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Mass intake of hydroxychloroquine or chloroquine in the present context of the Covid-19 outbreak: possible consequences in endemic malaria settings

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Abstract

World is currently experiencing a new pandemic for which no curative treatment is available. At this time, coronavirus disease 2019 (Covid-19) has reached 183 countries and has caused several deaths. Many reports presented chloroquine (CQ) and hydrochloroquine (HCQ), former drugs used against malaria, as the best current choice to fight this terrible disease. As these molecules had been withdrawn in malaria treatment policy due to chemoresistance, their reintroduction could have some consequences. Though local malaria prevalence could decrease for a while, molecular changes are likely to happen on some plasmodium falciparum genes involved in conferring drug resistance. This could threaten efforts in malaria control, if these molecules are widely administered.

Keywords: Malaria, Covid-19, SARS-Cov-2, Chloroquine, Hydroxychloroquine.

Ongoing COVID-19 outbreak and CQ

In December 2019, a new viral outbreak appeared in central China, in Wuhan province. It was quickly established that this new epidemic was due to a coronavirus which was recently named SARS-CoV-2 for severe acute respiratory syndrome coronavirus 2. This coronavirus disease (COVID-19) spread within a few months on all continents, causing numerous deaths and seriously disrupting both social and economic life. As of March 20th 2020, the number of cases worldwide amounted to 255,846 with 10,495 deaths (in 183 countries and territories) [1]. The absence of a curative treatment and an effective vaccine makes this struggle difficult, justifying current numerous testing of therapeutic molecules against this novel coronavirus (482 trials registered in China for example since December 2020) [2].

Among these molecules, chloroquine (CQ), an old antimalarial drug that had been widely used for decades and then withdrawn due to the spread of plasmodial resistant strains [3], was tested in China during the current COVID-19 outbreak and seemed to have given good results, justifying its inclusion in the 6th edition of the Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment published by the National Health Commission of the People's Republic of China [4]. In the same order of ideas, Wang et al. reported through a letter to the editor that chloroquine (and remdesivir) effectively inhibited SARS-Cov2 [5]. On another continent, in Europe, one French team have also discussed in their papers about the possible role of chloroquine against COVID-19 [6-7]. In addition to chloroquine, they also suggested that, hydroxychloroquine, a chemically similar molecule could be used in the management of Covid19 cases because of its less toxicity and its relative immediate availability [8]. Few days later, the same team published another article in which they reported encouraging results from a clinical trial comparing the use of hydroxychloroquine (HCQ) alone and in combination with azithromycin as treatment of COVID-19 [9]. One video posted online presenting these results was widely followed and shared (more than 800,000 views in only 4 days) [10]. In USA, President Donald Trump also publicly talked about the use of chloroquine in the fight against this new coronavirus [11].

As the number of Covid19 cases continue to rise worldwide without an "official" treatment, these two molecules become considered by many people as "the" solution to this pandemic.

It's wise to fear a future uncontrolled use of these two molecules by self-medication or even by a massive administration to confirmed cases.

Here we address a thought on the possible consequences of large use of chloroquine and/or hydroxychloroquine in countries where malaria is endemic.

Current CQ status in malaria endemic countries

Officially, CQ is no longer used in most endemic countries, as WHO recommended the use of artemisinin-based combination therapy in place [12]. Many studies showed reducing of CQ-resistant (CQ-R) strains pretty much everywhere, some years after treatment policy switch, but at variable levels [13-15]. It has even been suggested to reintroduce CQ, mostly in association with another molecule, in areas where CQ-sensitive (CQ-S) strains had taken back the top. But to date, no country has reused CQ in first-line malaria treatment.

Possible consequences on malaria prevalence

The use CQ or HCQ by a large number of individuals to protect themselves or to treat COVID-19 is likely to have an impact on the local malaria prevalence. It is now well admitted that there is an asymptomatic carriage of *P. falciparum* in areas of high or moderate transmission [16-17]. Therefore, it's probable that most of the people who will take CQ or HCQ would be asymptomatic carriers thus resulting in parasitaemia decrease or even suppression, depending on the posology administered and mostly if CQ-S strains supplants CQ-R strains.

This impact could be considered, to a certain extent, as a positive point for malaria control. Nevertheless, a rebound of malaria prevalence is to be feared some weeks after stopping CQ/HCQ intake due to the lack of associated vector control measures and movement of populations [18].

Possible consequences on chemoresistance

As CQ-R strains are still circulating, but at a lower level [19], use of CQ in areas where it was withdrawn for many years could lead to selection of resistant strains bearing mutations on the plasmodium falciparum chloroquine transporter (Pfcrt) gene, known as the basis of CQ-R [20]. It will mainly depend on the posology, treatment duration and the number of individuals who will take this molecule. In fact, sublethal drug concentrations have been incriminated in resistance development [21-22]. This would have no direct real consequence in the fight against malaria, since these molecules are no longer used in the management of active cases. However, many reports underline possible association between pfcrt gene and altered in vitro activity of other antimalarials, among which some drugs currently in use as partner-drug in ACT [23-26]. The current treatment strategy could be at risk if CQ or HCQ are largely used and over a long time period.

Conclusion

In the coming days, it's fair to assume that CQ and HCQ will be massively used in many parts of the world, in response to the ongoing COVID-19 outbreak. These molecules, if largely used, will surely have impact on local malaria prevalence and on chemoresistance in endemic regions.

Although a decrease in prevalence may seem positive, risk of molecular modifications within pfcrt gene is real. Assessment of drug resistance molecular markers should be scheduled within a short time after the end of the COVID-19 illness because no one can predict with certainty implications on global malaria control. Malaria scientists should be aware of this.

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