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Chloroquine and COVID-19 – a potential game changer?

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ABSTRACT

The novel coronavirus SARS-CoV-2, causing the disease COVID-19, first emerged in Wuhan, China in December 2019 and has now spread to 203 countries or territories, infected over 2 million people and caused over 133,000 deaths. There is an urgent need for specific treatments. One potential treatment is chloroquine and its derivatives, including hydroxychloroquine, which have both antiviral and anti-inflammatory effects. These compounds are effective against SARS-CoV-2 *in vitro*, but *in vivo* data are lacking. Although some encouraging outcomes have been reported, and these results have been received enthusiastically, we recommend careful and critical evaluation of current evidence only when all methods and data are available for peer review. Chloroquine is safe and cheap. However, further evidence from coordinated multicentre trials is required before it can be confidently said whether it is effective against the current pandemic.

KEYWORDS: COVID-19, chloroquine, SARS-Cov-2, 2019-nCoV, coronavirus

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Introduction

On 31 December 2019, a cluster of novel coronavirus cases, associated with fever, shortness of breath and bilateral lung infiltrates, linked to exposure to a seafood market, was reported to the WHO China Country Office.[1] A previously unidentified betacoronavirus, initially named 2019-nCoV, was isolated from broncheoalveolar-lavage samples of patients.[2] The novel coronavirus has since been named SARS-CoV-2 and the disease it causes, COVID-19.[3] SARS-CoV-2 is a member of the coronavirus family. These are large, enveloped, single-stranded RNA viruses. There are four endemic strains (HCoV 229E, NL63, OC43, HKU1) which infect humans causing mild illnesses such as 'the common cold'.[4] Also in this family are severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). Both are highly pathogenic, causing respiratory illnesses with high mortality rates: 9.6% in SARS-CoV and 36.1% in MERS-CoV.[5] As of 15 April 2020 there have been 2,069,246 cases of COVID-19 with 133,361 deaths (mortality rate 6.4%).[6]

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Initial evidence from Wuhan, China suggested that the most common symptoms at the onset of illness were fever (98%), cough (76%) and myalgia/fatigue (44%).[7] Older males with existing health conditions were more likely to be affected.[8] 19.6% of patients developed acute respiratory distress syndrome (ARDS); other complications included shock (8.7%), acute cardiac injury (7.2%), arrhythmia (16.7%) and acute kidney injury (3.6%). 61.1% of patients in the intensive care unit (ITU) had ARDS compared to 4.9% of non-ITU patients. The medium time from onset of symptoms to development of ARDS was 8 days.[9] There is a desperate need to develop methods to combat viral spread, including vaccine development and treatment options. A variety of medications have been suggested, including chloroquine phosphate, interferon-alpha and ribavirin.[10] There has been particular interest surrounding the use of antivirals with anti-inflammatory properties, as it has been proposed that the ARDS seen in COVID-19 patients could be a result of a cytokine storm when the immune system attempts to respond to the virus.[11] Chloroquine and its derivatives, including the less toxic hydroxychloroquine, have been used to treat a variety of diseases including systemic lupus erythematous, rheumatoid arthritis and malaria, among many other indications.[12] It has previously been studied as a treatment of other coronaviruses, making it a potential candidate for treating COVID-19. Chloroquine inhibited replication of HCoV-OC43 *in vitro*. *In vivo* the survival rate of newborns of pregnant mice treated with chloroquine was 100% when exposed to the coronavirus, compared to 0% in the offspring of untreated pregnant mice.[13] Chloroquine phosphate or related compounds have also been found to be effective at inhibiting SARS-CoV *in vitro*;[14–16] however, it showed no significant efficacy at reducing viral titres in the lungs of infected mice *in vivo*.[16]

The field is rapidly evolving, with new information about the virus, and about potential treatments, being published every day. This review will summarise the current evidence for chloroquine and its analogues in the treatment of SARS-CoV-2.

