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Brief Report

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BRIEF REPORT

Treatment of COVID-19 with Chloroquine: Implication for Malaria Chemotherapy Using ACTs in Disease Endemic Countries

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ABSTRACT

Based on reports of parasite resistance and on World Health Organization recommendation, chloroquine was replaced with the artemisinin-based combination therapies (ACTs) as the first choice of drugs for the treatment of uncomplicated malaria. Disuse of chloroquine led to restoration of drug-sensitive parasite to some extent in certain countries. Ever since chloroquine and hydroxychloroquine were touted as potential treatment for coronavirus disease 2019 (COVID-19), there has been a dramatic surge in demand for the drugs. Even in areas where chloroquine is proscribed, there has been an unexpected increase in demand and supply of the drug. This situation is quite worrying as the indiscriminate use of chloroquine may produce drug-resistant parasites which may impact negatively on the efficacy of amodiaquine due to cross-resistance. Amodiaquine is a partner drug in one of the ACTs and in some of the drugs used for intermittent preventive treatment. We herein discuss the consequences of the escalated use of chloroquine in the management of COVID-19 on chemotherapy or chemoprevention of malaria and offer an advice. We speculate that parasite strains resistant to chloroquine will escalate due to the increased and indiscriminate use of the drug and consequently lead to cross-resistance with amodiaquine which is present in some drug schemes aforementioned. Under the circumstance, the anticipated hope of reverting to the use of the 'resurrected chloroquine' to manage malaria in future is likely to diminish. The use of chloroquine and its derivatives for the management of COVID-19 should be controlled.

KEYWORDS: COVID-19, chloroquine, cross-resistance, amodiaquine, hydroxychloroquine, treatment

THE COVID-19 PANDEMIC

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus causing coronavirus disease 2019 (COVID-19), emerged in December 2019 and spread rapidly across the world with a fast rate of infection, leaving a significant morbidity and mortality on it trail. The pandemic has been described severally: as a global health crisis of our time and the

greatest challenge faced globally since World War II. Indeed, the disease is unleashing an unforetold devastation on social, economic and political lives of many Nations which will take a long time to resolve.

The virus attacks the respiratory tract system of the host. Genetic analysis by sequencing indicates that the virus is a betacoronavirus closely linked to the SARS virus [1]. As at now, there is no known specific, effective, proven and pharmacological treatment for COVID-19. However, scientists are working hard to find antivirals specific to the virus. It must be emphasized that the long-term strategy to combat COVID-19 would be to develop a vaccine. This may take some time, as the vaccine must be rigorously tested and its safety confirmed through clinical trials before routine use in humans. In the meantime, drugs for the management of the symptoms of the disease are urgently needed.

Many different treatment options have been proposed including the use of drugs such as chloroquine, hydroxychloroquine, arbidol and remdesivir among others [2]. These drugs are currently undergoing clinical studies to test their efficacy and safety in the treatment of the COVID-19. With regard to chloroquine, *in vitro* studies indicate that the drug is effective in reducing viral replication in infections including the SARS-associated coronavirus (CoV) and MERS-CoV [3–5].

Although largely undocumented, it is speculated that substantial amount of chloroquine and hydroxychloroquine are already being used unofficially as prophylaxis or for the treatment of the symptoms associated with COVID-19. This situation could have a dire consequences on management of malaria, as chloroquine-resistant parasites may increase, with a possible cross resistance to amodiaquine. This article, therefore, seeks to discuss the possible effect of the increased indiscriminate use of the drug on malaria management with some artemisinin-based combination therapies (ACTs) as well as intermittent preventive treatment (IPT) containing amodiaquine as partner drug and give an advice.

USES OF CHLOROQUINE AND HYDROXYCHLOROQUINE

Chloroquine was developed in 1934 as an antimalarial drug, whilst hydroxychloroquine was developed a decade later.

Hydroxychloroquine is generally used for the treatment of autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis in addition to malaria. It is known to regulate the activity of the immune system, which may be overly active in some conditions. It does so by modifying the underlying disease process, rather than treating the symptoms.

In the immediate past, chloroquine was the first-line drug for the treatment of uncomplicated malaria in disease endemic areas of the world and also used for the treatment of extra-intestinal amebiasis. However, towards the end of the 20th century, the malaria parasite, *Plasmodium falciparum*, developed serious resistance to chloroquine.

Due to the reported widespread parasite resistance to the drug, the World Health Organization (WHO) recommended its replacement with the ACTs as the first antimalarial drug of choice. This led to the dwindling use of chloroquine. Currently, chloroquine is used for mono-therapy of malaria only in countries such as Honduras where there are no reported parasite resistance to the drug.

