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BRIEF19

A daily review of covid-19 research and policy

RESEARCH BRIEFING

Will monoclonal antibodies quieting our own immune system help covid-19 patients?

Recent news has brought the treatment of monoclonal antibodies to the forefront as a new possible treatment for SARS-CoV-2 infection. These medications are made by cloning white blood cells from humans or animals that can bind to an antigen, a small fragment of material that causes an immune response. Monoclonal antibodies have a wide range of uses and are approved in the treatment of cancer, multiple sclerosis and various inflammatory diseases. A study released today in *JAMA Internal Medicine* reports on research using the monoclonal antibody, tocilizumab, which targets a molecule of our own immune system called the interleukin 6 (IL-6) receptor. IL-6 plays an important part in the body's inflammatory response.

This multi-center retrospective cohort study in the United States included almost 4,000 patients (part of a larger study called STOP-COVID) admitted to 68 participating hospitals. All patients included were admitted to the intensive care unit (ICU) implying they were critically ill from covid-19. These patients had a median age of 62 (63 percent male) and were hospitalized early on in the pandemic (March through May) with the primary reason for admission being covid-19 disease.

The authors used many exclusion criteria including hospitalization for one week before transfer to an ICU and any signs of liver dysfunction which would preclude medication use. The main outcome of interest to the researchers was time to death (30-day mortality was additionally studied). Patients had to receive tocilizumab within two days of ICU admission. If it was not given within the two days, those patients were considered to have been in the non-treatment group. All of the patients were followed up for a minimum of 28 days after their ICU admission. Of the 3,924 patients included in this analysis, only 11 percent (433) received tocilizumab in the first two days. The treated patients were slightly younger (58 years) and had fewer existing medical conditions. However, they were more likely to have low blood oxygen levels (47 percent versus 38 percent) while on mechanical ventilators. The tocilizumab patients were also more likely to receive corticosteroids (19 percent versus 13 percent), a treatment proven to have favorable effects on some critically ill covid-19 patients. After adjusting for other factors that may have otherwise influenced the outcomes of the cases ("confounding variable"), the patients treated with tocilizumab had a lower adjusted risk of death (HR 0.71) and a thirty-day mortality risk difference of 9.6 percent. These findings support the inflammation cascade theory as being a reason why critically ill covid-19 patients continue to decompensate.

Update: While this study provides hope for an additional promising treatment for covid-19, the authors stated that more rigorous randomized controlled trials would be needed. The authors were likely not aware that two other articles appeared in the same issue of *JAMA Internal Medicine* related to this drug. Both were randomized trials

(though not blinded) that tested tocilizumab versus usual care. One from Italy found no mortality difference at 28 days. The other trial (from France) also randomized patients to receive either tocilizumab or usual care and was also not blinded. It too found no major benefit, though there was a hint that the need for mechanical ventilation may have been reduced. Another promising finding is that while adverse events (side effects) were common in patients who received tocilizumab, they were in fact more common in the patients who did not receive it. This implies that on some level, the medical may be helping control disease symptoms that are hard to distinguish from medication side effects. While the sum total of these three papers is disappointing—especially in light of the fact that the retrospective study was positive and the two actual clinical trials most reported lackluster findings—there is still some hope for these medications. Larger trials of patients at various stages and severity of illness are still necessary before the door is shut on this particular medication as a treatment of covid-19.

—Christopher Sampson, MD FACEP

POLICY BRIEFING

Lingering questions about a vaccine rollout.

Many things are still unknown about some of the vaccine candidates currently being tested. Plans from the National Academies, Engineering, and Medicine (NASEM) and Operation Warp Speed offered different schedules and priorities, and a new timeline released by the United States Centers for Disease Control and Prevention (CDC) have further muddied the waters. Combine this with past tensions between state governors and the federal government relating to multiple aspects of who wields what authority during the pandemic, and might come as no surprise that governors are seeking to lay a foundation for vaccine rollout before it happens.

What is surprising is that leadership within the National Governors Association from both sides of the aisle are seeking a meeting to discuss logistics of a vaccine campaign with President Trump. The driving force behind this effort was the White House's September solicitation of plans from state health departments for a fully-realized vaccination plan. Unfortunately, the declared deadline for such plans has come and gone.

In the absence of a concrete production timeline, requirements for prioritization of inoculation, or even predicted quantities, state leaders have faced a shifting logistics quagmire in the middle of an unprecedented pandemic and have found themselves unable to comply. *Various.*

—Joshua Lesko, MD