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Safety and Efficacy of Chloroquine/Hydroxychloroquine in SARS-CoV-2 Infection

ALBERTO BORETTI

Prince Mohammad Bin Fahd University, Al-Khobar 31952, Kingdom of Saudi Arabia

Corresponding author: E-mail: a.a.boretti@gmail.com

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This work summarizes the available evidence of the use of chloroquine/hydroxychloroquine (CQ/HCQ) in SARS-CoV-2 infection. Most of the published works indicate CQ/HCQ is likely effective against SARS-CoV-2 infection, almost 100% in prophylaxis and mild-medium severity cases and 60% in late infection cases. The percentage of positive works is larger if those works conducted under a probable conflict of interest are excluded from the list. Despite this overwhelming evidence from independent studies, the use of CQ/HCQ is currently limited or prevented in many western countries, based on a very singular examination of the science. The case of a work published in late May 2020, despite being openly defective and then retracted, prompted the World Health Organization (WHO) to ban the use of CQ/HCQ. This position has not yet rectified, thanks to the results of the not less questionable RECOVERY trial, where very sick patients were administered more than double the dose, over more than double the time, recommended for asymptomatic patients in current protocols of other countries, where CQ/HCQ are used for asymptomatic and mild but not severe pneumonia critically ill patients. While the case fatality rate does not depend only on therapies, it is finally shown based on the number of cases and fatalities per million and the case fatality rate as the western countries enforcing the ban on CQ/HCQ did not perform better, but much worse, than other countries, also because of therapies.

Keywords: Chloroquine, SARS-CoV-2, Safety, Efficacy.

INTRODUCTION

Discovered in 1934, chloroquine has been widely and safely used across the world especially for malaria. It is on the World Health Organization's list of essential medicines and available as a generic medication. Proposed recently for SARS-CoV-2 infection, this drug is at the center of a controversy between those who support this specific use, mostly independent researchers and those who question efficacy and safety, mostly dependent researchers.

As of today, most of the works published on the matter indicate that chloroquine/hydroxychloroquine (CQ/HCQ) is likely effective against SARS-CoV-2 infection, almost 100% in prophylaxis and mild-medium severity cases and 60% in late infection cases [1]. The summary includes a total of 146 works and out of these works, *in vitro*, *ex vivo*, *meta*, theory, safety, review, news and retracted items are not included in the percentages and study count. There are then 88 studies left, with 50 of them peer-reviewed, classified as positive, negative, and inconclusive [1] concludes as global CQ/HCQ studies pre-exposure prophylaxis (PrEP), post-exposure prophylaxis (PEP) and early treatment studies show efficacy, while late treatment shows mixed results. It is noteworthy that some recent peer-reviewed works [2-34] supporting the use of CQ/HCQ for SARS-CoV-2 infection.

Despite the overwhelming evidence from the independent studies, the use of CQ/HCQ is prevented or discouraged in most western countries based on a very singular examination of the science behind this use. SARS-CoV-2 had so far a much higher number of fatalities in the supposed to be more advanced countries, believed to enjoy a better health system, for example, the United Kingdom, Belgium and the United States, than in poorer and supposed to be less advanced countries, for example, most of the countries of Africa or even Asia. While other factors are affecting the number of fatalities, where CQ/HCQ and other antivirals are not used, there are more fatalities rather than fewer.

A case study published in late May 2020 was discussed despite that openly flawed and then retracted after an outcry

by the scientific community, the World Health Organization (WHO) take a call for the ban of the use of CQ/HCQ and the performances in terms of fatalities, of countries which are using CQ/HCQ *versus* those countries are not using CQ/HCQ.

Biased judgment of poor safety and efficacy of CQ/HCQ: The judgment of poor safety and efficacy of CQ/HCQ for SARS-CoV-2 infection is based on two flawed works; the first work claimed that CQ/HCQ is unsafe and not efficient for SARS-CoV-2 infection [35]. It was based on an unrealistic dataset which was unavailable for review.

