Week in Review: 27 April – 1 May 2020

BRIEF19

A daily review of covid-19 research and policy.

RESEARCH BRIEFING

Breaking news briefing: Lancet lifts embargo to sound cautionary note about Remdesivir. The study in *The Lancet,* entitled "Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial," assessed patients with laboratory-confirmed SARS-CoV-2 infection with pneumonia who required supplemental oxygenation. Patients in this study, conducted in China, received either remdesivir or a placebo infusion, and all patients were allowed use of other medications, such as lopinavir–ritonavir, interferons, and corticosteroids. The researchers collected data on clinical improvement up to 28 days. Favorable outcomes were considered to be improvement in clinical status or being released from the hospital. Results: A total of 237 patients were enrolled and randomized in this study. The study found that, among patients with symptom duration of 10 days or less, those receiving remdesivir had a numerically faster time to clinical improvement than those receiving a placebo, but the difference was not statistically significant. The study was stopped early because as of March 12, there were not enough patients in Wuhan who qualified based on the inclusion criteria. Analysis: The results of two other Gilead-funded studies, cited by President Trump and Dr. Fauci, suggest that remdesivir may improve clinical outcomes in patients with covid-19. Those studies remain unpublished, however, and the data cannot yet be scrutinized. However, the trial designs that are already public indicate that neither study is likely to have game-changing findings. *Abbreviated from Breaking News Briefing on 29 April 2020.* ***For a full analysis of the existing remdesivir data****, refer to Brief19 for 30 April 2020.* *–Joshua Niforatos, MD & Jeremy Samuel Faust MD MS*

Can alpha-1 adrenergic receptor antagonists (α1-AR antagonists) prevent covid-19 cytokine storm? A preprint published in arXiv looked at the use of α1-AR antagonists to prevent the massive inflammation that seems to evolve in covid-19 patients who develop acute respiratory distress syndrome. Previous research in mice suggests that α1-AR antagonists can prevent these "cytokine storms" and death. The authors conducted a retrospective study in human patients with acute respiratory distress or pneumonia. Patients taking α1-AR antagonists for other conditions were 35% less likely to require mechanical ventilation, and were 56% less likely to experience mechanical ventilation *and* death (the researchers combined these outcomes into a composite, which occurred in 56% fewer patients than patients not on these drugs). Analysis: should we use α1-AR antagonists for patients with covid-19? This retrospective study of medications that have not been shown to improve outcomes in humans (but have shown possible benefit in mice) does not provide the answer. The medical literature is rife with studies that were promising in mice but that failed in humans. Treatments that work in both mice and humans are the exception, not the rule. *Abbreviated from Brief19 for 29 April 2020.*

News leak from the CORIMUNO-TOCI clinical trial. Patients with covid-19 and acute respiratory distress syndrome can develop an enormous immune response called "cytokine storm syndrome." The presence of that syndrome indicates an increased risk of death. One marker of this "hyperinflammation" is a cytokine known as interleukin-6 (IL-6). Many hospitals are testing patients with severe/critical covid-19 for IL-6 labs. However, IL-6 levels are what scientists call "surrogate markers" of disease. They indicate internal activity in the body, but not whether that

activity has any clinical effect or relevance. The medication tocilizumab is a "humanized monoclonal antibody" and was previously FDA-approved for use in cytokine storm syndrome. On April 27, the largest hospital system in Europe released a statement claiming that Tocilizumab "improves significantly clinical outcomes of patients with moderate or severe COVID-19 pneumonia." The claim is based on results of the CORIMUNO-TOCI trial, which is controlled (i.e. some patients in the trial did not receive the drug) but is not blinded. The statement reports that "a significantly lower proportion of patients reached the primary outcome in the tocilizumab arm." These data have not been published in a peer-review journal; until then, the strength of these findings cannot be assessed. *Abbreviated from Brief19 for 29 April 2020.*

Do people lose their sense of smell or taste when they have SARS-Cov-2?
A research letter published in JAMA analyzed data from 202 patients with laboratory-confirmed SARS-CoV-2 infection in Italy to measure how common loss of smell ("anosmia") and loss of taste (dysgeusia) were. Anosmia and dysgeusia were assessed with a survey tool somewhat humorously called the SNOT-22 score. A total of 130 patients, or 64.4 percent, reported some change in their sense of smell or taste. Many patients began to experience these symptoms either simultaneously with other covid-19 symptoms or after other covid-19 symptoms had already emerged (almost 50 percent). Only 11.9 percent experienced anosmia or dysgeusia prior to the start of other covid-19 symptoms. Importantly, only 3 percent of patients reported anosmia or dysgeusia as their only symptoms. Although this was a retrospective study that is biased by self-reported symptoms and whether a patient completed the survey, it provides the most compelling evidence to date that patients who develop anosmia or dysgeusia for the first time should potentially be considered as higher risk for covid-19 and tested accordingly. *27 April 2020.*

Does confinement or shelter-in-place affect the mental health of children? In a study from the epicenter of the covid-19 pandemic, researchers in Hubei in China assessed the prevalence of symptoms associated with depression and anxiety among students in the province. Published in *JAMA Pediatrics*, students grades 2 through 6 were invited to complete a survey. The survey was completed by 1,784 students who, at the time of the survey, had been at home for an average of 33.7 days. The prevalence of symptoms related to anxiety and depression were 18.9% and 22.6%, respectively. Children in the city of Wuhan were much more likely to have depressive symptoms than those outside of Wuhan. Previous estimates of depressive symptoms among students in primary schools of China reported figures around 17%. The precision of these new higher numbers is difficult to evaluate. However, from a humanistic perspective, these trends provide important insight relevant to children and parents facing this pandemic now. *Abbreviated from Brief19 for 27 April 2020.*

–Joshua Niforatos, MD, Research Section Editor

Kane Elfman PhD, Publishing and design. *Anna Fang, Week in Review.*
Jeremy Samuel Faust MD MS, Editor-in-Chief.

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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.