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Original article

Antimalarial drugs inhibit the replication of SARS-CoV-2: An in vitro evaluation

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A B S T R A C T

In December 2019, a new severe acute respiratory syndrome coronavirus (SARS-CoV-2) causing coronavirus diseases 2019 (COVID-19) emerged in Wuhan, China. African countries see slower dynamic of COVID-19 cases and deaths. One of the assumptions that may explain this later emergence in Africa, and more particularly in malaria endemic areas, would be the use of antimalarial drugs. We investigated the in vitro antiviral activity against SARS-CoV-2 of several antimalarial drugs. Chloroquine (EC$_{50}$ = 2.1 μM and EC$_{90}$ = 3.8 μM), hydroxychloroquine (EC$_{50}$ = 1.5 μM and EC$_{90}$ = 3.0 μM), ferroquine (EC$_{50}$ = 1.5 μM and EC$_{90}$ = 2.4 μM), desethylamodiaquine (EC$_{50}$ = 0.52 μM and EC$_{90}$ = 1.9 μM), mefloquine (EC$_{50}$ = 1.8 μM and EC$_{90}$ = 8.1 μM), pyronaridine (EC$_{50}$ = 0.72 μM and EC$_{90}$ = 0.75 μM) and quinine (EC$_{50}$ = 10.7 μM and EC$_{90}$ = 38.8 μM) showed in vitro antiviral effective activity with IC$_{50}$ and IC$_{90}$ compatible with drug oral uptake at doses commonly administered in malaria treatment. The ratio C$_{\text{tuag}}$/EC$_{90}$ ranged from 5 to 59. Lumefantrine, piperaquine and dihydroartemisinin had IC$_{50}$ and IC$_{90}$ too high to be compatible with expected plasma concentrations (ratio C$_{\text{tuag}}$/EC$_{90}$ < 0.05). Based on our results, we would expect that countries which commonly use artesunate-amodiaquine or artesunate-mefloquine report fewer cases and deaths than those using artemether-lumefantrine or dihydroartemisinin-piperaquine. It could be necessary now to compare the antimalarial use and the dynamics of COVID-19 country by country to confirm this hypothesis.

1. Introduction

In December 2019, a new severe acute respiratory syndrome coronavirus (SARS-CoV-2) causing coronavirus diseases 2019 (COVID-19) emerged in Wuhan, China [1]. Despite containment measures, SARS-CoV-2 spread in Asia, Southern Europe, then in America and in Africa. The global number of cumulative cases in world was 13,646,660 and 809,747 deaths in August 24, 2020 (https://www.coronavirus-statistiques.com/stats-globale/covid-19-cases-europe/). Currently, 54 countries are affected in Africa with 1,003,435 cumulative cases and 20,398 reported deaths (August 24, 2020) (https://who.maps.arcgis.com/apps/opsdashboard/index.html#/0c9b3a8b68d0437a8cf28581e9c063a9). African countries see slower dynamic of COVID-19 cases and deaths. Several hypotheses could explain the later emergence and spread of COVID-19 pandemic in Africa, like delay in systematic SARS-CoV-2 detection and appropriate epidemiological surveillance, limited international air traffic, climate conditions, demographic conditions with less people above 65 years old, genetic polymorphisms of the cell entry
receptor for the SARS-CoV-2 (angiotensin converting enzyme 2, ACE-2) [2]. Another hypothesis that may explain this later emergence in Africa, and more particularly in malaria endemic areas, would be the use of antimalarial drugs. Antimalarial drugs could be effective against SARS-CoV-2. In 2002, the World Health Organization (WHO) recommended the use of artemisinin-based combination therapy (ACT) in the treatment of uncomplicated falciparum malaria in Asia, South America and Africa. The combinations artesunate-amodiaquine (Burundi, Cameroon, Democratic Republic of Congo, Gabon, Ivory Coast), artesunate-mefloquine (Cambodia, Brazil), artemether-lumefantrine (Benin, Central African Republic, Malawi, South Africa) or dihydroartemisinin-piperaquine (Thailand, Vietnam) are currently used. Although chloroquine is no longer used to treat falciparum malaria due to high level of resistance, it remains the first-line treatment in combination with primaquine for vivax malaria in some African countries (Benin, Central African Republic, Malawi, South Africa) or Cameroon, Democratic Republic of Congo, Gabon, Ivory Coast), and Africa. The combinations artesunate-amodiaquine (Burundi, Indonesia) or dihydroartemisinin-piperaquine (Thailand, Vietnam) are currently used. Although chloroquine is no longer used to treat falciparum malaria due to high level of resistance, it remains the first-line treatment in combination with primaquine for vivax malaria in some African countries, such as Ethiopia, South Africa and Sudan, in American countries, such as Brazil, Colombia, Guyana, Nicaragua, Peru, Venezuela), in Eastern Mediterranean countries, such as Afghanistan, Pakistan, Sudan, in south-eastern Asian countries, such as India, Myanmar. Antimalarial drugs are potential candidates to be repurposed in both COVID-19 prophylaxis and therapy [3]. Are antimalarial drugs effective against SARS-CoV-2?

