To consider or not antimalarials as a prophylactic intervention in the SARS-CoV-2 (Covid-19) pandemic

These days, the entire scientific community is facing the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) emergency, characterised last 11 March by WHO as a pandemic. Social behaviour modification measures may somehow limit the spreading of the infection. However, in the case of an extremely contagious pathogen, the huge number of infected people may be a challenge for the health system. What if there was a prophylactic drug?

In the light of their in vitro effect and early clinical results, antimalarial drugs chloroquine (CQ) and hydroxychloroquine (HCQ) have been proposed for patients with SARS-CoV2-related pneumonia (Covid-19) and are now included in the Chinese guidelines for the management of Covid-19 (version 7, 3 March 2020).

Antiviral activity of antimalarials has been known for more than 10 years (see online supplementary text).

Recently, Wang et al demonstrated that at low micromolar concentration CQ was able to potently block viral replication of Covid-19, in vitro; the effective concentration of CQ was that achievable in patients receiving 500 mg/daily. HCQ also showed an anti-SARS-CoV2 effect, decreasing the viral replication in a time and concentration-dependent manner. Interestingly, CQ and HCQ prevent the viral replication also at entry stage (ie, when added in cell culture before the viral challenge). To date, more than 100 patients have been treated with CQ showing promising results. A very recent study showed that, already after 6 days, HCQ induced a negativity of viral RNA in nasopharyngeal sample: 70% of patients treated with HCQ alone and 100% of those treated with HCQ in combination with azithromycin determined a viral clearance compared with 12.5% of untreated patients. Table 1 summarises the data available to date on CQ and HCQ. Many clinical trials on the use of CQ or HCQ are now recruiting patients. Two more European trials, not yet recruiting, will assess the efficacy of CQ/HCQ in preventing symptomatic Covid-19 in healthcare workers, or other individuals at significant risk (ClinicalTrials.gov Identifiers: NCT04303507 and NCT04304053).

CQ and HCQ have been used for autoimmune rheumatic diseases since 1940s, being safe and well tolerated in most patients. Data from the literature, including our own experience, reported a low incidence of side effects, generally mild to moderate. The most serious complication (ie, the retinal toxicity) depends on weight-adjusted daily dose and, most of all, cumulative dose of antimalarials. Similarly, the (rare) cardiotoxicity seems to be related to the cumulative dose, even if mechanistic evidence is still lacking.

Mass drug administration is an intervention used as malaria-control measure delivering safe and inexpensive drugs to prevent or alleviate symptoms and morbidity while reducing transmission and improving global health. Is it ethical to propose CQ or HCQ for preventing the spreading of Covid-19 without any data coming from evidence-based medicine? Even though ‘primum non nocere’: is it permissible to take a controlled risk in the event of a pandemic? In such a case: would it be reasonable to consider antimalarials as primary prophylaxis in healthy subjects living in highest risk regions or, at least, to use them in those tested positive for Covid-19 but still asymptomatic? The advantage of CQ or HCQ is that they are safe and inexpensive to administer for a relatively short time, therefore good candidates for mass administration, whenever not contraindicated. Waiting for supportive data from clinical trials, the scientific community is moving towards pre-emptive use of antimalarials (see online supplementary figure 1). If mass prophylaxis was accepted as an option worldwide, this would raise the question of whether there is enough supply of CQ and HCQ to support this approach.

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REFERENCES
**Mode of action of chloroquine and hydroxychloroquine as anti-viral agents**

Antimalarials anti-viral activity was identified since the late 1960s and was extensively reviewed by Rolain et al in 2007 [S1]. CQ and HCQ exert their antiviral activity mainly by increasing pH within acidic organelles, including endosomes, lysosomes and Golgi vesicles; in particular, these drugs could inhibit the viruses requiring a pH-dependent step for entry into their host cells. In fact, some viruses, in a low-pH milieu, could change their structure facilitating fusion, penetration and/or uncoating. CQ might prevent the uncoating of influenza B virus by increasing the lysosomal pH above the critical value required for inducing fusion between virus envelope and lysosomal membrane; similarly, CQ seems to be able to inhibit uncoating of the hepatitis A virus [S1]. Moreover, antimalarial drugs seem to inhibit post-translational modifications of glycoproteins of virus envelope acting on proteases and glycosyltransferases, enzymes needing an acid pH milieu: by increasing pH, CQ/HCQ might impair the envelope maturation [S1].

The specific effect of CQ against corona viruses was studies soon after the first SARS epidemic.

In 2004 Keyaerts et al showed that after one day of incubation of Vero E6 cells with 4 μM CQ, no significant replication was observed, and 16 μM was required to inhibit by 99% the viral replication; CQ was equally effective when added during or 1 hour after the infection [S2].

In 2005 Vincent et al confirmed the ability of CQ to increase endosomal pH required for virus/cell fusion, as well as in interfering with the glycosylation of cellular receptors of SARS-CoV [S2]. In particular, antimalarial drugs could reduce the glycosylation of ACE2, which has been identified as a functional cellular receptor of SARS-CoV spike protein [S2].
Few years later, Keyaerts et al confirmed the data obtained in vitro in a murine model, showing a long-lasting protective effect of CQ against lethal coronavirus OC43 infection in new-born mice treated via maternal milk [S4].

**Supplementary references**


Supplementary Figure 1. Chloroquine and hydroxychloroquine in the management of COVID-19: from pre-clinical data to clinical application as treatment and prevention.

<table>
<thead>
<tr>
<th>Date</th>
<th>Event Description</th>
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<tbody>
<tr>
<td>4 Feb 2020</td>
<td>Wang et al [1] in vitro efficacy of CQ</td>
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<tr>
<td>11 Mar 2020</td>
<td>clinicaltrials.gov: two prevention RCTs posted</td>
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<tr>
<td>20 Feb 2020</td>
<td>Chinese Expert Consensus includes CQ for the treatment of COVID-19</td>
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<tr>
<td>17 Mar 2020</td>
<td>AIFA includes CQ and HCQ off-label use for the treatment of COVID-19</td>
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<tr>
<td>19 Mar 2020</td>
<td>Bayer donates 3 million CQ tables to United States</td>
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AIFA = Agenzia Italiana del Farmaco [Italian Medicine Agency]; CQ = chloroquine, HCQ = hydroxychloroquine; RCT = randomized clinical trial.