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Fabio Silvio Taccone, MD, PhD, Maya Hites, MD, PhD, Nicolas Dauby, MD, PhD

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From hydroxychloroquine to ivermectin: how unproven “cures” can go viral

Fabio Silvio TACCONE¹, MD, PhD, Maya HITES², MD, PhD, Nicolas DAUBY³, MD, PhD

¹Department of Intensive Care
Hôpital Erasme
Université Libre de Bruxelles
Brussels, Belgium

²Department of Infectious Disease
Hôpital Erasme
Université Libre de Bruxelles
Brussels, Belgium

³Department of Infectious Diseases
St Pierre Hospital
Université Libre de Bruxelles
Brussels, Belgium

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Correspondence:

Pr. Fabio Silvio TACCONE, MD, PhD
Department of Intensive Care
Hôpital Erasme, Université Libre de Bruxelles (ULB)
Route de Lennik, 808
1070 Brussels, Belgium
Email: fabio.taccone@ulb.be
Tel: +3225555587
Fax: +3225554698
Since the onset of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, various therapeutic agents have been repurposed to treat patients with coronavirus disease 2019 (COVID-19), and used empirically before adequate clinical studies were performed. One of the most controversial drugs in the very initial phase of the pandemic was hydroxychloroquine. This drug, which has been used to treat malaria, amebiasis and autoimmune diseases (e.g., systemic lupus erythematosus and rheumatoid arthritis), had promising results on in vitro studies and observational studies (1), although cohorts were limited and there were significant methodological limitations. Over subsequent months, several randomized clinical trials reported that hydroxychloroquine, alone or in combination with azithromycin, was ineffective at preventing SARS-CoV-2 transmission, providing more rapid resolution of clinical symptoms or reducing hospital admissions and mortality in COVID-19 patients, and was associated with no improved mortality compared to placebo (2-5). Nevertheless, despite these consistent data, and the publication of the living World Health Organization (WHO) guidelines recommending against the use of hydroxychloroquine in COVID-19 (6), the “effectiveness” of this drug is still asserted by some, who are using social networks and the media to spread their beliefs (7, 8). This (mis)information created doubt, angry debate, and even threats to hydroxychloroquine detractors. Arguments, such as “it was given too late” or “it was not administered at the right dose”, “it is cheap and safe”, or “it is unethical to perform a randomized trial and expose patients to placebo”, have been used to explain the poor trial results during the fierce discussions that have occurred concerning hydroxychloroquine use in COVID-19. The drug is still administered in several countries where national leaders have supported its use (9, 10).

