first, total enrolment; second, finished participants; third, COVID-19 positive participants; forth, reported numbers in the result; and fifth, percentages of the benefit. First, he designed to enroll 1,242 persons but ended in 821 persons, which will dramatically increase type I and type II errors. Second, among 821 participants who had undergone randomization, "96 did not complete the day 14 follow-up survey": 8 were officially withdrawn; 19 were checked by investigators; 17 completed (only) some follow-up surveys; and a total of 52 participants never completed any surveys after enrollment and did not respond to investigators e-mails, text messages, or telephone calls [1]. This means that only 725 among 821 participants finished the full study. Third, the report may need only confirmed cases as true COVID-19 patients. In the COVID-19 related study, the PCR-proven SARS-CoV-2 positivity can eliminate confounding patients with similar symptoms caused by Influenza, Parainfluenza, and Rhinovirus, etc. Even though the study presented 107 participants as probable COVID-19 patients, it had only 20 confirmed cases (19%) and the rest of 103 was unconfirmed and only had similar symptoms without PCR-proven SARS-CoV-2 positivity (81%). Forth, the final result included 96 participants, who did not complete the study, in the total number of participants who finished the study. Fifth, the percentage outcomes of Hydroxychloroquine therapy for postexposure prophylaxis against COVID-19 should be changed according to the final and true number of participants of the study by excluding "96 participants (who) did not complete the day 14 follow-up survey".

In the field of COVID-19 treatment, there are two groups of countries: one group uses Hydroxychloroquine for asymptomatic or mild symptomatic COVID-19 patients; and the other group not only renounces it but also recommends against the use of it. Republic of Korea (South Korea) and Turkey belong to the former group, and the United States belongs to the latter. In Republic of Korea, Korean COVID-19 patients have been treated with therapeutics including Hydroxychloroquine, and the cumulative mortality rate is 2.24% (282/12,602) [4] Turkey also treats COVID-19 patients with therapeutics including Hydroxychloroquine and has a cumulative mortality rate of 2.62% (5,025/191,657) [4]. But the mortality rate of the U.S. is 5.19% (120,955/2,329,463) as of June 26, 2020 [4]. The United States / the NIH has still revoked the use of Hydroxychloroquine and recommended against the use of it for the treatment of COVID-19 except in a clinical trial even on the June 26, 2020 update [5] Some portions of the difference of mortality rates of 2.57% ~ 2.95% between two groups of countries could be caused by adding or not adding Hydroxychloroquine as one of the treatment medications for asymptomatic and/or mild symptomatic high-risk COVID-19 patients.

Until now, Zinc, [6] Vit C, [7] and Vit D [8] have been proven to be a help to treat COVID-19 patients. Also, Hydroxychloroquine + Azithromycin are recommended for early symptomatic and high-risk COVID-19 patients [3]. But there are caveats in using the combination of Hydroxychloroquine + Azithromycin.

American College of Cardiology introduced risk levels and risk score for drug-associated QTc prolongation, and Hydroxychloroquine and Azithromycin can prolong QTc [9,10].

Intravenous injections of Remdesivir/Dexamethasone can be recommended only for admitted COVID-19 patients. But in an outburst of COVID-19 pandemics, oral medications for symptomatic COVID-19 outpatients and for asymptomatic SARS-CoV-2 carriers may be needed. In this context, not only to treat symptomatic, high-risk COVID-19 outpatients but also to prevent the full-blown progression to COVID-19 in asymptomatic SARS-CoV-2 carriers, a cocktail of medications is recommended (Table 1).

Table 1: A cocktail of oral medications for COVID-19 high-risk outpatients.

Risk Levels for Drug-induced QTc Prolongation [9,10]	HCQ 400 mg (200 mg)	Vit C, 2 gr	Vit D, 1,000 IU	Zinc 100 mg	Azithromycin (AZ) 500 mg for 5 days	Daily costs for prevention
Low risk (≤ 6points)	400 mg, ●	●	●	●	▲	0.7 US$ 0r 2.5 US$ for 5 Days and then 0.7 US$ in lower respiratory infectious cases
Moderate risk (7-10 points)	200 mg, ●				▲	
High-risk (≥ 11 points)	X				▲	
Possible Daily Cost	0.25 US$	0.25 US$	0.1 US$	0.1 US$	1.8 US$	

Legend: ● (Recommended), X (Not-recommended)
▲ (Treat in symptomatic or in respiratory infectious cases).
There are evidences, if not "proof", that the early use of HCQ + AZ for treatment of symptomatic high-risk COVID-19 patients showed major efficacy in two non-randomized controlled trials [3].
HCQ has direct antiviral effects and plays an ionophore to introduce zinc into cells, which interferes the replication of SARS-CoV-2 virus [6]. Orally administered vitamin C in doses of mean 2.0 grams per day reduced the length of ICU stay by 7.8% [7]. To reduce the concentrations of pro-inflammatory cytokines and the viral replication rates, the 25(OH)D concentrations should be above 40-60 ng/ml (100-150 mmol/L) [8]. The estimated mortality induced by the cardiac dysrhythmia is 9/100,000 in HCQ + AZ users, [3] so the high-risk group of drug-induced QTc prolongation [9,10] may not be recommended to treat with HCQ + AZ. Calculation of risk score for QTc interval prolongation can be done by adding the points of each risk factor, where the Maximum Risk Score is 21: 1 point for each risk factor (Age ≥ 68 years, Female sex, Using loop diuretics); 2 points for each risk factor (Serum K + ≤ 3.5 mEq/L, Admission QTc ≥ 450 ms, Acute MI); 3 points for each risk factor (Using more than two QTc-prolonging drugs, Sepsis, Heart failure, Using one QTc-prolonging drug) [10]

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