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Antimalarial artemisinin-based combination therapies (ACT) and COVID-19 in Africa: *In vitro* inhibition of SARS-CoV-2 replication by mefloquine-artesunate

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ABSTRACT

Objectives: At the end of November 2019, a novel coronavirus responsible for respiratory tract infections (COVID-19) emerged in China. Despite drastic containment measures, this virus, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), spread in Asia and Europe. The pandemic is ongoing with particular hotspot in Southern Europe and America. Many studies predicted a similar epidemic in Africa as that currently seen in Europe and the United States of America. However, reported data do not confirm these predictions. One of the hypotheses that could explain the later emergence and spread of COVID-19 pandemic in African countries is the use of antimalarial drugs to treat malaria, and more particularly artemisinin-based combination therapy (ACT).

Methods: The antiviral activity of fixed concentrations of ACT at concentrations consistent with those observed in human plasma when ACT are administered at oral doses for uncomplicated malaria treatment was evaluated *in vitro* against clinically isolated SARS-CoV-2 strain (IHUMI-3) in Vero E6 cells.

Results: Mefloquine-artesunate exerted the highest antiviral activity with % inhibition of 72.1 ± 18.3 % at expected maximum blood concentration (C_{\max}) for each ACT drug at doses commonly administered in malaria treatment. All the other combinations, artesunate-amodiaquine, artemether-lumefantrine, artesunate-pyronaridine or dihydroartemisinin-piperaquine, showed antiviral inhibition in the same range (27.1 to 34.1 %).

Conclusions: Antimalarial drugs for which concentration data in lungs are available, are concentrated from 10 to 160 fold in lungs than in blood. These *in vitro* results reinforce the hypothesis that antimalarial drugs could be effective as anti-COVID-19 treatment.

Keywords: SARS-CoV-2, COVID-19, Antiviral, Antimalarial drug, *in vitro*, malaria

Introduction

In December 2019, a new severe acute respiratory syndrome coronavirus (SARS-CoV-2) causing coronavirus diseases 2019 (COVID-19) emerged in Wuhan, China (Wu F et al., 2020). Despite containment measures, SARS-CoV-2 spread in Asia, Southern Europe, then in America and currently in Africa. Currently, 54 countries are affected in Africa with 332,820 cumulative confirmed cases and 8,733 reported deaths (June 25, 2020) (<https://www.afro.who.int/health-topics/coronavirus-covid-19>). The five most affected African countries are South Africa with 111,796 cases and 2,205 deaths, Nigeria with 22,020 cases and 542 deaths, Ghana with 15,013 cases and 95 deaths, Cameroon with 12,270 cases and 313 deaths, and Algeria with 12,248 cases and 869 deaths. The first African cases are supposed to have occurred on February 14, 2020 in Egypt and on February 27, 2020 in Nigeria for the Sub-Saharan Africa. Gilbert et al. (2020) estimated that the countries at highest importation risk of cases of COVID-19 from China were Egypt, Algeria, South Africa, Nigeria and Ethiopia according to air travel flows from infected provinces of China to Africa and African country's capacity to detect COVID-19. Another study estimated the number of cases of COVID-19 in each African country, and more especially the timing of reporting 10,000 cases for all African countries (Pearson et al., 2020). For instance, the timing of reporting 10,000 cases was between April 11 and 18 (6,129 cases on June 25, 2020) in Senegal, April 17 and 23 (12,270 cases) in Cameroon, May 7 to 21 (197 cases) in Angola and April 23 and May 3 (5,034 cases) in Ethiopia. The declared data to WHO indicated the spread of COVID-19 in Africa but with lower confirmed cases than expected. 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 (Kobia and Gitaka, 2020), quick implementation of lockdown measures, physical distancing and enhanced hygiene, limited international air travel flows (Haider et al., 2020), climate conditions (Huang et al., 2020; Wang et al., 2020), demographic conditions with less people above 65 years old (Diop

et al., 2020), genetic polymorphisms of the cell entry receptor for the SARS-CoV-2 (angiotensin converting enzyme 2, ACE-2) (Cao et al., 2020), cross-immunity to SARS-CoV-2 (Grifoni et al., 2020; Katoh et al., 2020).

Another hypothesis that may explain this later emergence in Africa, and more particularly in malaria endemic areas, would be the use of antimalarial drugs (Izoulet, 2020). Since 2002, the World Health Organization (WHO) has recommended the use of artemisinin-based combination therapy (ACT) in the treatment of uncomplicated falciparum malaria (artemether-lumefantrine, artesunate-amodiaquine, dihydroartemisinin-piperaquine or artesunate-mefloquine). The combination artesunate-amodiaquine is preferentially used as first-line treatment in Burundi, Cameroon, Democratic Republic of Congo, Gabon, Ivory Coast for instance, artesunate-mefloquine in Cambodia and Brazil, artemether-lumefantrine in Benin, Central African Republic, Malawi and South Africa and dihydroartemisinin-piperaquine in Thailand or Vietnam. Amodiaquine and mefloquine, two quinoline ACT partners, were found to be active *in vitro* at micromolar concentration against SARS-CoV-1 at 2.5 μ M and SARS-CoV-2 at 10 μ M, respectively (Barnard et al., 2006; Fan et al., 2020).