In a similar situation to that seen with hydroxychloroquine, ivermectin has been proposed as an interesting and potentially effective medication to treat COVID-19 patients. Ivermectin is an anti-parasitic molecule that showed potential anti-viral and anti-inflammatory properties against SARS-CoV-2 in animal models (11). However, the antiviral effects in *in vitro* and *in vivo* studies required serum and tissue drug concentrations that can only be obtained by administering daily doses significantly higher than for current antiparasitic regimens, with potentially toxic effects (12). As with hydroxychloroquine, initial in vitro and observational studies suggested some outcome benefits with use of ivermectin in patients with COVID-19. Some randomized trials, limited by heterogeneity of populations
receiving ivermectin, imbalanced allocation, selected doses and uncontrolled co-interventions, also reported some benefits with ivermectin in different populations of COVID-19 patients (13). A systematic review, which initially suggested an improved survival rate with ivermectin treatment compared to placebo in COVID-19 patients (14), reanalyzed the available data by excluding studies at a high risk of bias (i.e. either retracted or considered potentially fraudulent) and reported no significant effect on survival or hospitalizations in favor of ivermectin. Other systematic reviews have also confirmed the low quality of published studies and the lack of any effectiveness of ivermectin on clinically relevant outcomes in COVID-19 patients (15, 16). Although a large retrospective cohort of hospitalized COVID-19 patients in Florida suggested that those treated with ivermectin (n=173) had a significantly lower in-hospital mortality, even after adjustment for confounders and propensity matching analysis (13 vs. 25%), than untreated (n=107) patients (17), those receiving the drug also more frequently received steroids (which can improve mortality in hospitalized COVID-19 patients requiring oxygen therapy) and were enrolled more recently (resulting in timing bias with possible improvement in medical knowledge and global patient care). A good-quality double-blind randomized trial conducted in Colombia assigned 400 patients with mild COVID-19 disease within the first 7 days of symptoms to receive ivermectin (300 μg/kg of body weight per day for 5 days) or placebo and reported a non-significant reduction of 2 days for symptom resolution but no effects of the drug on escalation of therapies or mortality (18). In another randomized study conducted in Argentina, ivermectin had no significant effect on preventing hospitalization of patients with COVID-19 (19). Taking all these data into consideration, the WHO guidelines recommended against the routine use of ivermectin in COVID-19 patients (4). However, adherence to these recommendations has again been hindered by social media’s spread of incorrect information. Similar to the situation with hydroxychloroquine, the clinical efficacy of ivermectin in COVID-19 patients has been strongly supported by some organizations, including the Front Line COVID-19 Critical Care (FLCCC) Alliance and America’s Frontline Doctors in the United States, Physicians for Life association in Brazil and the BIRD group in United Kingdom, and promoted on social media. In Brazil, unproven drugs against COVID-19, such as hydroxychloroquine and ivermectin, have been largely promoted in the so-called ‘Covid Kit” by national authorities to the detriment of established interventions, such as social distancing, mask-wearing and vaccination (10). Another major source of
misinformation has been the “c19early.com”, a dedicated website containing several meta-analyses without credibility on the efficacy of many drugs against COVID-19, including ivermectin. The resultant popular success of this drug has led to inappropriate therapeutic use. However, just recently, a manuscript promulgating ivermectin use by the FLCCC group was retracted by a main journal because of inappropriate report of mortality (20). Importantly, no clinical study has adequately addressed the potentially toxic adverse effects of this drug, such as interactions with anticoagulants, gastro-intestinal symptoms, hypotension, allergic reactions, dizziness, ataxia and seizures, which might jeopardize the clinical condition of COVID-19 patients. Even the manufacturer (Merck) raised concerns about use of the drug, after the first cases of people being hospitalized after the ingestion of ivermectin doses bought at animal feed stores were reported.

In conclusion, therapy with ivermectin has several similarities with the use of hydroxychloroquine during COVID-19; after initial encouraging experimental and poor-quality clinical results, there is no scientific evidence to support its routine use. Physicians should continue to enroll patients in properly designed randomized clinical trials (the TOGETHER study in Brazil has already been halted because of futility, while the PRINCIPLE and ACTIV-6 networks are actually evaluating ivermectin) to understand whether any useful effects of this drug, alone or in combination, can be identified against COVID-19. The development of Adaptive Platform Trials, which test multiple interventions, with some entering and leaving the platform on the basis of predefined decision algorithms, has significantly accelerated the evaluation process of therapeutic options in COVID-19. People have been eager for an easy solution to prevent infection, and willing to latch on to any seemingly safe, reasonable therapy, especially when apparently supported by renowned professionals.

The vicious progression of “anti-science”, shedding doubts about vaccination and promoting treatments with unproven efficacy, such as hydroxychloroquine and ivermectin, has also shown that a firm condemnation by the scientific community is not sufficient. As such, scientists should attempt to vulgarize medical information in newspapers and social media and even accept debates on television with fake news and disinformation providers, explaining to audiences without medical knowledge and using non-polarized arguments how complex is the medical treatment of COVID-19.
Conflict of interests

FST is in the Advisory Board of Nihon Khoden, Eurosets and Neuroptics and received lecture fees by BD, Zoll and Xenios. MH has been in Advisory Boards for the management of fungal diseases for Gilead. ND has acted as consultant for Roche.

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