Week in Review: 19 – 23 October 2020

BRIEF19

A daily review of covid-19 research and policy.

RESEARCH BRIEFING

Another hope dashed? Tocilizumab not as promising as hoped in a new trial.

Earlier this week we covered three *JAMA Internal Medicine* papers assessing drug called tocilizumab, a monoclonal antibody that targets interleukin-6 receptors, thought to contribute to the human body's counterproductive immune response to SARS-CoV-2, the virus that causes covid-19. The studies from earlier this week were disappointing overall but left us with a glimmer of hope that the medication might still benefit a subset of patients.

The idea is that this medication reduces the inflammatory response seen in critically ill patients with covid-19. Released today in *New England Journal of Medicine* is an industry funded study looking at this drug's efficacy. Sadly these results are also not promising. Researchers at Massachusetts General Hospital studied whether drug administration affected the need for mechanical ventilation or death, prior to intubation. This well performed double-blind placebo-controlled study required patients to have confirmed SARS-CoV-2 and at least two of the following clinical features: fever, abnormal lung findings on radiological imaging (such as chest x-rays of CT scan), or the need for supplemental oxygen.

A total of 243 patients (58 percent of whom were men) were enrolled who had a median age of 59.8 years. Tocilizumab was found to have a hazard ratio of 0.83 for intubation or death, but the ratio crossed the 1.0 threshold (less than 1.0 would indicate fewer deaths, more than 1.0 would indicated more deaths), meaning that it cannot be said to be a statistically meaningful result (the authors are 95 percent certain that the "true" ratio is somewhere between 0.38 and 1.81). At two weeks, 18 percent of the patients who received tocilizumab had disease worsening compared to 15 percent among those who received placebo. The discontinuation of supplemental oxygen was very similar in both groups as well (5.0 days vs 4.9 days).

Of note, a reasonable portion of the patient group studied was Hispanic or Latino (45 percent) which does tend to reflect previous studies looking at patient demographics hospitalized with severe or critical cases of covid-19. Unfortunately the use of tocilizumab was not found to prevent death or intubation in patients with covid-19. Given the very large confidence intervals it was hard for the authors to draw a conclusion as to whether this medication is harmful or helpful to patients with respect to a number of different clinical outcomes. *22 October 2020*. —*Christopher Sampson, MD, FACEP*

Who would and who would not get a covid-19 vaccine in the United States?

A paper out this week in *JAMA Network Open* surveyed the general public regarding adults' willingness to accept a hypothetical covid-19 vaccine. The survey took place on the website *LUCID*, an online marketplace of adults who take surveys in exchange for a small payment and was designed to ascertain whether an individual would be willing to receive a hypothetical covid-19 vaccine. The scenario asked the individual if they would choose among two described vaccines, or neither vaccine. Each scenario varied with regards to different vaccine's attributes, including efficacy, safety, how long the effect of the vaccine would last, adverse effects, and approval by the U.S. Food and Drug Administration, among other features.

A total of 1,971 individuals completed the survey. Participants were more willing to accept a vaccine if it was more likely to be effective, the effects were to last longer than a single year, and if the Centers for Disease Control and Prevention and The World Health Organization endorsed a vaccine than they would be when compared to a scenario in which President Trump endorsed a vaccine. Participants were less likely to accept a vaccine if the vaccine had major adverse effects, was given FDA "emergency approval" (compared to full approval), and if the vaccine originated in a non-U.S. country.

Factors that potentially limit the generalizability of these results include the average age (43 years), and that the individuals who participated were predominantly white; 36 percent were liberal, 33

percent were moderate, 48 percent had a college degree or graduate degree, and almost one-fourth had an annual income of over $100,000.

LUCID is generally considered to be a fairly nationally representative sample of the U.S. population, which means that it is reasonable to extrapolate the results from this survey study to the broader U.S. population. Despite that, this is a study based on a survey alone. This means it can be "hypothesis generating" and can help anticipate barriers in vaccine uptake that make occur in the coming months, influencing how public messaging should be tailored when a vaccine is finally approved for generalized use. The results likely confirm most of our prior assumptions that affluent and educated individuals are more likely to accept a vaccine. *21 October 2020.* *—Joshua Niforatos, MD*

Repurposed antiviral drugs unable to lower covid-19 mortality, interim WHO study finds.

A major preprint publication by scientists working with the World Health Organization (WHO) went live late last week. The "Solidarity" study is a randomized clinical trial aiming to answer a simple but important question: are patients who are hospitalized with covid-19 who receive antiviral medications less likely to die while in the hospital compared to those who receive placebo in addition to other standard care?

The Solidarity trial is a large, multi-country, open-label (not blinded) randomized study. This clinical trial, a monumental effort, has been rolled out in 405 hospitals across 30 countries with 11,266 patients randomized to one of handful of treatment arms, which included: remdesivir, hydroxychloroquine (HCQ), lopinavir, lopinavir plus interferon, interferon only, or placebo. All patients received standard of care, which was supportive treatment.

The results were sobering. 28-day mortality was 12 percent overall, and 39 percent of the patients required mechanical ventilation at the time of enrollment into the trial. The *overall* death rate ratios (RR) were as follows: Remdesivir RR = 0.95 (95% CI, 0.81-1.11, p = 0.5); HCQ RR = 1.2 (95% CI, 0.8-1.8, p = 0.23); Lopinavir RR = 1.0 (0.8-1.3, p = 0.97); Interferon RR = 1.2 (0.96-1.4, p = 0.11).

In other words, at the time of this interim analysis, this trial was neither able to detect clear benefit or harm for any of the aforementioned antivirals in preventing in-hospital mortality *or* shortening the duration of symptoms. In subgroup analyses stratified by patient age and oxygen needs for each antiviral, no clear benefit was noted for any of the antivirals. Furthermore, there was no evidence that remdesivir prevented progression of disease in those without oxygen needs at the time of enrollment. Signals of potential *harm* leading to death were noted in the subgroup analyses for HCQ, specifically for patients aged 50-69 years of age.

How does this study fall in line with ACTT-1 trial of remdesivir, which we have covered before? The authors of Solidarity included a meta-analysis as part of their interim results, which included ACTT-1, a trial conducted in Wuhan, the SIMPLE trial, in addition to the Solidarity data. They found that for patients *not on mechanical ventilation*, remdesivir did not improve mortality. The death ratio for this group was 0.80 (0.63-1.01) which is at least a *signal* for benefit given the vast majority of entirety of the 95% confidence interval fells on the side of "favor".

So, does remdesivir improve overall mortality in patients hospitalized with covid-19? The answer is still likely no. But might there a group of patients who may benefit from it? It's possible that those patients hospitalized with covid-19 who have less severe disease might benefit. But the evidence is not definitive, and overall unimpressive. We eagerly await the final report of the Solidarity trial. *Abbreviated from Brief19 for 19 October 2020.* *— Joshua Niforatos, MD, Research Section Editor*

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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.