Mechanism of action

The mechanism of action of chloroquine and its derivatives, both as an antiviral and an anti-inflammatory, have not been fully elucidated. Certainly, there are numerous ways in which these drugs could exert their anti-SARS-CoV-2 effects. Chloroquine and hydroxychloroquine act as weak bases which can have several intracellular effects, including affecting intracellular trafficking and disrupting enzymes. The antiviral mechanisms in general can be broken down into two different mechanisms. First, chloroquine may inhibit viral entry steps such as pH-dependent endocytosis,[17] as many of the different stages of any viral entry rely on specific pH ranges to allow conformational change.[18] Second, the altered pH of

the cellular environment may disrupt post translational modifications of glycoproteins and therefore affect the infectivity of the virus.[18]

In vitro evidence investigating chloroquine on SARS-CoV virus would appear to support these mechanisms of actions. SARS-CoV enters cells via spike glycoprotein, and chloroquine was found to inhibit the transduction of cells with SARS-CoV pseudovirions (with only the spike glycoprotein on the cell surface). However, chloroquine did not inhibit transduction with pseudovirions with a pH-independent surface glycoprotein, suggesting that the SARS-CoV spike protein required an acidic pH for cell entry.[19] Additionally, chloroquine does not affect the levels of cell surface ACE2 (the receptor for spike glycoprotein), suggesting that it does not mediate its antiviral effects by downregulating the number of available receptors. However, chloroquine was found to increase the electrophoretic mobility of ACE2, which infers that chloroquine impaired terminal glycosylation of this receptor. Therefore the spike protein on the surface of the SARS-CoV virion is not able to interact with its receptor as effectively, reducing viral entry into the cell.[15] Using immunofluorescence, Liu *et al* found that both chloroquine and hydroxychloroquine reduced the transport of SARS-CoV-2 virions from early endosomes to endolysosomes, likely due to blocking endosome maturation via prevention of acidification. This blocked the transport of infective virions to their release site from the infected cell.[20]

As well as their antiviral effects, these medications have an anti-inflammatory component, which is utilised in treating a variety of immunological conditions. Biochemical studies on the initial cohort of COVID-19 patients in Wuhan, China noted that they had elevated levels of cytokines, with those requiring ITU admission (and therefore suffering from more severe disease) having higher levels of cytokines than those that didn't. This may suggest that the increased disease severity is due to the induction of a cytokine storm.[7] Again, there are likely to be a variety of complex and interconnecting effects which chloroquine exerts in order to reduce inflammation, but one of these is likely to be a reduction in the production of inflammatory cytokines via inhibition of Toll-like receptor pathways.[21] Hence, as well as acting as an antiviral, chloroquine or its derivatives could also mitigate some of the destructive sequelae of SARS-CoV-2 infection such as the cytokine storm, which contributes to the severity of disease.

In vitro evidence

Wang *et al* carried out a study investigating the antiviral effects on SARS-CoV-2 of several drugs, some of which had previously been used against SARS or MERS. These included ribavirin, penciclovir, nitazonanide, nafamostat, remdesivir and favipiravir as well as chloroquine. These compounds were tested against SARS-CoV-2 *in vitro*, to assess the cytotoxicity, virus yield and infection rates. They found that chloroquine was effective at reducing viral yield in cell supernatant and additionally did so when the cells were treated 1 hour before infection as well as 2 hours post infection.[22] Further investigation by this group focused on the antiviral effects of hydroxychloroquine, as this is a more widely utilised and better tolerated chloroquine derivative. They found that hydroxychloroquine was similarly effective at inhibiting viral infection both before and after viral entry.[20]

Yao *et al* found that both chloroquine and hydroxychloroquine reduced viral replication of SARS-CoV-2 in a dose-dependent manner, but the EC_{50} values for hydroxychloroquine were lower than those for chloroquine, suggesting that hydroxychloroquine was more efficacious. In addition hydroxychloroquine was a more potent antiviral than chloroquine when the cells were pre-treated with the drug before viral infection.[23]

Finally, while much of the current evidence focuses on either chloroquine or hydroxychloroquine, a further anti-malarial which may prove effective against COVID-19 is mefloquine. Mefloquine is a 4-methanolquinolone, compared to chloroquine and hydroxychloroquine which are 4-aminoquinolones.[24] A recent study found that mefloquine demonstrated complete cytopathic effect against cells infected with a closely related coronavirus with no pathogenicity towards humans.[25]

In vivo evidence

While these *in vitro* experiments appear promising, supporting the hypothetical use of hydroxychloroquine and chloroquine in the treatment of COVID-19, the real test is whether similar results can be replicated not only *in vivo* but in humans.

