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BRIEF19

A daily review of covid-19 research and policy

RESEARCH BRIEFING: FOCUS ON MONOCLONAL ANTIBODIES

Editor's note: Recently, monoclonal antibodies have grabbed headlines as possible therapeutics for covid-19. There are two broad categories to consider. Some monoclonal antibodies are drugs targeting specific parts of the SARS-CoV-2 virus; these compounds, made by Regeneron and Eli Lilly, for example, are the types of monoclonal antibodies taken by President Trump during his recent covid-19 bout. Currently one of Eli Lilly's trials has paused enrollment due to an unspecific safety concern. The second type of monoclonal antibodies target our own immune system, binding to receptors on molecules that are thought to be involved in the body's self-defeating response to infection. This second type of monoclonal antibody has made headlines in the last few days due to four major studies investigating their effectiveness.

Today, we cover the latest trial in a briefing by Dr. Christopher Sampson, and then turn to a guest briefing summarizing the week's research, written by the senior author and principal investigator of one of the four major studies, Dr. David Leaf. —Jeremy Samuel Faust, MD MS

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. *—Christopher Sampson, MD, FACEP*

Four clinical studies on the monoclonal antibody Tocilizumab. What does it all mean?

Tocilizumab is a monoclonal antibody that inhibits a molecule known as interleukin-6 (IL-6). IL-6 is a part of our immune system and is involved in inflammation. Recently, there has been substantial interest in studying the effect that inhibiting IL-6 might have in treating patients with covid-19. The goal of these efforts is to identify whether such an approach might diminish inflammation and improve outcomes in hospitalized patients with covid-19. Unlike steroids such as dexamethasone, which blunt the immune system more broadly, tocilizumab is a more targeted drug. As with any targeted approach, the hope is that it can treat covid-19 with fewer downsides.

Four important clinical studies of tocilizumab in COVID-19 have been published in the last several days: one was a large observational study called STOP-COVID (for which I served as principal investigator), while the other three were randomized clinical trials.

STOP-COVID, published in *JAMA Internal Medicine*, found a sizable mortality benefit in patients who had received tocilizumab. Patients who received the drug in the first two days of an admission to an intensive care unit had 30 percent lower mortality compared to those who did not receive the drug. The benefit was even greater among patients with a rapid disease trajectory; those admitted to the ICU within 3 days of initial symptom onset had a 60 percent lower mortality rate if they received tocilizumab compared to those who did not receive that treatment.

The findings from the three randomized controlled trials (RCTs), by contrast, were mixed. Two of the RCTs, one of which was published in the *New England Journal of Medicine* and the other in *JAMA Internal Medicine*, found no benefit with tocilizumab compared to placebo. A third RCT, published in *JAMA Internal Medicine*, found a beneficial effect of tocilizumab for one of the study's primary outcomes—a decrease in either the need for mechanical ventilation or death by day 14. However, no benefit with respect to the other primary outcome (clinical status on day 4) was detected.

These seemingly conflicting findings have generated uncertainty with respect to tocilizumab's potential in treating covid-19. However, although limited by its observational design, our effort in STOP-COVID differed from the RCTs in 3 important ways:

1) Patient population. STOP-COVID exclusively enrolled patients ill enough to require an intensive care unit admission; nearly two thirds of the patients required a ventilator on enrollment. By contrast, mechanically ventilated patients were *excluded* from the three RCTs. Thus, these were fundamentally different patient populations.

2) Timing of administration. STOP-COVID focused on *early* use of tocilizumab – defined as treatment within the first two days of ICU admission. The rationale was to study tocilizumab in very sick patients but before irreversible organ injury had occurred. In contrast, the RCTs did not limit the randomization period to early use only.

3) Sample size. STOP-COVID included 3,924 patients. In contrast, the three RCTs enrolled just 126, 131, and 243 patients. The total number of deaths in STOP-COVID was 1,544 versus just 12 deaths in the largest of the RCTs. Accordingly, the RCTs may have been underpowered, and certainly were not adequately powered to assess mortality.

—David E. Leaf, MD, MMSc