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BRIEF19

A daily review of covid-19 research and policy

RESEARCH BRIEFING

The first study showing meaningful clinical benefit for monoclonal antibodies in a subset of covid-19 patients.

One of the many challenges of the covid-19 pandemic has finding effective therapeutics. Extensive efforts have yielded mostly failures and a few glimmers of hope. The main exception has been dexamethasone, an inexpensive steroid which was shown in the RECOVERY trial to provide important reductions in mortality among covid-19 patients requiring supplemental oxygen, and especially those requiring mechanical ventilation. Meanwhile, the RECOVERY Group performed excellent research which have unfortunately found no benefit from a range of other potential therapies including [azithromycin](#), [convalescent plasma](#), [aspirin](#) and [colchicine](#), all of which have fallen flat.

Monoclonal antibody infusions have gained national attention as a potential therapeutic for covid-19 patients and have been touted by medical experts. This drug class acts by binding to domains on SARS-CoV-2 spike protein blocking its ability to bind to receptors on cells and thus stopping cellular invasion. Despite the compelling theory, as we have [reported previously](#), until now that has been “no convincing data that monotherapy or a cocktail of antibodies improves meaningful outcomes in patients with COVID19.” However, the RECOVERY group has submitted a new study that was released as a preprint today that may change that headline for a subset of patients.

The [RECOVERY study](#) initially randomized patients already sick enough to require hospital admission to either standard care, standard care plus convalescent plasma, or standard care plus REGEN-COV (Regeneron’s monoclonal antibody “cocktail” of casirivimab and imdevimab). There was no difference in 28-day mortality for all-comers. However, prior to the data being unblinded and analyzed, it became clear to the researchers that patients who *already had an antibody response* to SARS-CoV2 would be highly unlikely to benefit from an infusion of a monoclonal antibody cocktail. Our previously coverage offered the same analysis in response to other trials which had been disappointingly negative: *“The idea of treating patients with established COVID with monoclonal antibodies may in itself be a flawed paradigm as even patients with early disease are likely to have already generated antibodies as seen in the REGN-CoV2 study.”*

Recognizing this issue, the researchers hope that a subgroup analysis limited only to patients who had not mounted a substantial antibody response (“seronegative”) to SARS-CoV-2 might find a benefit for the REGEN-COV cocktail. Indeed, in this subgroup, the investigators found a benefit: a 6 percent absolute reduction in mortality was seen 28 days (24 percent vs 30 percent), which was statistically significant. The mortality curves show a dramatic difference in response between the seronegative and seropositive groups. But this finding only applied to the approximately 1/3 of patients who did not have sufficient antibodies (i.e. a 6 percent improvement was found among the 32 percent of patients who qualified as having “low antibody” levels). A similar reduction in the need for supplemental oxygen (including high-pressure oxygen masks)

and mechanical ventilation was seen among the seronegative patients receiving REGEN-COV.

These data are important. But we must understand the meaning and limitations of the findings. First, finding the appropriate patient group that can benefit from this treatment in real life will be a challenge. Rapid testing to determine whether a patient is seronegative or seropositive will be required in order to assure that the right patients receive the cocktail. Many US hospitals still struggle to rapidly test for SARS-CoV-2 (many are limited to only testing those who require admission with hours long wait times for results), let alone antibody status. Second, REGEN-COV is expensive. Though exact costs are difficult to obtain, a [report in October 2020](#) estimated the cost to be between \$1,500 and \$6,500 per patient. This will markedly limit use in the US and virtually prohibit use in countries with lower economic means. Third, it's unclear if REGEN-COV will be effective against emerging variants. We have already seen monoclonal antibodies lose their efficacy as the predominant variant shifted in different regions causing Eli Lilly to pull one of its products from use. The RECOVERY data was collected from September 2020 to May 2021 and therefore likely included a majority of patients with the Alpha (i.e. original) variant. The prevalence of the Delta variant among patients in this study group was likely much lower. As the Delta variant grows in the share of cases, this monoclonal antibody cocktail may be rendered ineffective as well.

Despite this, REGEN-COV may still play some role in covid-19 treatment, albeit a limited one. While vaccines are cheaper and clearly more effective, there are groups of people who will not achieve the same benefit from them. This includes rare persons that have true contraindications to coronavirus vaccinations, those who remain unvaccinated by choice, and those who don't mount as robust a response to vaccines, including patients on immunosuppressant medications or certain advanced blood cancers and severe autoimmune conditions. That said, it's unclear if REGEN-COV would offer a benefit to those populations.

The bottom line is that the REGEN-COV monoclonal antibody cocktail does not lead to a reduction in 28-day mortality for all hospitalized patients but appears to have a significant benefit in those patients who have not yet mounted an antibody response to SARS-CoV2 infection.

—Anand Swaminathan, MD

POLICY BRIEFING

Massachusetts lifts state of emergency, among leaders in vaccinations.

Governor Charlie Baker lifted the state of emergency in Massachusetts this week. Over 4 million residents are fully vaccinated, among a total population over 6.9 million. The 7-day rolling daily average fell under 100 cases yesterday for the first time since the covid-19 pandemic erupted, amounting to just 1.4 new cases per 100,000 residents. The state is now averaging just 5 covid-19 deaths per day, down from over 200 at the peak of the first wave last spring.

Nevertheless, there are still regions of the state with lower vaccination rates, and the percent of fully vaccinated people among Hispanic and Black residents has yet to top 50 percent statewide. Meanwhile, a majority of White (62 percent), Asian (65 percent),

and Native Hawaiian/Pacific Islander (93 percent) have been fully vaccinated here. This leaves certain areas of the state vulnerable to flare ups, and underscores that the work here in Massachusetts, while 3rd in the nation overall by percent vaccinated, remains incomplete. *Various.*

—*Jeremy Samuel Faust, MD MS*

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