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BRIEF19

A daily review of covid-19 research and policy.

RESEARCH BRIEFING

New antiviral drug candidates targeting the SARS-CoV-2 lifecycle. Currently, there are no fully-approved therapeutics against coronavirus. Drugs that interrupt the lifecycle of coronavirus might limit the spread of the virus between individuals and decrease the severity of illness in infected individuals. Azithromycin, dexamethasone, and hydroxychloroquine have been proposed because laboratory studies suggest that they interfere with the lifecycle of SARS-CoV-2. In a new study appearing in the journal *Science*, researchers synthesized two inhibitors of a major workhorse of viral replication of SARS-CoV-2. The target of the inhibitors is an enzyme known as a viral protease. In infected cells, a viral proteases divide up the virus's genetic material so that it can be packaged and released. Inhibiting a SARS-CoV-2 protease should prevent infected cells from making infectious virus particles. The infected cells may still make and release viral particles; they just won't be able to infect other cells. The authors reasoned that a drug targetting components specific to coronavirus are less likely to cause "off-target effects," such as the heart toxicity of azithromycin or hydroxycholoroquine, or the endocrine system side effects of dexamethasone. In this study, the synthesized inhibitor compounds decreased the number of functional viral copies made in experiments conducted in cells taken from the kidney of the African green rhesus monkey. In a small toxicity study, one out of four rats died after receiving a one-time dose and zero of four beagles died after receiving the compound daily for one week. The authors did not report drug levels in the animals and so it is unclear how the doses the animals received relate to the doses given to the monkey cells in the lab. The discrepancy between the dose needed to achieve an effect in disembodied cells and the dose needed to treat the virus in humans is a source of controversy that came up recently in the debate over the use of hydroxycholorquine. Protease inhibitors are an important and effective class of medications, perhaps most widely known in the treatment of HIV. The development of a covid-19 protease inhibitor could help put a lid on the infection until a vaccine arrives. Guided by our experience with HIV, Ebola, MERS, and SARS drug development, much more work is needed to understand whether these new candidates can be developed into effective non-toxic drugs and whether they are best used alone or in combination, and in which patients they are effective. *–Michael Chary, MD, PhD*

Dexamethasone appears to be first drug shown to reduce covid-19 deaths. Dexamethasone, an inexpensive steroid that is widely available appears to be the first medication shown in a high-quality study to reduce the rate of death in any subset of covid-19 patients. After a press release last week announced that patients on mechanical ventilators in particular survived substantially more often than those who did not, many experts called for the immediate release of more data. While some were willing to change their protocols based on the information in the press release alone (based on the fact that the study protocol had been published in advance and that the drug was not studied by researchers with financial ties to the drug), others felt that more information would allow clinicians to more fully interpret the findings, enabling them to decide whether the standard of care for critically ill covid-19 should change immediately. Today, that call was heeded and a substantial amount of data from the study was posted on medRxIV; the paper has not yet undergone peer review. The results come from a larger conglomerate of trials being conducted in the United Kingdom known as the Recovery Trial. The data shared today showed that the primary

outcome of the study--death rate among subjects 28 days after entering the study--was significant; 21.6 percent of patients who were randomly selected to receive dexamethasone were dead at 28 days versus 24.6 percent among patients who received all other aspects of intensive care, but not dexamethasone. This suggests that 20 patients would need to receive the drug for one life to be saved. However, the researchers previously planned to analyze the results of patients who were already on mechanical ventilators at the time they entered the study, those requiring oxygen (but not in comas on ventilators), and those without either requirement. Among those groups, those on mechanical ventilators had by far the greatest effect: 40.7 percent of patients who did not receive the drug had died by day 28 compared with 29% among those who did. A reduction in deaths of over 11 percent is not only an unusually large effect for an ICU study of any kind. Patients who needed oxygen only (but were not in comas on ventilators) also fared better, dying 21.5 percent of the time versus 25 percent among controls. However, among patients who did not require any oxygen, dexamethasone did not help, and in fact, more patients in that group who received the drug died, though the increase was not statistically significant. Whether the extra 11 percent of patients who survived to day 28 among patients on ventilators had improved enough so as to be awake was not reported in the manuscript. The document will require peer review and there are several areas of the paper that are incomplete, a reflection of the speed with which the document was prepared over the last week or so. However, experts on social media began performing that service immediately. *–Jeremy Samuel Faust MD, MS*

POLICY BRIEFING

Antibody tests hold uncertain promise. Antibody testing as the key to reopening? Not so fast, experts say. Some have looked to tests that check for coronavirus antibodies, known as serology tests, as society's best hope, short of a vaccine, to reopen safely, potentially enabling individuals who are found to have the antibodies to go back to workplaces and resume normal life. But experts are now saying that is not realistic at this point. Speaking before a virtual meeting of the House Committee on Oversight and Reform's Subcommittee on Economic and Consumer Policy, Dr. Jesse Ehrenfeld, immediate past chair of the Board of Trustees for the American Medical Association, argued that due the high rate of false-positive results and the unknown significance of antibody levels, serology tests should not be used as a determinant for decreased safety measures. The concerns raised by the American Medical Association were also incorporated into recent Centers for Disease Control and Prevention guidelines on serology testing. The CDC's website states that serology tests have only been designed and validated for surveillance and research and should not be used to determine past infection nor as an indication of immunity, as it is unknown how much immunity such markers indicate, or how long any immunity would last. Meanwhile, the CDC is working with federal agencies to validate commercially-produced serology tests, with results added to the Food and Drug Administration's Emergency Use Authorization page for serology tests as they become available. *Various*. *–Joshua Lesko, MD*

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