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Hydroxychloroquine against COVID-19? Let's listen to monkeys!

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ABSTRACT

Since the beginning of the COVID-19 pandemic, many drugs have been tested to improve patient outcomes or reduce transmission. One of these drugs has generated hopes and tensions around the globe: hydroxychloroquine. We studied its effect against the virus responsible for the coronavirus pandemic under robust experimental conditions, on the most appropriate animal model we have: macaques.

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There is no need to introduce the COVID-19 pandemic and its toll on humanity, as everyone has been affected by the coronavirus in some way. Let us go back to 2020 when it started spreading quickly, when hospitals were filling with patients that required respiratory support, while no treatment was available. Like several other viruses affecting our lungs, this coronavirus causes a two-step disease. First, the virus spreads throughout the body. Then, for some infected people, the body itself – not the virus! – creates a very strong immune reaction that damages major organs, especially the lungs. Thus, at the start of the pandemic, doctors and researchers were looking for two types of drugs: antiviral drugs to stop virus from spreading in the body, and anti-inflammatory drugs that reduce the immune reaction of patients with severe symptoms.

One of the first approaches was to test all available antiviral drugs in vitro, that is, on virus-infected cell cultures in a laboratory, and select promising ones. Here, hydroxychloroquine emerged as a cheap, well-used candidate with a demonstrated antiviral effect. The drug is widely used to treat malaria, and its side effects are well-understood. Therefore, it was used very early in the pandemic, before having clinical trial results as they were only starting.

It became a priority to test this drug in controlled and robust experiments to evaluate its antiviral effect within live animals. Animal studies are the best way

to do this, as you can work on a controlled population in terms of age, sex, and health. You can precisely control the quantity of virus you use and the treatment used, with less variability than when testing on people. Importantly, we can give the drug before infecting the animals, and this way we can easily evaluate if the drug prevents disease or further transmission of the virus. Among animal models we could use, we chose the closest to human in terms of physiology, immune responses and symptoms: macaques.

First step: we gave hydroxychloroquine to non-infected, healthy, macaques and measured the levels of the drug in their blood stream and the lungs. This way, we could be sure that our doses were right and comparable to the levels seen in humans treated for COVID-19. The correct dosage of any drug is different for every animal, so this step is very important. If we find that the drug is not effective against COVID-19, we need to be sure it's not because of an incorrect dosage.

Then, we studied the macaques that we exposed to the virus without treatment. During the experiment, we monitored different aspects of the health of the animals. We monitored general health (appetite, body temperature, symptoms), and lung damage. Furthermore, we used the blood to monitor the immune reaction produced by the body. Using PCR (like the tests done on humans), we measured the amount of the virus in several parts of the body.
These monkeys developed an infection very similar to most humans, showing mild symptoms with high amounts of the virus in the nose, throat, lungs and gut. The concentration of the virus peaked 2-3 days after infection, followed by a slow decline until day 14. All animals developed lung damage, and a drop in the number of white blood cells circulating in the blood.

Finally, we exposed 4 groups of macaques to the virus while treating them, before or shortly after infection, with different drug regimens: either a high or a low dose of hydroxychloroquine, and with or without azithromycin (an antibiotic often used in combination with hydroxychloroquine).

We found absolutely no difference between the macaques treated with hydroxychloroquine and the untreated animals. It does not matter if they received the treatment before or after infection, at a high or low dose, and with or without azithromycin, the results were always the same as for untreated animals; hydroxychloroquine did not have any antiviral effect. Not on the concentration of the virus, not on development of lung damage, not on white blood cell numbers, no effect at all!

Alongside the macaque study, our colleagues in CIRI (Lyon, France) tested if hydroxychloroquine protects against infection in a type of human airway cells cultured in the laboratory. These cells are particularly relevant because they compose the lining of the respiratory system. However, no anti-viral effects were observed here either.

Using relevant cells and animals to pre-screen drugs against new diseases helps us to rapidly predict, with greater precision, the most promising drugs for clinical trials and emergency treatments. The COVID-19 pandemic is the first of this magnitude since the Spanish Flu, and has been a challenge for researchers and doctors. And as we have seen with hydroxychloroquine, among other examples, misinformation can really slow down their work and confuse patients: some patients have been treated with hydroxychloroquine months after various robust studies had shown it had no effect on the infection.
We do not know what is ahead of us, but the recent global joint efforts on COVID-19 research have developed the framework to be better prepared for future pandemics lurking on the horizon. And hopefully, we will learn from COVID-19 to inform people better about treatments, vaccines, and science in general.