Although *in vitro* activity is not necessarily linked to clinical efficacy, access of *in vitro* effectiveness of ACT against SARS-CoV-2 may provide some answers if antimalarial use may have been involved in the later emergence and spread of COVID-19 pandemic in Africa. The aim of this study was to evaluate the antiviral activity of ACT at concentrations consistent with those observed in human plasma when ACT are administered at oral doses for uncomplicated malaria treatment.

Methods

Antimalarial drugs

93 All the drugs were provided by Sigma (Saint Louis, MO, USA). Stock solution of
94 pyronaridine and piperaquine were prepared in water, in methanol for mefloquine,
95 desethylamodiaquine, and dihydroartemisinin and in DMSO for lumefantrine. All the stock
96 solutions were diluted in Minimum Essential Media (MEM, Gibco, ThermoFischer). Fixed
97 concentrations of drug combination were prepared according to human plasma concentrations
98 expected during oral intake of ACT. The expected maximum blood concentration (C_{\max}) was
99 estimated from literature for each drug at doses commonly administered in malaria treatment.
100 The artemisinin compound (artemether, artesunate) C_{\max} was determined as bioequivalent
101 concentration of its active metabolite, dihydroartemisinin. Indeed, artesunate or artemether
102 were metabolized rapidly in dihydroartemisinin after oral administration of fixed-dose
103 combinations (30min to 3h). A fixed dose of artesunate-amodiaquine led to plasma C_{\max} of
104 dihydroartemisinin and desethylamodiaquine (200 mg/ 540 mg) around 802 and 879 ng/ml
105 (experimental fixed-dose estimated at 5 and 4 μ M) (Navaratnam et al., 2009). A fixed dose of
106 artemether-lumefantrine (80 mg/280 mg) led to plasma C_{\max} of dihydroartemisinin and
107 lumefantrine around 126 ng/ml and 6.98 μ g/ml (experimental fixed-dose estimated at 1 and
108 33 μ M) (Ali et al., 2010; Ashley et al., 2007). A fixed dose of dihydroartemisinin-piperaquine
109 (120 mg/960 mg) led to plasma C_{\max} of dihydroartemisinin and piperaquine around 387 ng/ml
110 and 539 ng/ml (experimental fixed-dose estimated at 3.1 and 1 μ M) (Hanboonkunupakarn et
111 al., 2019). A fixed dose of artesunate-mefloquine (250 mg/550 mg) led to plasma C_{\max} of
112 dihydroartemisinin and piperaquine around 698 ng/ml and 1392 ng/ml (experimental fixed-
113 dose estimated at 5 and 8.3 μ M) (Valea et al., 2014). A fixed dose of artesunate-pyronaridine
114 (180 mg/540 mg) led to plasma C_{\max} of dihydroartemisinin and pyronaridine around 109
115 ng/ml and 130 ng/ml (experimental fixed-dose estimated at 1 and 0.5 μ M) (Jittamala et al.,
116 2015). ACT were evaluated *in vitro* at 0.5X, 1X and 2X of experimental fixed-dose estimated
117 for each combination.

Virus and cells

The clinically isolated SARS-CoV-2 strain (IHUMI-3) (Gautret et al., 2020) 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).

Antiviral activity assay

Briefly, 96-well plates were prepared with 5.10^5 cells/mL of Vero E6 (200µL per well), as previously described (Andreani et al., 2020). ACT concentrations were added 4 h before infection. Vero E Cells were infected with IHUMI-3 strain at an MOI of 0.25. Controls 0% (Vero E cell infected without drug) and 100% of inhibition (Vero E cell infected with 100 µM of ferroquine, Sigma, Saint Louis, MO, USA) were included. After 48h post-infection, the replication was estimated by RT-PCR using the Superscript III platinum one step with Rox kit (Invitrogene) after extraction with the BIoExtract SuperBall kit (Biosellal, Dardilly, France). The primers used were previously described (Amrane et al., 2020).

Data analysis and interpretation

The percentage of inhibition of SARS-CoV-2 replication was estimated for each combination as following: $(\text{mean CT}_{\text{combination}} - \text{mean CT}_{\text{control 0\%}})/(\text{mean CT}_{\text{control 100\%}} - \text{mean CT}_{\text{control 0\%}})*100$. Data were expressed as mean and standard deviation of 5 different experimentations.

Results

Estimations of the % of inhibition of the SARS-CoV-2 replication by fixed-doses of ACT were summarized in Table 1. Mefloquine-artesunate exerted the highest antiviral activity with

% inhibition of 72.1 ± 18.3 % at expected maximum blood concentration (C_{\max}) for each ACT drug at doses commonly administered in malaria treatment. All the other combinations showed antiviral inhibition in the same range (27.1 to 34.1 %).

