

Death threats after a trial on chloroquine for COVID-19

Unfavorable results from a chloroquine clinical trial led to death threats and animosity towards researchers in Brazil. Estella Ektor reports.



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"The only conclusion you can take from the study is that this drug, when used in high doses, is not safe", declared Marcus Lacerda, the principal investigator of the first randomised controlled clinical trial that tested chloroquine, a congener of the supposedly less toxic hydroxychloroquine, to treat patients with severe symptoms of COVID-19. The study involved 21 research institutions in Brazil, Spain, and Mozambique and was initially available on the reprint repository *medRxiv* and later published in *JAMA*.

The study was carried out in the city of Manaus, in the Brazilian state of Amazon, and aimed to evaluate two different doses of chloroquine diphosphate (CQ). While 41 patients received a high dose of 600 mg of CQ twice daily for 10 days, the other group of 40 patients received a lower dose of 450 mg daily for 10 days. Patients in both arms received 500 mg of azithromycin daily for 5 days. On day 5, the high-dose arm of the study had to be interrupted due to the death of 11 patients, against four in the low-dose group. "This was a phase 2 study to evaluate safety and we used a high dose of chloroquine that has been used before" said Lacerda. This same high dose was previously used to treat oncological patients for periods much longer than 10 days; it was also used in China with COVID-19 patients.

However, the unfavorable outcome of the study provoked the animosity of those who support using chloroquine to treat COVID-19, first in the USA, and then in Brazil. Micheal Coudrey, an American political activist with 256 700 Twitter followers referred to the study as "a left-wing funded study that intentionally administered extremely high doses and used a less-safe version

of the drug hydroxychloroquine, then used this as a pretense to indicate that chloroquine was ineffective and dangerous". Soon after, Brazilian president's son Eduardo Bolsonaro (who has 2 million Twitter followers) called it "a fake study aimed at demonizing the drug".

In another inflamed tweet, Eduardo Bolsonaro claimed that the study's authors were affiliated to the party funded by former Brazilian President Luiz Inácio Lula da Silva and asked for an investigation. Soon after, Lacerda started to receive death threats through social media and had to request police protection, which was kept for more than 2 weeks. "When the paper was published in *JAMA*, the threats stopped" revealed Lacerda, indicating that publishing the study in a peer-reviewed high-impact journal may have shielded the researcher and his family.

Besides suffering the death threats, the authors of the study may soon need to respond a legal action taken by three public prosecutors. With 32 points that the authors should justify, the legal action mainly challenges the high dose used in the trial, the choice for chloroquine instead of hydroxychloroquine, and the patient population. "When we first announced we were going to test chloroquine to treat COVID-19 we were seen as heroes in Brazil, people sent us encouraging messages and everyone was excited. However, when the study's results came out, the attitude changed", says Lacerda, still in disbelief.

Besides politicians and activists, the study has also been strongly condemned by some doctors and scientists, who cite observational and retrospective studies with lower level of evidence, and anecdotal accounts,

to support treating COVID-19 with chloroquine, a drug traditionally used to treat malaria and having potential adverse effects, in particular relative to cardiovascular function. "These studies lack controls, so as in the case of anything done without proper control ... you can see anything you want", believes Nikolaos Vasilakis, vice chair of research at the Center for Biodefense and Emerging Infectious Diseases and Center for Tropical Diseases at Institute for Human Infections and Immunity at University of Texas in Galveston, United States.

For Mauro Schechter, a specialist in infectious disease and epidemiology and a professor in Brazil and in the USA at the University of Pittsburgh, and the Bloomberg School of Hygiene and Public Health at Johns Hopkins University, "the main problem is that doctors have no idea how a clinical trial works or what it takes to establish that a drug is effective". Schechter, who is recovering himself from COVID-19, says that he was offered hydroxychloroquine when hospitalised but refused it "in respect to science".

Whether or not to adopt hydroxychloroquine to treat COVID-19 has turned into a political dispute that seems to benefit no one. "We may pass through this pandemic without knowing if this drug works or not", regrets Lacerda. In a letter issued by the Brazilian Society of Virology repudiating the threats received by Lacerda's research group, the society warns: "Only good science can save us in this pandemic of the new coronavirus; thus we supplicate, leave scientists alone to do their work!"

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For more on the trial on chloroquine see *JAMA* 2020; published online April 24. <https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2765499>