23 May 2020

BRIEF19

A daily review of covid-19 research and policy.

******BREAKING RESEARCH BRIEFING******

Two major studies shed light on possible covid-19 treatments. The news is mixed.

By Joshua Niforatos, MD

Two highly anticipated studies evaluating possible treatments for covid-19 were released yesterday. The first, published in *The Lancet* presents data on hydroxychloroquine/chloroquine. The second, published in *The New England Journal of Medicine*, presents the preliminary data from the Adaptive Covid-19 Treatment Trial (ACTT-1) on remdesivir.

The study published in *The Lancet* represents the largest study to-date on the use of hydroxychloroquine/chloroquine in covid-19. In this study, researchers utilized a multinational registry of patients who were given hydroxychloroquine or chloroquine with or without the antibiotic azithromycin to treat covid-19. The data come from 671 hospitals across six continents. Patients were divided into two groups: The treatment group was categorized as any patient with laboratory confirmed SARS-CoV-2 who received one of the following treatment regimens within 48 hours of the diagnosis: chloroquine alone, chloroquine with azithromycin, hydroxychloroquine alone, hydroxychloroquine with azithromycin. Patients who did not receive these medications were considered to be the control group. 96,032 patients were included in the study with an average age of 53 years. The treatment group included 14,888 patients. Between both groups, 11.1 percent (10,698) of patients died in the hospital. The blockbuster result though is that approximately 35 percent of patients who received hydroxychloroquine or chloroquine (with or without azithromycin) died in the hospital compared to only 9.3 percent of patients who did not receive these medications. These results were statistically significant even after controlling for many confounding variables, including age and pre-existing medical conditions. Also concerning, the rate of serious abnormal heart rhythms in the treatment group was noted be more than double that of seen in the control group.

While this was a large and well-designed study with rigorous statistical methods, it was a retrospective study. This means that patients were *not* randomized either to receive the medications of interest or placebo, and the data were extracted from the medical records of patients who had already been treated. Nevertheless, given the literature to-date, the case against hydroxychloroquine and/or chloroquine to treat covid-19 is becoming increasingly insurmountable. It is beginning to appear that these medications may increase the risk of dying from covid-19 in hospitalized patients. Randomized controlled prospective trials are underway.

Last month, Dr. Anthony Fauci, the director of the National Institute of Allergy and Infectious Diseases, announced preliminary results of the ACTT-1 trial on remdesivir during a press event at the White House. Yesterday, that data was finally published in *The New England Journal of Medicine*. ACTT-1 was a double-blind, randomized, placebo-controlled trial of remdesivir given to patients within 72 hours of diagnosis of laboratory-confirmed SARS-CoV-2 infection in the in-patient hospital setting. 1,063 patients were randomized. The average age was 58.8 years, 64.3

percent were male. The average number of days between symptom onset and randomization to either remdesivir or placebo was 9 days. 88.7 percent of patients had "severe" covid-19 at the time of enrollment. Severe disease was defined as requiring invasive or non-invasive mechanical ventilation, requiring supplemental oxygen, oxygen saturation of <95 percent (without supplemental oxygen), or respiratory rates >23 breaths per minute. Mild and moderate disease was defined by a higher oxygen levels, and respiratory rates < 24 breaths per minute, without the need for supplemental oxygen.

The primary outcome of interest was time to recovery. Recovery was defined as either being well enough to have been released from the hospital or remaining in the hospital for infection-control purposes only (i.e. to protect their families, not due to the severity of their illness). Currently, the data are considered preliminary because the published data comprise approximately two-thirds of the enrolled patients in this study; the remaining one-third had not yet reached day 29 of their courses by the time the study was submitted for publication. The average recovery time was 11 days in the remdesivir group compared to 15 days in the placebo group. While the study was not designed to directly and properly measure mortality *per se*, 7.1 percent of patients receiving remdesivir died by day 14 compared to 11.9 percent in the placebo group (hazard ratio 0.7, 95% confidence interval 0.47 to 1.04). While this appears promising, rigorous scientific principles dictate that when a confidence interval straddles 1.0, no responsible conclusion can be made. Of note, remdesivir did not seem to improve time to recovery in patients were already receiving high-flow oxygen, non-invasive mechanical ventilation, mechanical ventilation, or ECMO (extracorporeal membrane oxygenation) at time of enrollment. Put another way, critically ill patients remained sick whether or not they received remdesivir.

The authors conclusions offer some perspective. They note the relatively high mortality rate in SARS-CoV-2, regardless of remdesivir. They therefore note that treatment with an antiviral drug alone such as remdesivir is unlikely to be sufficient.

Although this manuscript contains only the preliminary results of the ACTT-1 trial, there appear to be two important benefits associated with use of remdesivir; one benefit for hospitals and one for patients. For hospitals, remdesivir use reduces length of stay, which could be important during any future surges that occur during the pandemic when resources may become limited. For patients, there appears to be a preliminary signal that remdesivir may decrease mortality. Although follow-up data through day 29 is needed for approximately one-third of patients in the ACTT-1 trial, as well as patient-level analyses of mortality, the results of this trial are promising. Nevertheless, even if the absolute difference in mortality turns out to be statistically significant once all the results are accounted for, it appears that approximately 21 severely ill covid-19 patients would need to be given remdesivir in order to save a single life.

Joshua Niforatos, MD Research Section Editor. Kimi Chernoby, MD, JD, Policy Section Editor.
Kate Taylor, Editor-at-Large.
Kane Elfman PhD, Publishing and Design. *Jeremy Samuel Faust MD MS, Editor-in-Chief.*
http://www.brief19.com/ Twitter: @brief_19 submissions@brief19.com

Brief19 is a daily executive summary of covid-19-related medical research, news, and public policy. It was founded and created by frontline emergency medicine physicians with expertise in medical research critique, health policy, and public policy.