A retrospective study [35], published on May 22, 2020, was immediately employed to call for an end to the use of CQ/HCQ for SARS-CoV-2 infection by the WHO [36], which was openly defective. If the data could have been reliable, nevertheless the conclusions will not have been warranted. This retrospective study was nominally only an examination of carefully selected registries, in the vast majority from selected hospitals in the United States of America (66% of total). For completely unclear reasons, somewhere patients were given one specific option in one specific hospital in one specific state or one specific country. Which were the reasons that guided the choice of the selected hospitals and patients were not known.

This was not a double-blinded, placebo new study where patients were randomly given the option to use CQ, HCQ, CQ + macrolide, HCQ + macrolide or placebo, as claimed necessary to evaluate safety and efficacy of CQ/HCQ use for SARS-CoV-2 infection. This was a selection of registry. This study only considered severe cases and not prophylaxis or mild/medium cases, which are otherwise the best opportunities offered by CQ/HCQ. This article should not have impacted on the other uses, as the use of CQ/HCQ on mild/medium cases or prophylaxis was not covered.

While parameters under CQ/HCQ administration (*e.g.* zinc or vitamin C or D) must be controlled, there was no mention these parameters were monitored and controlled. CQ/HCQ should be used "*giving no contraindication applies*" and are suggested not to be used simultaneously with other medications. There was no mention these guidelines were followed. Finally, the main author was reporting the personal fees from the pharmaceutical companies and the database was claimed to be funded by a corporation, with the opportunity of conflict of interest impact judgment.

Most importantly, there were also doubts about the reliability of the data [37,38]. For example, no Australian health official confirmed the sharing of SARS-CoV-2 data that is claimed to have collected and analyzed the huge amount of data [38]. How this company could have collected and analyzed all these tens of thousands of patient records from hundreds of hospitals worldwide was unclear. Data and code were not made available upon submission.

Many independent researchers immediately wrote to The Lancet raising the flag about this work. Being one of them, my comments were rejected many weeks after the paper was retracted. The retraction was motivated because the company that purportedly analyzed the raw data did not allow their validity to be independently validated [39]. None of the many comments submitted to The Lancet got published. On the opposite, one minor flaw was commented by the editors [40] on May 30, 2020. Then the editors published an expression of concern [41] on June 3, 2020. Finally, 3 of the 4 authors published a retraction on June 5, 2020 [42]. Since then, the original paper only reports the "*retracted*" word in front of the title, and the word retracted across the text. However, it has not been removed, as occurred to other discredited works. Not my comment nor the comments by others got published.

A work of Mehra *et al*. [35] has been cited so far 424 times (Google scholar), with most of the citations neglecting the fact the work was flawed and it has been withdrawn. This work is still considered by some proof CQ/HCQ are unsafe and not effective. The failure to address the major flaws during the peer review, and also the similarly improper post-publication review of the work, namely the commenting and citation processes, casts serious doubt about the reliability of the peer review process strangled by the conflict of interest. The list of donors of the WHO is the most likely explanation why a flawed paper was overrated to call for the ban of CQ/HCQ for SARS-CoV-2 use, while all the works in favor of the use of CQ/HCQ were simply neglected.

While the work [35] should have been recognized as flawed during the peer review, and it was not, much different treatment is now reserved for late works supporting the use of CQ/HCQ for SARS-CoV-2 infection. For example, the review paper [43] was proposing an objective analysis of papers in favour or again the use of CQ/HCQ for SARS-CoV-2 infection, also mentioning the bias by a conflict of interest and concluding CQ/HCQ were very likely helpful in some circumstances, and opposite even negative in others, which are very well established in the literature. The acceptance communicated July 17, 2020, was then transformed in rejection on the way to production by July 27, 2020, likely because of the politically incorrect conclusion as well as the mention of the evident conflict of interest biasing the assessment. The fact that every submission is communicated to the WHO before being published does not speak in favor of independence.