Chloroquine, a quinoline, has been shown to be effective in vitro against SARS-CoV-2 in Vero E6 cells (African green monkey kidney cells) with median effective concentration (EC50) at micromolar range [4–6]. Hydroxychloroquine, an analogue of chloroquine used in autoimmune diseases such as rheumatoid arthritis and lupus, has also demonstrated in vitro antiviral activity against SARS-CoV-2 with EC50 at micromolar range [4,6,7]. Twenty-three clinical trials have been conducted in China to investigate the efficacy and safety of chloroquine and hydroxychloroquine in the treatment of COVID-19 [8–10]. Although the clinical trial was not performed according to the randomized double blind method, preliminary data indicated that chloroquine phosphate has demonstrated efficacy in treatment of COVID-19 with few severe adverse reactions in more than 100 patients by shortening hospital stay and improving the clinical evolution [9]. Hydroxychloroquine could shorten time to clinical recovery [11,12]. Effects of hydroxychloroquine were potentiated in vitro and in vivo by azithromycin [7,13]. Ferroquine, a ferrocene analogue of chloroquine with anti-malarial activity [14], was shown to be an effective inhibitor of SARS-CoV-1 replication with EC50 of 1.4 μM [15].

In 2002, the World Health Organization (WHO) recommended the use of artemisinin-based combination therapy (ACT) in the treatment of uncomplicated P. falciparum malaria (artemether-lumefantrine, artesunate-amodiaquine, dihydroartemisinin-piperaquine or artesunate-mefloquine). Marketed artemisinin derivatives exhibited in vitro anti-viral activity at micromolar concentrations against human cytomegalovirus [16–18]. Amodiaquine, a quinoline antimalarial and one of the partner of artemisinin derivative in ACT, was found to be active in vitro at micromolar concentration against SARS-CoV-1 (2.5 μM) but was inactive in vivo on SARS-CoV-1 in BALB/c mice [19]. Another quinoline, mefloquine, which has been used in combination with artesunate for the treatment of uncomplicated falciparum malaria, exerts in vitro cytotoxic effects on Vero cells infected by SARS-CoV-2 at 10 μM [20]. Pyronaridine, a quinoline component of the EU-approved antimalarial Pyramax (pyronaridine-artesunate), was effective in vitro against Ebola virus with EC50 of 1.14 μM and protected mice when administered 1 h after infection [21].

Taken together, these reports suggest that antimalarial drugs may have antiviral effects and be effective against SARS-CoV-2. Chloroquine, hydroxychloroquine, ferroquine, quinine, mefloquine, desethylmefloquine (the metabolite of amodiaquine), lumefantrine, pyronaridine, piperaquine and dihydroartemisinin (the metabolite of artemisinin derivatives) were assessed in vitro against a clinically isolated SARS-CoV-2 strain.

