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BRIEF19

A daily review of covid-19 research and policy.

RESEARCH BRIEFING

Remdesivir finds no benefit for patients with moderate covid-19 illness.

In May, preliminary results of the ACTT-1 clinical trial found that remdesivir may have potential benefit in the treatment of covid-19. That trial, published in the *New England Journal of Medicine,* showed that patients admitted to the hospital with *severe* covid-19 pneumonia who received remdesivir had a shorter hospital length of stay (11 versus 15 days). Since those results were published, the medical community has eagerly awaited more complete results. In particular, the 28-day mortality data from that trial, funded by the National Institute of Allergy and Infectious Diseases (NIAID), has yet to be published, three months on.

Today, more results, this time in a study funded by Gilead, were published in the *Journal of the American Medical Association*. This time, patients admitted to the hospital with *moderate* covid-19 pneumonia (thee ACTT-1 trial focused on *severe* covid-19 illness)—defined as infiltration of the lungs by SARS-CoV-2 and oxygen saturation >94 percent—were randomized to one of three treatment arms: a 10-day course of remdesivir, a five-day course, or standard-of-care. The primary outcome of this trial was the clinical outcomes in these three treatment arms measured on day 11, using a seven point scale ranging from death to discharge.

This study included over 500 patients across 105 hospitals and three continents (North America, Europe and Asia). By day 11, patients in the five-day remdesivir arm had higher odds of improving compared to those who received 10 days of the drug or standard-of-care (odds ratio, 1.65; with 95 percent chance that the odds are between 1.09 and 2.48). (Of note, patients randomized to receive 10 days of the trial drug on average only received the drug for 6 days). The score among patients in the 10-day arm was not statistically different from patients who received standard of care only. However, by day 14, there were similar improvements in clinical status distribution for both 10-day and five-day remdesivir treatments compared to standard-of-care. Interestingly, by day 28 *only* those in the 10-day remdesivir group showed improvement in clinical status distribution compared to standard-of-care. There was no improvement for the five-day group. Additionally, there was no statistical difference between the three groups with respect to 28-day mortality. Regarding side effects, nausea, low potassium levels, and headaches were more common in the patients who received remdesivir.

Ultimately, as was seen with ACTT-1, there remains a lack of impressive evidence to state that remdesivir improves mortality in patients with covid-19 pneumonia. ACTT-1 *was* able to show that those receiving remdesivir are discharged from the hospital slightly earlier. This new trial similarly confirms that by day 11 and 14, patients receiving remdesivir are likely to have improvement in clinical status or be discharged from the hospital. But for patients who are not improving by day 14, the data seems to suggest that remdesivir is unable to change the covid-19 disease trajectory in those destined for lengthy hospital admissions. It is unclear why there was any difference between the 5-day and 10-day treatment arms given that the average patient in the 10-day arm only took remdesivir for six days. Nevertheless, Gilead's study adds to the growing body of literature that remdesivir seems to be relatively safe.

Hope still remains that the 28-day ACTT-1 trial will show some mortality benefit. Regardless, the mortality rate of those with moderate covid-19 pneumonia who are admitted to the hospital remains around one percent.

—Joshua Niforatos, MD

POLICY BRIEFING

Plasma therapy not ready for prime time.

Last week, the Food and Drug Administration was on the verge of completing an Emergency Use Authorization (EUA) to allow blood plasma from recovered coronavirus patients to be used as a treatment for the virus, when a group of federal health experts banded together in an effort to stop its finalization. Led by Dr. Francis Collins, the Director of the National Institutes of Health (NIH), Dr. Anthony Fauci, the director of the National Institute of Allergy and Infectious Disease (NIAID), Dr. H. Clifford Lane (NIAID), and members of the White House coronavirus task force, this group believes that the data on plasma efficacy is not yet robust enough to warrant an EUA issuance. The main concern is that many of the published studies have conflicting results on the true benefit of plasma, with differences in time to intervention, concentration of plasma components, and the severity of patient illness in the trials, all of which complicate the overall picture.

A randomized trial assessing the use of convalescent plasma (antibodies recovered from patients who have survived covid-19) for the treatment of covid-19 published in *JAMA* in June showed no benefit. A recent non-peer-reviewed article (published on a preprint server) that combined results from multiple studies of plasma purported to show that the treatment works; however, two of the three major studies included in the paper's main analysis have themselves not been peer reviewed, creating an unusual situation in which a preprinted review article heavily relied on data from preprinted research articles. In addition, the methods of at least one of the major articles included in the review have come under fire; the authors of a study conducted in Iraq claimed they performed a randomized controlled trial (RCT) of the effect of plasma on patients with serious covid-19, when in fact it appears that the methods used were not truly consistent with RCTs.

However, Drs. Collins, Fauci, and Lane focused their arguments against moving forward with an FDA emergency use authorization for convalescent plasma largely on the fact that the support for plasma relies on shaky historic evidence of plasma's effectiveness, animal studies, and a few human studies. These experts requested more time be given in ordere to review the pool of existing and emerging data and to develop rigorous study protocols that would definitively ensure that plasma provides benefit to covid-19 patients. There are multiple trials of plasma currently underway in several nations around the world. *The New York Times and others.*

—Joshua Lesko, MD