As soon as the claims of the work [35] were demystified, immediately the preliminary results of the RECOVERY trials were proposed to the mainstream media to permit enforcement of the ban by the WHO [44]. The RECOVERY (Randomised Evaluation of Covid-19 therapy) was suggesting higher fatalities for those treated with CQ/HCQ, however the result of using much higher than reasonable doses administered over much more time than reasonable for those not intended to receive these doses [44], very sick patients often under oxygen or ventilation. The RECOVERY trial demonstrates absolutely nothing against the safety and efficacy of CQ/HCQ when properly used. The work was supported by the same charity is the major donor of the WHO. The University who supported the RECOVERY trials is deeply involved in the development of a SARS-CoV-2 vaccine. Similarly supportive of a SARS-CoV-2 vaccine is the charity, which is the first and foremost supporter of the WHO, also support the GAVI vaccine alliance. The present director-general of the WHO is a former board director of GAVI. This could be configured as a conflict of interest.

Assessment of safety *versus* efficacy of CQ/HCQ by comparing protocols and fatality rates: Most of the peer

review works is still in favour of the use of CQ and HCQ against SARS-CoV-2, especially in mild and asymptomatic cases. It is important to note as those countries that have been free to decide their therapies and continued to use CQ/HCQ do not have higher fatalities, but lower than those who followed the suggestions of the WHO (or the US NIH and UK NIH). As the more or less effective lockdown policies and therapies should not be decided by the media of the western countries, here in Fig. 1 are the number of cases, the fatalities, and the case fatality rate (the number of fatalities divided by the number of cases) of reference countries such as the US, the UK, Belgium, Sweden, Israel, UAE, Qatar, Taiwan, South Korea and Japan.