2. Material and methods

2.1. Antimalarial drugs, virus and cells

All the drugs were provided by Sigma (Saint Louis, MO, USA). Stock solution of chloroquine diphosphate, hydroxychloroquine and ferroquine were prepared in water, in methanol for quinine, mefloquine, desethylmefloquine, pyronaridine, piperaquine and dihydroartemisinin and in DMSO for lufenamtrine. All the stock solutions were diluted in Minimum Essential Media (MEM, Gibco, ThermoFisher) in order to have 7 final concentrations ranging from 0.1 μM to 100 μM. The clinically isolated SARS-CoV-2 strain (IHUMI-3) [12] was maintained in production in Vero E6 cells (American type culture collection ATCC® CRL-1586™) in MEM with 4% of fetal bovine serum and 1% glutamine (complete medium).

2.2. Cytotoxicity assay

In vitro cell viability evaluation on the VERO E6 cell line was performed according to the method described by Mosmann with slight modifications [22]. Briefly, 105 cells in 200 μl of complete medium were added to each well of 96-well plates and incubated at 37 °C in a humidiﬁed 5% CO2. After 24 h incubation, 25 μl of complete medium and 25 μl of each concentration of antimalarial drugs were added and the plates were incubated 48 h at 37 °C. After removal of the supernatant, 100 μl of MTT (3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-te-trazolium bromide, Sigma Aldrich, France) solution (0.5 mg/ml in MEM without FBS) were then added to each well. Cells were incubated for 2 h at 37 °C. After incubation, the MTT solution was removed and 100 μl of dimethyl sulfoxide (DMSO) was added to dissolve the formazen crystals. Then, plates were shaken at 700 rpm for 10 min at 37 °C. The absorbance was measured at 570 nm using a TECAN Infinite F200 Microplate Reader. DMSO was used as blank. The 50% cytotoxicity concentration (CC50) was calculated with the inhibitory sigmoid Emax model, which estimated the CC50 through nonlinear regression by using a standard function of the R software (ICEstimator version 1.2, http://www.antimalarial-icestimator.net). CC50 value resulted in the mean of 6 different experimentations.

2.3. Antiviral activity assay

Brieﬂy, 96-well plates were prepared with 5.104 cells/mL of Vero E6 (200 μl per well), as previously described [7]. Antimalarial concentrations were added 4 h before infection. Vero E Cells were infected with IHUMI-3 strain at an MOI of 0.25. After 48h post-infection, the replication was estimated by RT-PCR using the Superscrt III platinum one step with Rox kit (Invitrogen) after extraction with the BloExtract SuperBall kit (Bioseill, Dardilly, France). The primers used were previously described [23]. EC50 and EC90 were calculated with the inhibitory sigmoid Emax model, which estimated the EC50 and EC90 through nonlinear regression by using a standard function of the R software (ICEstimator version 1.2). EC50 value resulted in the mean of 6 different experimentations.

2.4. Data analysis and interpretation

Selectivity index (SI) as ratio of CC50/EC50 was estimated for each antimalarial drug. The expected maximum blood concentration (Cmax) was estimated from literature for each drug at doses commonly administered in malaria treatment. The ratios Cmax/EC50 and Cmax/EC90 were estimated to find out if the effective concentration in plasma to cure SARS-CoV-2 is achievable in human. If data on drug accumulation into lung was available, the ratios Clung/EC50 and Clung/EC90 were calculated.
### 3. Results

CC₅₀, EC₅₀, EC₉₀ and SI for each antimalarial drug are presented in Table 1. Chloroquine, hydroxychloroquine, ferroquine, desethylmalarone, mefloquine and pyronaridine showed EC₅₀ and EC₉₀ at low micromolar range (Table 1). The ratio Cₘₐₓ/ECₙ₀ in blood ranged from 0.22 to 0.5 for chloroquine, hydroxychloroquine, mefloquine, pyronaridine and quinine (Fig. 1). But, these drugs were known to accumulate in lungs. The expected concentrations in lungs after an oral uptake at doses commonly administered in malaria treatment were sufficient to exert antiviral effects on SARS-CoV-2 (Fig. 2).