Resistance to chloroquine is associated with specific genetic point mutation at various codons in the *P. falciparum* chloroquine resistance transporter (*pfcrt*) gene [6–8] and is modulated by mutations in the *P. falciparum* multidrug resistance locus 1 (*pfmdr1*) [7]. Substitution of adenylate with cytidylate at position 76 of *pfcrt* gene which changes lysine to threonine (K76 to T76) is a single molecular marker that strongly correlates with chloroquine drug resistance in *P. falciparum* [9, 10]. The mutations in codons 76 (*pfcrt,* K76T) and 86 (*pfmdr1,* N86Y) are therefore important regarding parasite resistance to chloroquine [8, 11]. It has also been reported that other mutations at different codons of the *pfcrt* gene are associated with chloroquine resistance [9, 11, 12]. Drug pressure driven by high chloroquine usage in an area is a major determinant of selection and spread of chloroquine-resistant genes among *P. falciparum* population [10, 11].

Interestingly, disuse of chloroquine as the first-line antimalarial drug for the treatment of uncomplicated malaria in certain endemic areas resulted in the re-appearance of strains of parasites sensitive to the drug [13–15]. This situation gives hope that sooner

than later, chloroquine, which is one of the safe and cheapest antimalarial drugs, may be re-considered in a combination-therapy rather than in mono-therapeutic use in the management of malaria.

CHLOROQUINE AND HYDROXYCHLOROQUINE AS POTENTIAL DRUG IN THE MANAGEMENT OF COVID-19

Since the onset and spread of COVID-19, chloroquine and hydroxychloroquine have been touted as a possible cure or chemoprevention of the novel disease. The rationale for the choice of these drugs against COVID-19 is based on the reported increased in the endosomal pH which inhibits fusion of the SARS-CoV-2 and the host cell membranes [16]. *In vitro*, 'both drugs block the transport of SARS-CoV-2 from early endosomes to endolysosomes, which may be required for release of the viral genome' [17].

Reports touting chloroquine and hydroxychloroquine as potential treatment for COVID-19 mostly carried out by the international press have led to a dramatic increase in demand and supply of the drugs. Chloroquine, which has been banned in many malaria endemic countries, and hydroxychloroquine have suddenly surfaced and it is being use as treatment or prophylaxis against COVID-19.

It is important to state that, lately, the publicity given to these drugs for the treatment or chemoprophylaxis of COVID-19 has dwindled due to the reported side effect and efficacy of the drugs in the management of COVID-19. The FDA has released a report indicating serious problems with the treatment of COVID-19 with these drugs. Heart rhythm problems, blood system disorders and kidney injuries among others have been reported to be associated with hospitalized patients treated with the drugs [18]. In his media briefing on COVID-19 on 25 May 2020, the WHO Director-General announced the suspension of hydroxychloroquine and chloroquine from Solidarity trial because of their safety and efficacy concerns [19]. The WHO decision was based on reports from ongoing clinical trials. However from news reports globally, this announcement seemed not to have abated the demand and use of the drug for the management of COVID-19, especially in economically poor settings where most of the burden of malaria happens to situate and the fear of contracting COVID-19 is likely to be high.

DOSE REGIME OF CHLOROQUINE FOR MALARIA OR COVID-19 MANAGEMENT

The usual chloroquine dose for the treatment of malaria for an adult weighing least 60 kg is: 1 g salt (600 mg base) orally as an initial dose, followed by 500 mg salt (300 mg base) orally after 6–8 h, then 500 mg salt (300 mg base) orally once a day on the next 2 consecutive days.

Treatment or chemoprophylaxis regime using chloroquine or hydroxychloroquine against COVID-19 varies. Usually, the adult dose used against the disease is 1 g salt (600 mg base) orally on Day 1, followed by 500 mg salt (300 mg base) orally once a day for a total duration of 4–7 days depending on clinical evaluation.

It is obvious from these dose regimes that quite a substantial amount of the drug is used in the management of COVID-19. It is speculated that, in some places, very high doses of chloroquine and its derivative are used indiscriminately for chemoprevention and treatment of COVID-19. Such practices must be discouraged through intense and sustained education as continuation may lead possibly to serious health implications.

INCREASED USE OF CHLOROQUINE TO TREAT COVID-19 AND ITS EFFECT ON MANAGEMENT OF MALARIA

It is important to state that the reason for the choice of ACTs to treat malaria is to slow down the development of resistance to the antimalarial drugs involved [21]. The principle behind the combination is that, the fast-acting drug, which is the artemisinin, quickly reduces the parasite load whilst the slow acting, partner antimalarial, gradually mob up the residue parasites [22]. The potency of the ACTs is therefore dependent on the efficacy of both the artemisinin component and the partner drug. Therefore, reduced susceptibility of parasites to the partner drugs in the ACTs can potentiate the development of resistance to the artemisinin with time. Amodiaquine is a partner drug in one of the ACTs (artesunate-amodiaquine, AS-AQ). This combination is one of the most popular choice of ACT for

the treatment of uncomplicated malaria because of cost and ease of administration. Amodiaquine is also a partner in combined drugs used in the management of malaria in interventional preventive measures, recommended for specific high-risk groups in areas of high malaria transmission. For instance, in 2013, WHO recommended the use of amodiaquine in combination with sulfadoxine and pyrimethamine (SP-AQ) for seasonal malaria chemoprevention (SMC) in children at high risk areas. SMC is defined as 'the intermittent administration of full treatment courses of an antimalarial medicine during the malaria season to prevent malarial illness with the objective of maintaining therapeutic antimalarial drug concentrations in the blood throughout the period of greatest malarial risk'. This intervention has been shown to be effective, cost-effective, safe and feasible for preventing malaria among children younger than 5 years of age in areas with highly seasonal malaria transmission.

