



## EDITORIALS

# Chloroquine and hydroxychloroquine in covid-19

Use of these drugs is premature and potentially harmful

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*The BMJ* in 1925 cautiously endorsed Moellgaard's gold treatment for tuberculosis,<sup>1</sup> although it found his pharmacological reasoning "both interesting and instructive."<sup>2</sup> We should be similarly cautious about proposed treatments for people infected with SARS-CoV-2, the virus that causes covid-19. Many proposals are based on in vitro investigations, studies in experimental animals, or experience with interventions in infections with other viruses, whether similar to SARS-CoV-2 (eg, SARS-CoV-1) or not (HIV).

This is all true of chloroquine and hydroxychloroquine, both 4-aminoquinolines, which have been suggested as potential treatments for covid-19. Currently, at least 80 trials of chloroquine, hydroxychloroquine, or both, sometimes in combination with other drugs, are registered worldwide.

The possible activity of 4-aminoquinolines in infectious mononucleosis was first proposed in 1960, before its viral cause was known.<sup>3</sup> Several unsatisfactory clinical trials followed, some with positive results and some negative. In 1967 the authors of a small but well conducted randomised, double blind, placebo controlled trial of chloroquine concluded that "except for supportive measures, infectious mononucleosis is essentially untreatable."<sup>4</sup>

Since then, many studies have shown that 4-aminoquinolines are active in vitro against a range of viruses. Their efficacy has been attributed to different mechanisms. For example, they are weak bases and increase endosomal pH in host intracellular organelles, inhibiting autophagosome-lysosome fusion and inactivating enzymes that viruses require for replication.<sup>5</sup> They may also affect glycosylation of angiotensin converting enzyme-2, the receptor that SARS-CoV-2 uses to enter cells.<sup>6</sup>

## Laboratory studies

In cell cultures and animal studies, the effects of 4-aminoquinolines on viruses from avian influenza virus (H5N1)<sup>7</sup> to Zika<sup>8</sup> have been variable. In cells infected by Epstein-Barr virus, for example, chloroquine increased viral replication.<sup>9</sup> In one study, chloroquine reduced transmission of Zika virus to the offspring of five infected mice.<sup>10</sup> Chloroquine

inhibited Ebola virus replication in vitro but caused rapid worsening of Ebola infection in guinea pigs<sup>11</sup> and made no difference to mortality in mice and hamsters.<sup>12</sup> In chikungunya virus infection, chloroquine was active in laboratory studies but worsened the clinical course of infection in macaque monkeys.<sup>13</sup>

The translation from laboratory to clinic has also led to disappointments. For example, chloroquine inhibited dengue virus in some cell cultures<sup>14</sup> but failed to shorten the illness in a randomised study of 37 patients.<sup>15</sup> And although laboratory studies suggested activity against influenza virus, chloroquine did not prevent infection in a large randomised trial.<sup>16</sup> The disparity between laboratory and clinical experiments may be partly due to the complex pharmacokinetics of 4-aminoquinolines,<sup>17</sup> making it difficult to extrapolate from concentrations in culture media to doses in humans.<sup>18</sup>

## Poor methods and reporting

Hydroxychloroquine and chloroquine inhibit SARS-CoV-2 in vitro, and a Chinese commentary, mentioning 15 trials, reported that, "Thus far, results from more than 100 patients have demonstrated that chloroquine phosphate is superior to the control treatment in inhibiting the exacerbation of pneumonia,"<sup>19</sup> without giving any further details. A preliminary account of one of those trials, a placebo controlled randomised study of two different doses of hydroxychloroquine in 62 patients with radiological findings of pneumonia but without severe hypoxia, reported small improvements in body temperature and cough in the higher dose treatment group.<sup>20</sup> However, the endpoints specified in the published protocol differed from those reported, the results in the low dose group were not described, and the trial seems to have been stopped prematurely.<sup>21</sup>

An open, non-randomised study of hydroxychloroquine, published in preprint, reportedly supported efficacy in 20 patients, but the trial design was poor and the results unreliable: six patients dropped out of the treatment arm (two because of admission to an intensive care unit and one because he died); the measure of efficacy was viral load, not a clinical endpoint; and assessments were made on day 6 after starting treatment.<sup>22</sup>

Advocates, including Donald Trump, have argued that hydroxychloroquine is widely used and safe. Its use is now permitted by the US Food and Drug Administration<sup>23</sup> and advocated by the Indian Council for Medical Research.<sup>24</sup> But no drug is guaranteed to be safe, and wide use of hydroxychloroquine will expose some patients to rare but potentially fatal harms, including serious cutaneous adverse reactions,<sup>25</sup> fulminant hepatic failure,<sup>26</sup> and ventricular arrhythmias (especially when prescribed with azithromycin)<sup>27</sup>; overdose is hazardous and difficult to treat.<sup>28</sup>

We sorely need an effective treatment for covid-19, but prevention by a vaccine or treatment with drugs that target specific structures in the virus are more likely to succeed than old drugs that may work in the laboratory but lack data supporting clinical use. No intervention should be assumed to be efficacious. Even drugs initially supported by evidence of effectiveness may later prove to be more harmful than beneficial. Too many medicines have been withdrawn because of adverse reactions after showing clinical promise.<sup>29</sup> We need better, properly powered, randomised controlled trials of chloroquine or hydroxychloroquine. For now, except for supportive measures, infection with SARS-CoV-2 is “essentially untreatable.”

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Competing interests: JKA is a member of the Centre for Evidence-Based Medicine in Oxford, which jointly runs the EvidenceLive Conference with the BMJ and the Overdiagnosis Conference with some international partners, which are based on a non-profit model. He is an associate editor of *BMJ Evidence Based Medicine* and was until recently vice-president publications for the British Pharmacological Society. REF was until recently a member of the Birmingham, Sandwell and Solihull Area prescribing committee, is a series editor of *The BMJs Therapeutic Series*, and has an honorary position at University College London.

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