Gao *et al* reported a news briefing describing results of multicentre clinical trial in China investigating the use of chloroquine in patients diagnosed with COVID-19, although the data are as yet unpublished. They reported that in over 100 patients chloroquine phosphate performed better than the control drug in treating COVID-19 through a variety of outcomes including improvement in imaging findings, negative virology findings and shorter disease course, without any significant adverse effects. Chloroquine was therefore recommended to be included in the guidelines for COVID-19 management by the National Health Commission of the People's Republic of China.[26] In their letter to *BioScience Trends*, the authors refer to the results of this trial as a 'breakthrough' and while the potential outcomes are huge, they do not provide the data to support this claim. A study on around 100 patients, with unpublished methods and data, is not sufficient to recommend a treatment to hundreds of thousands of affected people. The implications of this study at present should therefore be carefully and cautiously considered. A systematic review of current evidence for chloroquine and its derivatives in treatment of COVID-19 additionally reviewed the above letter and screened trial registries for evidence of the data described and did not find any.[27]

A further recent study on 30 patients with coronavirus showed that a 5-day course of hydroxychloroquine made a significant difference to the progression of COVID-19; however, the authors note the need for much larger sample sizes to adequately assess the utility of the drug as a treatment.[28]

A French research group reported early results from their ongoing trial of the use of hydroxychloroquine in 26 confirmed COVID-19 cases to reduce respiratory viral loads. In addition, azithromycin was added depending on clinical presentation to prevent bacterial superinfection. They did not compare these treatments against a placebo; instead, their negative controls were 16 patients who were untreated. They found that 70% of the hydroxychloroquine-treated group had negative SARS-CoV-2 nasopharyngeal swabs at day 6 post first dose, compared to 12.5% in the control group. Furthermore, 100% of patients treated with both azithromycin and hydroxychloroquine were virologicaly negative at day 6 compared to 57.1% of those treated with just hydroxychloroquine.[29] Certainly, these results are encouraging. The successful use of hydroxychloroquine and azithromycin have been met with hope and excitement, including being lauded as potential 'game-changers' by United States president Donald Trump.[30] However, again, while we eagerly await further data and ongoing results from these (and other) trials, there is a need to be cautious.

Safety

Important aspects to focus on when considering (hydroxy) chloroquine as a treatment for COVID-19 are its side effect profile, safety and tolerability. Certainly, we would expect chloroquine to be well tolerated in general given that it has been successfully used in humans for treating disease since 1934[17] and can be taken long-term (as travellers visiting countries with a risk of malaria take chloroquine as prophylaxis[31]). Chinese researchers announced that in multicentre trials chloroquine had demonstrated 'acceptable safety' – however, the data to support this in these particular trials is lacking.[26] A recent systematic review on the efficacy and safety of chloroquine for COVID-19 concluded that while there are sufficient safety data from the long term use of chloroquine and its derivatives for a variety of indications, there is an ongoing need for further data in the use of chloroquine in COVID-19.[27]

The frequency of adverse effects for chloroquine and hydroxychloroquine is generally low but higher in patients taking chloroquine (28%) compared to hydroxychloroquine (15%).[32] A systematic review found that the most common adverse effects were gastrointestinal side effects, cutaneous effects including skin rash, and retinopathy.[33] An expert consensus of Chinese scientists listed several contraindications to the use of chloroquine phosphate in COVID-19 such as pregnancy, chronic liver disease, chronic kidney disease, chronic heart disease, retinal disease and glucose-6-phosphate deficiency.[34] As patients with medical comorbidities such as cardiovascular disease appear to be more at risk of COVID-19,[8] such contraindications could limit the use of chloroquine as an effective drug in this disease.

