BRIEF19

A daily review of covid-19 research and policy.

RESEARCH BRIEFING

Monoclonal antibody does not reduce SARS-COV-2 viral load in humans.

Early in the pandemic we published a series of *Briefs* looking at the pathophysiology of SARS-CoV-2 virus. In those briefs, we explained how the SARS-CoV-2 virus binds to receptors on the surface of human cells called angiotensin-converting enzyme 2 (ACE-2) receptors. Binding to ACE-2 allows the virus to connect to the cell and initiate entry. A potential way to prevent covid-19 might be by stopping SARS-CoV-2 entry into human cells via ACE-2.

An antibody that neutralizes the SARS-CoV-2 protein that binds human ACE-2 receptors was developed from the "convalescent" plasma of a patient who recovered from covid-19 and called neutralizing antibody LY-CoV555. Now, the pharmaceutical giant Eli Lilly has published interim results of its Phase 2 randomized clinical trial studying the safety and efficacy of the therapy.

In this study, published yesterday evening in the *New England Journal of Medicine*, patients in the outpatient, non-hospitalized setting who were diagnosed with mild or moderate syndromic covid-19 were randomized to either placebo or a single intravenous infusion of one of three doses of neutralizing antibody (700 mg, 2800 mg, 7000 mg). The primary outcome of the study was the change in nasopharyngeal viral load of SARS-CoV-2 at day 11. Other endpoints assessed included safety, symptoms, and hospitalizations (ER visits and hospitalizations).

The results of the study were interesting but underwhelming. By day 11, most patients had significant decreases in nasopharyngeal viral load, *including the placebo group*, of almost 99.97 percent reduction. Only the 2800 mg infusion of neutralizing antibody LY-CoV555 had a more significant decrease in viral load compared to both 700 mg and, interestingly, the higher dose regimen of 7000 mg as well. The finding many people are excited about is a difference in hospitalization for patients receiving the antibody versus placebo; 1.6 percent and 6.3 percent, respectively. While this sounds good, the sample size is way too small to be confident that this is meaningful. A single patient's outcome could have made a drastic difference here, which is a sign that this finding is on very tenuous ground. A more reliable conclusion is that the antibodies were found to overall be safe when contrasted to the placebo.

The results from the interim analysis of this Phase 2 trial for patients with mild to moderate covid-19 did not appear to significantly reduce viral load of SARS-CoV-2 in non-hospitalized patients. Although the dose of 2800 mg was marginally statistically significant—though of questionable clinical significance—compared to the placebo, it is both irregular and eyebrow raising that the 7000 mg dose was not effective. Regarding the slight decrease in hospitalizations, we take these results as hypothesis generating without knowing more about the patient population and without a sufficient number of events to as to render the data sturdy enough to interpret. *29 October 2020*.

Hospitalizations for non-covid-19 conditions in New York confirmed lower this Spring. A new paper published in *JAMA Internal Medicine* looks at trends in hospitalizations for non-covid-19 acute and chronic medical conditions across four hospitals in the NYU Langone Health system in New York City. Hospital admission from the peak of the pandemic (March 1 to May 9, 2020) were analyzed and compared to hospital admission trends during the same time period in the years 2018 and 2019. The researchers identified 3,657 non-covid-19 hospitalizations during the aforementioned period in 2020. When compared to 2018 and 2019 admission, there was no significant difference in admission rates during the early pandemic period, though decreases in admissions were noted during the peak of the early pandemic period. Consistent with prior research, the researchers observed decreases in hospitalizations for the following disease processes: sepsis, heart failure, heart attacks, strokes, gallbladder disease, seizures, appendicitis, and emphysema (or chronic obstructive pulmonary disease/COPD) exacerbations. The authors note in their study, "while hospitalizations for acute events began recovering in the late

covid-19 period, many of those related to chronic diseases generally did not." This study is limited by its inability to demonstrate causation. By nature of the study design, it does not and cannot prove with certainty that the results are due to sick patients avoiding the hospital during the pandemic. However, this study is yet another data point in the sea of data that suggest that there was less treatment of acute medical problems during the pandemic period. The question remains whether there were people who needed treatment who avoided it, or whether there were fewer triggers for these emergencies, such as decreases is stress, less pollution, and people staying home and eating healthier meals rather than eating out. *27 October 2020*.

Can aspirin improve inpatient mortality for patients with covid-19?

A new study conducted by researchers at the University of Maryland School of Medicine suggests a potential benefit of aspirin use for severe covid-19 patients. Aspirin is a commonly used medication for prevention and treatment of strokes and heart attacks as it helps prevent formation of blood clots. As previously discussed in *Brief19*, covid-19 results in a hypercoagulable state, meaning it puts patients at an increased risk for clots, particularly in the legs ("deep vein thrombosis") and lungs ("pulmonary embolism").

Published in *Anesthesia & Analgesia*, the retrospective study included patients admitted to the hospitals participating in a multicenter project called the Collaborative Research to Understand the Sequelae of Harm in COVID (CRUSH COVID) registry. Aspirin use was defined as administration within 24 hours of hospitalization or in the week prior. The main outcome of the study was the need for invasive mechanical ventilation. Other outcomes included admission to the intensive care unit and in-hospital mortality.

A total of 412 patients were included in the study, approximately 25 percent of whom received aspirin. Unsurprisingly, those receiving aspirin had significantly more existing medical conditions, which in turn placed them at a higher risk of covid-19-related mortality. In the final statistical analysis adjusting for patient characteristics, aspirin use was associated with a decreased risk of mechanical ventilation (adjusted hazard ratio=0.56, 95% confidence interval 0.37-0.85, p=0.007), ICU admission (adjusted HR 0.57, 95% CI 0.38-0.85, p=0.005) and in-hospital mortality (adjusted HR 0.53, 95% CI 0.31-0.90, p=0.02). Other predictors included older age, obesity and self-identifying as Latinx.

But does aspirin actually decrease the need for mechanical ventilation, ICU admissions and in-hospital mortality? Unlikely. The effect sizes reported above are quite large and lack "face validity." Furthermore, patients are risk stratified and placed on prophylactic heavy-duty blood thinning medications to prevent pulmonary emboli and deep vein thromboses. Based on these other treatments and the limitations of the study, it doesn't seem as though there is sufficient proof to determine aspirin's true benefit for covid-19 patients.

Nevertheless, the authors should be commended for this hypothesis-generating research and for their appropriate conclusion that "a sufficiently powered randomized controlled trial is needed to assess whether a causal relationship exists between aspirin use and reduced lung injury and mortality in COVID-19 patients." *30 October 2020*.

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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.