BRIEF19

A daily review of covid-19 research and policy.

RESEARCH BRIEFING

Final remdesivir results published after 139 days of waiting.

The preliminary results of the Adaptive Covid-19 Treatment Trial (ACTT-1) randomized trial were published May 22 in *The New England Journal of Medicine* and covered by *Brief19*. ACTT-1 was a double-blind, randomized, placebo-controlled trial of the antiviral drug remdesivir, given to patients intravenously within 72 hours of laboratory-confirmed diagnosis of SARS-CoV-2, among hospitalized patients.

The primary outcome of the preliminary report was time to recovery from covid-19, which was broadly defined as either being released from the hospital or remaining in the hospital for infection-control purposes only. In the preliminary report, the average time to recovery in the remdesivir group was 11 days versus 15 days in the placebo group. No other results were statistically significant, including mortality or the percent of patients receiving oxygen therapy. Missing from the preliminary report was approximately one-third of patients who were enrolled in the study but had not reached day 29 of follow-up.

139 days later, the final report of the ACTT-1 trial has been published in *The New England Journal of Medicine* with the remainder of the participants included. Patients receiving remdesivir had a median recovery time of 10 days compared to 15 days in the placebo group. The authors also report that patients receiving remdesivir had non-statistically significant differences in mortality at both day 15 and day 29; by day 15, mortality rates were 6.7 percent (remdesivir) and 11.9 percent (placebo); by day 29, mortality rates were 11.4 percent (remdesivir) vs 15.2 percent (placebo). While these results were *not* statistically significant, the overall confidence intervals of the hazard ratio *suggests* there may be a mortality benefit though the trial itself did not include enough test subjects to detect either a net survival benefit or harm. Any mortality difference would be important, but not "game changing," in contrast to initial hype. The survival curves suggest that the patients most likely to benefit are those on nasal supplemental oxygen only. Furthermore, it seems that those ages 18 to 40 years and those with an onset of symptoms fewer than 10 days before treatment began are the most likely to benefit from remdesivir.

Similar to the preliminary report, the rate of serious adverse events was actually *less* in the remdesivir group (24.6 percent) compared to those in the placebo group (31.6 percent). One worrying finding emerged when assessing the time it took until recovery, divided into certain subgroups. While is important to remember that unless subgroups analyses are pre-planned and adequately planned for (statistically), any resulting data should be considered "hypothesis-generating" only. That said, Black, Asian, and Hispanic/Latinx people did not benefit from remdesivir while white patients did. It is uncertain why this is the case and whether this represents ethnic / racial disparities, such as when the medication was given, how severe the cases were, or other potential factors. We hope the authors or other experts will address this issue soon.

Overall, the final report does not change the preliminary conclusions. Based on the research to-date, for critically ill covid-19 patients, remdesivir is unlikely to change survival or the need for mechanical ventilation. The only drug to-date that has shown to improve mortality remains dexamethasone, a generic and inexpensive drug. *9 October 2020*. *—Joshua Niforatos, MD*

An early hopeful for an effective covid-19 therapy comes up short in a major trial. Lopinovir-ritonavir is a combination of antiviral medications that was proposed as a potential treatment for SARS-CoV-2 as laboratory data demonstrated that the medication stopped the virus from replicating.

The RECOVERY group from the United Kingdom have now reported the results in *The Lancet* from a randomized controlled trial in which 1,616 patients were randomized to receive lopinavir-ritonavir plus standard care and 3,424 patients were randomized to standard care alone. The study was open-label, meaning both the patients and clinicians were aware of the treatment patients received. Most patients were on oxygen (70 pecent) and very few were mechanically ventilated (4 percent). There was no difference in 28-day mortality between the groups – 23 percent of patients allocated to lopinavir-ritonavir died and 22 percent of those allocated to standard care died. Researchers analyzed several groups to assess for any effects among specific cohorts; there was no difference in mortality based on age, sex, ethnicity, time from symptom onset, degree of respiratory support, or baseline risk. An earlier trial also found no clear benefit to the medication. This larger study confirms that this medication does not change important outcomes in patients with covid-19. This study is an important reminder that treatments that appear effective in the laboratory setting often do not translate into effective therapies in the real-world setting. *8 October 2020*. *—Lauren Westafer, DO, MPH*

Facemasks have no effect on oxygen levels even in users with existing lung disease.

One of the great unfounded and highly misleading notions about mask wearing is that prolonged use leads to decreased delivery of oxygen to the lungs and increased carbon dioxide retention. This argument is easily discredited by over 100 years of safe mask use, and now researchers at the University of Miami have released confirmatory findings in *Annals of the American Thoracic Society*. The authors primarily studied whether any gas exchange abnormalities (eg. oxygen and carbon dioxide) can occur in those who wear masks by comparing healthy subjects and those with underlying pulmonary disease such as Chronic Obstructive Pulmonary Disease (COPD, or emphysema). COPD patients are at a baseline risk of increased carbon dioxide retention.

A group of 15 physicians in training (median age 31) was compared to 15 military veterans (median age of 71.6). The veteran group was 100 percent male compared to 60 percent of the physician group.

Measurements of oxygen saturation and end-tidal carbon dioxide (the amount exhaled) were recorded with and without masks being worn. The COPD group was also assessed during a routine 6 minute walk test performed in the clinic. After 5 and 30 minutes, no major changes in either value of gas exchange was detected. The COPD group had additional routine blood work performed as part of their clinical assessment. None of the subjects demonstrated the often falsely reported dangers of carbon dioxide retention from mask use.

This simple study exhibits that surgical face masks affect neither healthy individuals nor those with underlying lung disease with respect to impairing normal breathing function. It is important to note that surgical masks were studied, which are recommended for the general public, and not N-95s worn by healthcare providers in high risk settings. Much of the discomfort that some people have reported related to mask wearing is likely related to neurological reactions or psychological phenomena such as anxiety. Hopefully these results along with other studies can help improve public confidence about the safety of mask wearing to help prevent the spread of covid-19. *7 October 2020*. *—Christopher Sampson, MD, FACEP*

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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.