### 4. Discussion

Chloroquine and its analogues ferroquine and hydroxychloroquine showed in vitro activities at low-micromolar range with EC₅₀ of 2.1 ± 0.7 μM (SI > 47.6), 1.5 ± 0.3 μM (SI > 66.7) and 1.5 ± 0.3 μM (SI > 13.6), respectively. The EC₅₀ values for chloroquine and hydroxychloroquine are lower than those obtained in a previous work on Vero E6 cells at MOI of 0.2 (7.1 and 17.3 μM, respectively) [4]. EC₅₀ values depend on several methodological conditions like MOI, duration of incubation [6]. Ferroquine has already shown in vitro anti-coronavirus activity against feline coronavirus with EC₅₀ of 2.9 μM and SARS-CoV-1 virus with EC₅₀ of 1.4 μM [15]. These concentrations were consistent with concentrations observed in human plasma and lungs. Chloroquine given at 100 mg day in the prophylaxis of malaria leads to a plasma concentration of 0.01–0.4 mg/l, ie 0.03–1.25 μM [24]. Chloroquine has an excellent diffusion and tissue concentration which would lead to chloroquine levels 200 to 700 times higher in the lung than in the blood (a concentration which can go up to 280 mg/kg in the lung) [25]. An oral uptake of 400 mg of hydroxychloroquine led to a Cₘₐₓ of 1.22 μM [26]. Hydroxychloroquine accumulated 30 times more in lungs than in blood (around 0.3 μM vs 7.8 μM at 6 h) [27]. An oral uptake of 800 mg of ferroquine led to a mean Cₘₐₓ (maximum blood concentration) value of 155 ng/ml (around 0.6 μM) and t₁/₂ (elimination half-life) of 10.9 days [28]. No data is available on ferroquine accumulation in lungs. However, as ferroquine is an analogue of chloroquine, we can assume that it may accumulate at least 10 times than in blood. The antiviral activity of chloroquine and its analogues against SARS-CoV-2 are compatible with oral uptake at doses administered in malaria treatment. Chloroquine and hydroxychloroquine inhibited SARS-CoV-2 entry [4,5]. Chloroquine impaired the terminal glycosylation of ACE-2 receptor required for virus entry that resulted in reduced binding affinities between SARS-CoV-1 and its ACE-2 receptor and blocked SARS-CoV-1 viral spike protein binding [30]. Additionally, the ORF8 viral protein could bind to the porphyrin. At the same time, viral orflab, ORF10 and ORF53a proteins could attack the heme to dissociate the iron to form the porphyrin and inhibit the human heme metabolism leading to a decrease of hemoglobin amount which carry oxygen and carbon dioxide. Chloroquine could inhibit the binding of ORF8 to porphyrin and prevent the attack of the 1-beta chain of hemoglobin by orflab, ORF10 and ORF53a proteins [31]. Besides its antiviral activity, chloroquine and hydroxychloroquine have anti-inflammatory effects by decreasing the expression of various pro-inflammatory cytokines including interleukin 6 (IL6), tumor necrosis factor-alpha (TNF) and interferon gamma (INFγ) by mononuclear cells [32]. These cytokines were considerably increased in the cytokine storm due to COVID-19 [33]. Many clinical trials on hydroxychloroquine alone or in combination with azithromycin to treat COVID-19 are in progress. The efficacy of hydroxychloroquine alone or in combination with azithromycin has been controversial. Hydroxychloroquine showed antiviral activity Vero E6 cells (African green monkey kidney cells) [4–6,34] but not in a model of reconstructed airway epithelium [34]. Moreover, neither hydroxychloroquine alone or in combination with azithromycin showed significant effect on the viral load levels in comparison with placebo [34]. Some studies showed that early treatment with hydroxychloroquine alone or in combination with azithromycin was associated with a reduced risk of hospitalization, reduced risk of death and shorter duration of viral presence [35–39]. Early treatment with hydroxychloroquine decreased the level of secreted inflammatory cytokines (IL6, TNF and INFγ) [40]. Conversely, some studies showed that treatment of mild-to-moderate or mild-to-severe COVID-19 with hydroxychloroquine alone or in combination with azithromycin did not improve clinical status or duration of viral shedding in comparison with standard care [41–45]. Moreover, therapeutic interventions using high dosage chloroquine and/or in combination with macrolides may have severe side-effects including