The same consensus described the recommended dosing for management of COVID-19 to be 500mg twice a day for 10 days. They also recommended monitoring electrolytes and myocardial enzymes as well as checking ECG before commencing treatment and repeating it on the fifth and tenth day of treatment.[34] A recent modelling study calculated the optimum dosing of hydroxychloroquine sulfate for SARS-CoV-2 at 400mg twice daily, followed by a maintenance dose of 200mg given twice daily for 4 days.[23]

It must also be noted that there is a risk to patients who are already taking these medications for other indications, as demand for them has now rapidly increased with the renewed interest in them.[35] It is important that the current manufacturing chains are able to increase the production of these medications to ensure supply to patients who are taking them for rheumatological diseases. Additionally, any recommendations for one medication over the other may require flexibility based on the ease of access to medication in different countries; for example chloroquine has limited availability in Iran and therefore hydroxychloroquine may have to be used instead, or vice versa depending on supplies.[36]

The future

As of 28 March 2020, there are 22 trials across China registered (www.chictr.org.cn/index.aspx) to research the use of either chloroquine or hydroxychloroquine in COVID-19: ChiCTR2000031174, ChiCTR2000030987, ChiCTR2000030417 (withdrawn by researchers), ChiCTR2000030054, ChiCTR2000030031 (withdrawn by researchers), ChiCTR2000029992, ChiCTR2000029988, ChiCTR2000029975, ChiCTR2000029939, ChiCTR2000029935, ChiCTR2000029899, ChiCTR2000029898, ChiCTR2000029868, ChiCTR2000029837 (withdrawn by researchers), ChiCTR2000029826 (withdrawn by researchers), ChiCTR2000029803, ChiCTR2000029761, ChiCTR2000029760 (withdrawn), ChiCTR2000029741, ChiCTR2000029609, ChiCTR2000029559, ChiCTR2000029542.

Additionally, as of 28 March 2020 there are at least 21 trials registered on clinicaltrials.gov investigating hydroxychloroquine and/or chloroquine: NCT04324463, NCT04323631, NCT04323527, NCT04322396, NCT04322123, NCT04321993, NCT04321616, NCT04321278, NCT04319900, NCT04318444, NCT04318015, NCT04316377, NCT04315948, NCT04315896, NCT04308668, NCT04307693, NCT04304053, NCT04303507, NCT04303299, NCT04286503, NCT04261517.

Finally, as of 28 March 2020 there are two trials for chloroquine and coronavirus registered on the ISRCTN registry (www.isrctn.com) investigating chloroquine or hydroxychloroquine in COVID-19 (ISRCTN86534580, ISRCTN83971151).

The apparently successful use of chloroquine and its derivatives in treating COVID-19 is therefore obviously encouraging more trials. The sheer number of these already registered is impressive; however, there is need for trials to be planned and carried out in a coordinated manner, allowing larger numbers of patients included across multiple centres to ensure the data is of the highest quality possible.

Another avenue to explore (given the above *in vitro* evidence suggesting that chloroquine or its analogues can reduce viral infection if applied before exposure to the virus[20,22,23]) is whether these drugs could be used prophylactically to reduce viral spread and therefore the extent of the pandemic.[37] One application of this could be giving these medications to frontline medical staff prophylactically to prevent them from getting infected and passing it on to other patients within their healthcare setting.

Conclusion

In the midst of a global health emergency, chloroquine or its analogues could seem like a 'game changer' or a breakthrough. However, at present, the World Health Organization (WHO) does not recommend any particular antiviral medications, citing insufficient evidence to recommend any specific treatment.[3] Instead, current management includes the consideration of empirical antibiotics or neuraminidase inhibitors, as trials are continuing to attempt to find a specific treatment.[38]

Chloroquine is cheap, widely regarded as safe, has been used for decades,[27] and early results of *in vitro* studies are promising; therefore further investigation is definitely warranted. However, so far there have not been enough translational investigations to say whether chloroquine could be an effective treatment in humans with COVID-19. The present *in vivo* data should be appraised critically, with full methodology and data available for peer review. We can and should continue to be cautiously optimistic and appraise evidence as it becomes available, as making bold claims about the evidence as it stands is at best irresponsible and at worst dangerous. There should be a push for further comprehensive, multicentre, global clinical trials to ensure that a drug, whether chloroquine or any other potential treatment, is fully assessed for efficacy before being hailed as the answer. ■

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