Amodiaquine is also used in combination with SP for intermittent preventive treatment during pregnancy (IPTp) in some disease endemic countries. IPTp reduces maternal malaria episodes, placental, maternal and foetal anaemia, parasitaemia, low birth weight and neonatal mortality.

Increased use of chloroquine to manage COVID-19 is likely to trigger the development and emergence of strains of malaria parasites resistant to chloroquine. In addition to the mechanism of parasites resistance to chloroquine described above, there could be subsequent selection of additional changes in genes regulating *P. falciparum* response to chloroquine [23, 24]. Such situations will favour cross-resistance between chloroquine and amodiaquine, which is part of some ACTs and IPT in many disease endemic areas [23–25].

It can therefore be conjuncture that the indiscriminate and escalated use of chloroquine or it analogies to manage COVID-19 may impact negatively on amodiaquine efficacy due to structural similarities. Chloroquine, hydroxychloroquine and amodiaquine are all derivatives of the drug classified as *4-aminoquinoline*. 4-Aminoquinoline have an amino group at 4-position of the quinoline moiety. Amodiaquine differ from chloroquine by only a side chain (Fig. 1). Therefore, the possibility of cross resistance between chloroquine or its derivatives and amodiaquine is very high.

Indeed, there are numerous reports in literature indicating cross resistance between chloroquine and amodiaquine. Various *in vitro* parasite sensitivity assays attest to this: work carried out in India by AnupKumar, *et al.* [26], in Philippines by Smrkovski, *et al.* [27], in Senegal by Diawara, *et al.* [28], and in Colombia by Fall, *et al.* [29], in South America by Young [30] and in Gabon by Pradines, *et al.* [31].

It must however be noted that a significant positive correlation suggesting *in vitro* cross-resistance may not necessarily be predictive of cross-resistance *in vivo*. Nevertheless, information on *in vitro* cross-resistance of one compound to an existing antimalarial is important as it becomes a potential indicator of future resistance: a marker or an early warning sign of an emerging parasite resistance, especially when chemical structures of the compounds involved are similar.

Therefore, as the use of chloroquine or hydroxychloroquine increases, the possibility of amodiaquine losing it current potency due to the aforementioned phenomenon is eminent.

Such an occurrence may lead to increased failure of the AS-AQ combination and a more serious consequences on the IPT used for pregnant women and children (SP-AQ), especially in areas where the efficacy of SP is already weakened. Again, under such circumstances, the planned future use of chloroquine

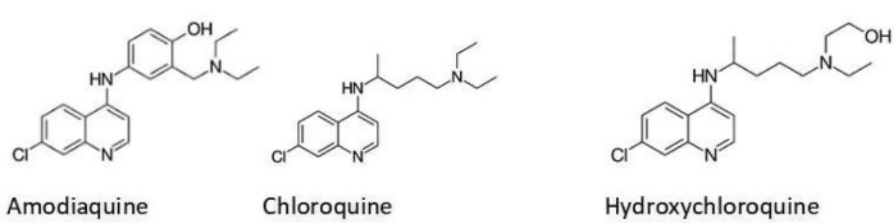

Fig 1. Chemical structures of amodiaquine, chloroquine and hydroxychloroquine.

in the management of malaria in the manner previously described [32] is likely to be jeopardized.

All put together, it must be said that the escalated use of chloroquine and its derivatives to manage COVID-19 is likely to be problematic for the control of malaria using some of the existing control drugs schemes. Measures must therefore be put in place to monitor and control the use of chloroquine and its derivatives to manage COVID-19 to avert these expectancies. There is the need to continuously monitor the efficacy of amodiaquine in disease endemic settings where it is used.

CONCLUSION

It is quite worrying, as the increased use of chloroquine or hydroxychloroquine to manage COVID-19 disease will lead to increased drug pressure and consequently the selection of drug-resistant parasite, as happened in the era preceding the introduction of the ACTs. Resistant strains of the malaria parasites to chloroquine or derivatives with cross-resistance to amodiaquine are likely to appear due to increased drug pressure as a consequence of the escalated use of the drug for the treatment of COVID-19. The use of chloroquine or it derivative to manage COVID-19 must therefore be strictly controlled. Education of the general populace on the issues associated with the use of the drugs must be done. There is also the need to constantly monitor the efficacy of amodiaquine in disease endemic countries.

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