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.[1] HCQ also showed an anti-SARS-CoV-2 effect, decreasing the viral replication in a time and concentration-dependent manner.[2] Interestingly, CQ and HCQ prevent the viral replication also at entry stage (ie, when added in cell culture before the viral challenge).[2] To date, more than 100 patients have been treated with CQ showing promising results.[3] 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 patients who did not receive HCQ.[4] 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).

Table 1 Preclinical and clinical data on chloroquine (CQ) and hydroxychloroquine (HCQ) in coronavirus disease 2019 (Covid-19)

	Type of study	Main results
Wang *et al*[1]	In vitro	At low micromolar concentration, CQ blocks viral infection at both entry and at post-entry stages of the 2019-nCoV infection in Vero E6 cells.
Yao *et al*[2]	In vitro	HCQ is more potent than CQ in inhibiting viral infection at entry and post-entry stages; EC50 values CQ and HCQ decreased with longer incubation times providing higher intracellular concentrations and a better antiviral effect. Suggested dosing for HCQ: 400 mg/two times a day at day 1, followed by 200 mg/two times a day.
Gao *et al*[3]	Case series	CQ phosphate is superior to the control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus-negative conversion and shortening the disease course. No severe adverse events were reported.
Gautret *et al*[4]	Case control	HCQ induces viral clearance after 6 days of treatment, either alone or in combination with azithromycin (respectively, 70% and 100% negative nasopharyngeal samples among treated patients compared with 12.5% of untreated patients).

EC, effective concentration 50; nCoV, novel coronavirus.

CQ and HCQ have been used for autoimmune rheumatic diseases since 1940s, being safe and well tolerated in most patients.[5] Data from the literature, including our own experience, reported a low incidence of side effects, generally mild to moderate.[5 6] 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.[5]

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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