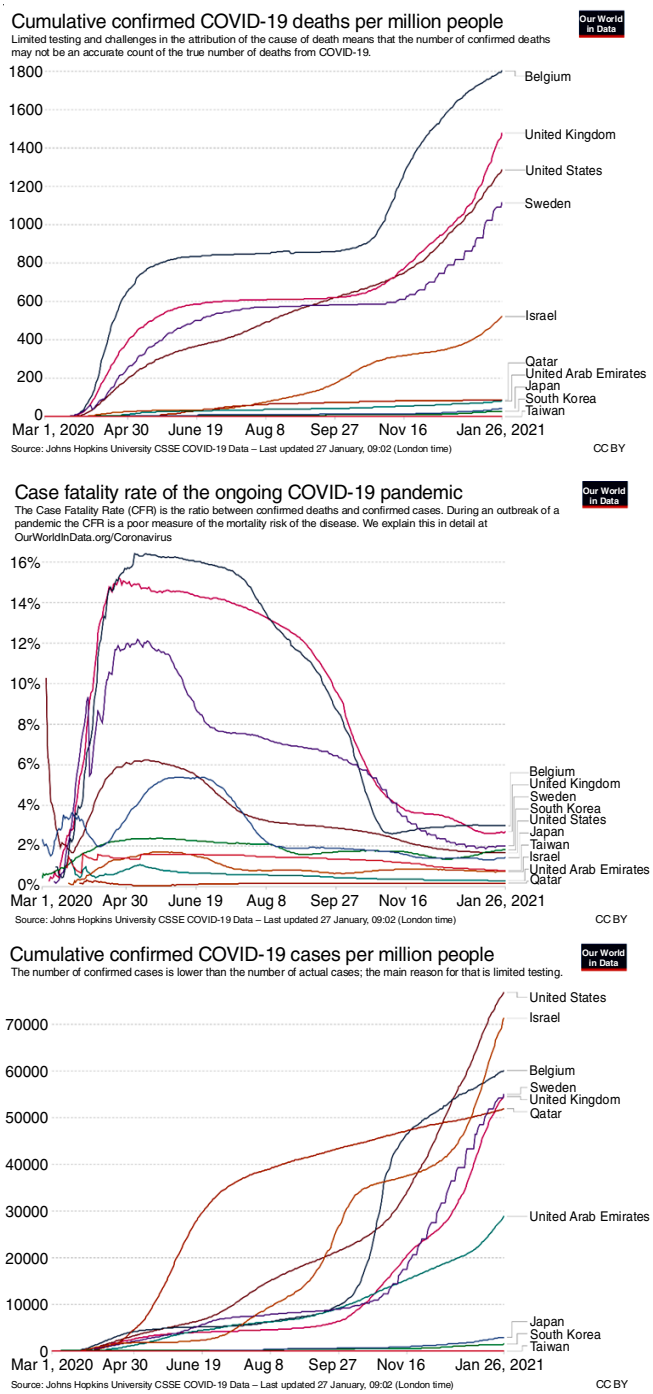

Fig. 1. Cumulative number of cases, number of fatalities and the case fatality rate for the US, UK and Belgium, Sweden, Israel, Taiwan, South Korea, Japan, Qatar and United Arab Emirates. Images from ourworldindata.org.

The media is promoting the false view that the fatalities of the western countries and their closer satellites are inevitable, and that only more restrictions could have reduced them. They attribute the different number of fatalities to the different restrictions, and the different spreading, as it is not the case. The SARS-CoV-2 emergency will not be solved by harsher restrictions enforced over longer times but by learning from experience.

The number of casualties is not only a result of the number of infected, but of who specifically is infected, and how this specifically infected person is treated. The cumulative number of cases, number of fatalities, and the case fatality rate show the US, UK and Belgium performed badly. Sweden and Israel performed better. Taiwan, South Korea, Japan, Qatar and United Arab Emirates performed much better, following different approaches, limiting cases or limiting fatalities between cases. Qatar had about the same cases as UK and Belgium. But a case fatality rate of 0.2 *versus* 2.7 and 3%. Japan, South Korea and Taiwan had very few cases. The UAE had half the cases of Belgium, but 10 times smaller case fatality rate, 0.3 *versus* 3%. From 0.2 to 0.3% to about or well above 3% the difference is huge and also involves similar individuals for age or comorbidities.

The UK, Belgium and the US did and are doing almost everything wrong not only in containment but also in treatment. Going up and down with generalized, unsustainable, lockdowns does not help. Leaving infected patients untreated till they get to ventilation or oxygen, packed in hospitals, refusing to use the therapies successfully implemented somewhere else, only produces more fatalities. Fatalities in confirmed cases are not only driven by therapies, as many other factors are relevant. However, countries such as Qatar and the UAE successfully use CQ/HCQ in asymptomatic and mild cases, while the use of this antiviral and the many other antivirals proposed in combination in Qatar and the UAE, but is practically prevented in the US, UK and Belgium. In the UAE [45], CQ/HCQ is part of the therapeutic options for high-risk asymptomatic patients, symptomatic patients without pneumonia for 5 days or patients with pneumonia for 7 days at doses one half over half the time of what was administered to severely ill patients mostly under ventilation in the RECOVERY trial.

Conclusion

There are many studies published in the literature which show positive results of the use of CQ/HCQ in SARS-CoV-2 infection, especially asymptomatic and mild to medium severity cases. Then, there are fewer studies that show neutral or negative results, in the most severe, late cases. For patients in the late stage of SARS-CoV-2 infection, CQ/HCQ is not supposed to work that much the same as every other known antiviral. The most relevant works that have been used to ban CQ/HCQ suffer from major flaws, being works which have been retracted or even works never peer-reviewed such as the RECOVERY trial. The CQ/HCQ is helpful in SARS-CoV-2 infection when properly used in asymptomatic and mild to medium severity cases.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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