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Table 1: Median effective concentration (EC₅₀), 90% effective concentration (EC₉₀) against SARS-CoV-2, 50% cytotoxicity concentration (CC₅₀) and selectivity index (SI) for antimalarial drugs.

| Drug              | EC₅₀ in μM | EC₉₀ in μM | CC₅₀ in μM | SI     |
|-------------------|------------|------------|------------|--------|
| Chloroquine       | 2.1 ± 0.7  | 3.8 ± 1    | >100       | >47    |
| Hydroxychloroquine| 1.5 ± 0.3  | 3.0 ± 1.9  | 20.4 ± 1.4 | 11     |
| Ferroquine        | 1.5 ± 0.3  | 2.4 ± 0.9  | >100       | >67    |
| Desethylmalarone  | 0.52 ± 0.2 | 1.9 ± 1.0  | 86.1 ± 10.5| 166    |
| Quinine           | 10.7 ± 3.0 | 38.8 ± 34  | >100       | >9     |
| Mefloquine        | 1.8 ± 1.0  | 8.1 ± 3.7  | 14.4 ± 2.1 | 8      |
| Pyronaridine      | 0.72 ± 0.6 | 0.75 ± 0.4 | 15.9 ± 1.6 | 22     |
| Lumefantrine      | 24.7 ± 3.6 | 59.8 ± 26.8| 87.7 ± 11.9| 4      |
| Piperaquine       | 33.4 ± 3.8 | 65.4 ± 25.6| 55.0 ± 4.8 | 2      |
| Dihydroartemisinin| 20.1 ± 4.5 | 41.9 ± 18.0| 58.9 ± 7.4 | 3      |
cardiac toxicity. A prophylactic approach with chloroquine at lower dosage could be administered in vulnerable persons with comorbidities at-risk of severe COVID-19 or in health workers [46]. Chloroquine at 100 mg daily was used for decades for the antimalarial chemoprophylaxis. Several trials on prophylaxis with chloroquine are currently in progress (NCT04349371, NCT04303507). Chloroquine could be evaluated alone or in combination with antibiotics like doxycycline in prophylactic trials. Indeed doxycycline showed in vitro antiviral activity against SARS-CoV-2 (EC₅₀ = 5.6 μM) and low toxicity [47]. Doxycycline at 100 mg daily was used for many years for the antimalarial chemoprophylaxis and combining chloroquine to doxycycline in daily prophylaxis did not increase the risk of adverse effects [48].

Desethylamodiaquine, the metabolite of amodiaquine, showed the best in vitro efficacy with EC₅₀ of 0.52 ± 0.2 μM (SI = 166). Amodiaquine was used in combination with arteunate in the treatment of uncomplicated malaria in Africa (306 mg amodiaquine base and 100 mg arteunate). Amodiaquine given at 612 mg day led to a plasma concentration of 753 ng/ml of desethylamodiaquine (around 1.9 μM) and a t₁/₂ of 8.9 days [49]. About 0.07% of the administered dose was found in rat lung [50]. This suggests that for an uptake of 612 mg in human, 428 μg would be found in lungs. Amodiaquine, was found to be active also in vitro against SARS-CoV-1 with EC₅₀ of 2.5 μM but was inactive in vivo on SARS-CoV-1 in BALB/c mice [19]. Chloroquine, effective in vitro with EC₅₀ of 2.5 μM, was also inactive in vivo on SARS-CoV-1 in BALB/c mice. Amodiaquine also inhibited dengue virus type 2 replication with EC₅₀ of 1.08 μM and EC₉₀ of 2.69 μM [51]. The antiviral activity of desethylamodiaquine against SARS-CoV-2 is compatible with oral uptake of amodiaquine at doses commonly administered in malaria treatment. Amodiaquine can only be recommended as treatment and not as prophylaxis due to risk of hepatitis and agranulocytosis during long-term administration [52].