Discussion

A patient, who is treated with fixed-doses of ACT at commonly recommended doses for uncomplicated malaria, shows maximum blood concentrations (C_{\max}) of the two drugs which are able to inhibit 27.1 to 72.1 % of the Vero E Cells infected with the SARS-CoV-2 IHUMI-3 strain. Treatment with artesunate-amodiaquine, artemether-lumefantrine, piperaquine-dihydroartemisinin or artesunate-pyronaridine leads to replication inhibition around 30%. Additionally, some of these antimalarial drugs are concentrated in lungs. A single oral dose of 2 mg (10 mg/kg) of pyronaridine in rats led to a blood C_{\max} of 223 ng/ml and a lung C_{\max} of 36.4 μ g/g (163 more concentrated in lung than blood) (Park and Pradeep, 2010). About 0.07% of the administered oral dose (8.6 mg/kg) of amodiaquine was found in rat lung (Winstanley et al., 1988). Treatment with artesunate-mefloquine (expected blood C_{\max} at 8.3 and 1 μ M) leads to replication inhibition above 70%. This is consistent with the *in vitro* antiviral activity of mefloquine previously reported at 10 μ M (Fan et al., 2020). A study on postmortem human cases showed that mefloquine levels are 10 times higher in lung than in blood (concentration can go up to 180 mg/kg in the lung) (Jones et al., 1994). No data is available on drug accumulation in lungs for the other antimalarial drugs, and more particularly dihydroartemisinin. The data on pyronaridine and mefloquine suggest the concentrations expected in lungs allow a 100% replication inhibition of SARS-CoV-2.

Additionally, artesunate exerts anti-inflammatory effects by decreasing the secretion of various pro-inflammatory cytokines including interleukin 6 (IL6), tumor necrosis factor-alpha (TNF), interleukin 1 beta (IL1beta) and interleukin 6 (IL6) through inhibition of nuclear

factor kappa B (NF- κ B) (Xu et al., 2007). The secretions of IL1beta, IL6, interferon gamma (INF γ) were considerably increased in the cytokine storm due to COVID-19 (Huang et al., 2020; Qin et al., 2020). The combination of antiviral activity and anti-inflammatory effects could allow a better clinical efficacy of mefloquine-artesunate.

These *in vitro* results reinforce the hypothesis that antimalarial drugs could be effective as anti-COVID-19 treatment. Based on our results, we would expect that countries which commonly use ACT report fewer cases and deaths during malaria season. It could be necessary now to evaluate clinically the ACT efficacy to treat COVID-19, and more particularly that of mefloquine-artesunate, and the potential prevention of ACT against SARS-CoV-2 by comparing the antimalarial use and the dynamics of COVID-19 country by country.

Contributors

MG carried out *in vitro* and molecular investigations, analyzed the data, and participated in drafting the paper. ID participated in cellular and viral cultures. MB carried out molecular investigations. OD participated in *in vitro* and molecular investigations. PJ, MLB, JA and CR participated in virus isolation and its maintenance in culture. IF, JM and SH participated in *in vitro* investigations. BLS supervised the study and participated in drafting the paper. BP designed and supervised the study, analyzed the data and drafted the manuscript.

Declaration of interest

M Boxberger received a PhD grant supported by L'Occitane Society. All the other authors have no conflict of interest to declare.

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Ethical approval

No ethical approval is required.

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285

Table 1

Estimation of the % of inhibition of the SARS-CoV-2 replication by fixed-doses of ACT (1x corresponds to expected maximum blood concentration (C_{\max}) for each ACT drug at doses commonly administered in malaria treatment)

Combination	Inhibition % at 2x plasma C_{\max}		Inhibition % at 1x plasma C_{\max}		Inhibition % at 0.5x plasma C_{\max}	
	Concentrations	Mean \pm SD	Concentrations	Mean \pm SD	Concentrations	Mean \pm SD
Mefloquine-dihydroartemisinin	8.3-5 μ M	99.6 \pm 0.7	4.1-2.5 μ M	72.1 \pm 18.3	2.0-1.25 μ M	30.9 \pm 14.1
Desethylamodiaquine-dihydroartemisinin	4.0-5.0 μ M	85.8 \pm 9.9	2.0-2.5 μ M	32.3 \pm 9.9	1.0-1.25 μ M	17.2 \pm 6.5
Pyronaridine-dihydroartemisinin	0.5-1.0 μ M	38.2 \pm 5.7	0.25-0.5 μ M	34.1 \pm 7.1	0.12-0.25 μ M	16.3 \pm 5.0
Lumefantrine-dihydroartemisinin	33.0-2.0 μ M	37.7 \pm 3.4	16.5-0.5 μ M	27.1 \pm 6.0	8.2-0.25 μ M	12.3 \pm 4.4
Piperaquine-dihydroartemisinin	1.0-3.1 μ M	29.7 \pm 16.8	0.5-1.5 μ M	29.3 \pm 4.6	0.25-0.75 μ M	14.0 \pm 4.2

SD = standard deviation