Chloroquine or hydroxychloroquine for prophylaxis of COVID-19

In-vitro studies have shown that chloroquine is effective against several viruses, including severe acute respiratory syndrome coronavirus (SARS-CoV).[1] Multiple mechanisms of action have been identified for chloroquine that disrupt the early stage of coronavirus replication. Moreover, chloroquine affects immune system activity by mediating an anti-inflammatory response, which might reduce damage due to the exaggerated inflammatory response.[1] At the time of the SARS epidemic, chloroquine was suggested as a drug that could be used to treat this infection.[2] However, randomised, double-blind, controlled studies in humans to evaluate its efficacy for this use were not done, and the true clinical efficacy of chloroquine in treating coronavirus infections was not established.

Because coronavirus disease 2019 (COVID-19) is associated with substantial morbidity and mortality,[3] and no specific pharmacological treatment that is effective against it is available, chloroquine and chloroquine-related formulations have been tentatively included among drugs for use in limiting the total burden of COVID-19.[4,5] However, no studies have evaluated the use of chloroquine for prophylaxis.

Chloroquine is a cheap drug that has been used for decades—predominantly for malaria prophylaxis, for which it had excellent results and good safety and tolerability.[1] Severe adverse events, which mainly involve retinal and psychiatric symptoms, occur only when doses prescribed for malaria are substantially higher than required.[1] Inhibition of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication seems essential to reduce the risk of spread and development of COVID-19. SARS-CoV-2 is highly contagious.[5] Most people who live in areas with a high incidence of COVID-19 are apparently healthy, but they can be SARS-CoV-2 negative and healthy or healthy but with asymptomatic infection. In both cases, effective drugs such as chloroquine and its related formulations might prevent infection (ie, in those who are SARS-CoV-2 negative) or the development of severe symptomatic disease (ie, in those who are SARS-CoV-2 positive and asymptomatic or with minor symptoms), substantially reducing morbidity and mortality due to COVID-19. The dose used might be the same as that usually administered for malaria treatment given chloroquine inhibited SARS-CoV replication at a 50% effective concentration of 8·8 μmol/L. The half-maximal inhibitory concentration (IC_{50}) of chloroquine inhibition of SARS-CoV replication in Vero E6 cells, 8·8 μmol/L, is substantially lower than the plasma concentrations that are reached in humans when the drug is prescribed to treat malaria at a dose of 25 mg/kg over 3 days.[1] For long-term prophylaxis, even lower doses could be used. Doses of 3·6 mg/kg, similar to those generally prescribed to treat rheumatoid arthritis, lead to plasma concentrations of 1–3 μmol/L—ie, the same concentration range as the IC_{50} for SARS-CoV inhibition.[1] Alternatively, hydroxychloroquine could be used, for which even greater efficacy has been reported in in-vitro studies.[5] Prophylaxis could last for the whole duration of an outbreak, and in countries in which malaria is not endemic, there is no risk of negative events associated with the development of resistance to this drug. In countries where malaria is endemic, appropriate monitoring of resistance among *Plasmodium* spp is needed.

Future studies might better elucidate the most effective schedule of administration and potential adverse events. We advocate for studies to evaluate whether chloroquine or hydroxychloroquine prophylaxis should be considered in a country such as Italy, where there are thousands of cases and deaths as a result of COVID-19.

We declare no competing interests.

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