Mefloquine showed anti-SARS-CoV-2 activity with EC₅₀ of 1.8 μM and EC₉₀ of 8.1 μM. These results are consistent with previous study which showed that mefloquine at 10 μM inhibited completely cytopathic effect on Vero E6 cells infected by SARS-CoV-2 [20]. Mefloquine administered at malaria therapeutic dose (1250 mg) lead to a blood concentration of 1648 ng/ml (around 4 μM) in healthy males [53]. A study on postmortem cases showed that mefloquine levels are 10 times higher in the lung than in the blood (a concentration which can go up to 180 mg/kg in the lung) [54]. The antiviral activity of mefloquine against SARS-CoV-2 is compatible with malaria oral therapeutic doses. But mefloquine can cause neuropsychiatric adverse effects [55].

Pyronaridine showed effective antiviral activity with EC₅₀ of 0.72 μM and EC₉₀ of 0.75 μM. Pyronaridine tetraphosphate given at 720 mg day led to a plasma concentration of 271 ng/ml (around 0.3 μM) in human and a t₁/₂ of 33.5 days [56]. A single oral dose of 2 mg (10 mg/kg) in rats led to a blood Cmax of 223 ng/ml and a lung Cmax of 36.4 μg/g (165 more concentrated) [57]. The antiviral activity of pyronaridine against SARS-CoV-2 is compatible with malaria oral therapeutic doses. Acute and sub-acute toxicity was less than that of chloroquine. Cardiovascular toxicity was also less than that of chloroquine [58].

Quinine was shown effective concentration in lungs to cure SARS-CoV-2 is achievable in human. If its clinical efficacy in human would be confirmed, quinine could be administered in intravenous in patients before cytokine storm. Quinine can cause haemolytic anemia in patients with G6PD deficiency and severe side-effects including cardiac toxicity [52]. Additionally, quinine could be associated with doxycycline against COVID-19, as is done in malaria treatment [62].

5. Conclusion

Chloroquine, hydroxychloroquine, ferroquine, desethylamodiaquine, mefloquine, pyronaridine and quinine showed in vitro antiviral effective activity against SARS-CoV-2 with IC₅₀ and IC₉₀ compatible with drug oral uptake at doses commonly administered in malaria treatment. These in vitro activities are higher than those obtained with drugs which are evaluated in clinical trials worldwide like remdesivir (23 μM), lopinavir (26.6 μM) or ritonavir (~100 μM) [66]. However, these results must be taken with caution regarding the potential use of antimalarial drugs in SARS-CoV-2 infected patients: it is difficult to translate in vitro study results to actual clinical treatment in patients. Experts agree on the in vitro activity of chloroquine or hydroxychloroquine against SARS-CoV-2 but disagree on hydroxychloroquine efficacy in COVID-19 treatment, which remains controversial [67,68]. In vivo evaluation in animal experimental models is now required to confirm the antiviral effects of these antimalarial drugs on SARS-CoV-2. The antiviral effects of some antimalarial drugs could partially explain the later emergence and spread of COVID-19 pandemic in Africa. It could be necessary now to compare the antimalarial use and the dynamics of COVID-19 country by country to confirm the potential effects of antimalarial drugs. Based on our results, we would expect that countries which commonly use arteunate-amodiaquine or arteunate-mefloquine report fewer cases and deaths than those using artemether-lumefantrine or dihydroartemisinin-piperaine.

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Ethical approval

Not required.

CRediT authorship contribution statement

Mathieu Gendrot: Conceptualization, Investigation, Writing - review & editing. Julien Andreani: Investigation, Writing - review & editing. Manon Boberger: Investigation, Writing - review & editing. Priscilla Jardot: Investigation, Writing - review & editing. Isabelle Fonta: Investigation, Writing - review & editing. Marion Le Bideau: Investigation, Writing - review & editing. Isabelle Duflot: Investigation, Writing - review & editing. Joel Mornier: Investigation, Writing - review & editing. ClaraROLLAND: Investigation, Writing - review & editing. Hervé Bogreau: Methodology, Investigation, Writing - review & editing. Sébastien Hutter: Conceptualization, Investigation, Writing - review & editing. Bernard La Scola: Conceptualization, Supervision, Writing original and revised draft.
All the other authors have no conflict of interest to declare.

Declaration of competing interest

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