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BRIEF19

A daily review of covid-19 research and policy

RESEARCH BRIEFING

Monoclonal antibodies yet to show important clinical benefit in patients with covid-19. A review of what we know, including the latest clinical trial data.

One of the many challenges of the covid-19 pandemic has been the lack of targeted therapeutics. Extensive efforts have been invested into research with only glimmers of benefit for most drugs. The exception to this has been dexamethasone which was shown in the RECOVERY trial to have remarkable impacts on death in patients requiring oxygen and in those requiring invasive mechanical ventilation. Other drugs, some of which showed varying degrees of promise in observational and retrospective studies (from hydroxychloroquine to convalescent plasma) have largely fizzled in randomized trials, while fancier newer drugs, namely remdesivir, have generated inconsistent (and certainly disappointing) results, at best.

Monoclonal antibody infusions have gained national attention as a potential therapeutic in covid-19 patients. The hype in part comes from some medical experts touting them. Part of the optimism about this class of drugs comes from the elegance of how they are supposed to work. By design, these molecules bind to specific "domains" of the SARS-CoV-2 spike protein, thereby blocking its ability to bind to receptors on human cells and thus, it is hoped, stopping cellular invasion and cutting off the virus' "life cycle."

Let's review how well these molecules work "in real life." The ACTIV-3 trial, published in December 2020, found no benefit to hospitalized patients receiving bamlanivimab (the Eli Lily product also known as LY-CoV555) along with remdesivir. Since then, the focus has shifted to treating non-hospitalized patients. There is logic to this shift; once patients are sick enough to require hospitalization, they are likely out of the so-called "viral phase" of illness. So, clearing the virus from the body is no longer relevant. At that point, the body is busy generating polyclonal antibodies (i.e. antibodies that target a number of different parts of the virus) in response to infection; adding a monoclonal antibody infusion is unlikely to help beyond this point. All of this explains the emphasis on delivering monoclonal antibodies to covid-19 patients *early*.

The two major opportunities to assess this are the BLAZE-1 (Eli Lily) and REGN-CoV2 (Regeneron) trials. An interim analysis of BLAZE-1 (published in October, 2020) demonstrated a small reduction in viral load with one of the three studied doses of bamlanivimab (another name for LY-CoV555) when given to patients early in their disease (a median of four days from symptom onset). However, this difference fell below the author's preset threshold and raised questions around the biological plausibility of the endeavor, as only the middle dose (2800 mg) showed a viral load reduction. (Treatments that work well often have a "dose-response" curve, meaning that within a certain range, higher doses correlate to more measurable changes; these findings went against that). Even putting methodological shortcomings aside, a reduction in viral load alone is meaningless to the patient as it is not a clinical outcome. Viral loads only matter if they correlate to outcomes patients might notice, such as the severity and duration of their symptoms, or whether there is a change in mortality. Despite these lackluster findings, bamlanivimab (LY-CoV555) was granted Emergency Use Authorization by the US Food and Drug Administration. Since then, thousands of patients have been referred to infusion centers and emergency departments to receive this therapy.

The REGN-CoV2 Trial data (published in December, 2020) investigated infusion of two monoclonal antibodies (known as casirivimab and imdevimab) to outpatients early in their covid-19 disease course. The monoclonal antibody cocktail was used in an effort to reduce the emergence

of treatment-resistant virus mutations. Similar to the BLAZE-1 group, the REGN-CoV2 investigators reported a reduction in viral load with this treatment. However, the methodological flaws of this study were considerable, including the fact that the group did "no formal hypothesis testing." This means that the trial amounted to a fishing expedition to find a benefit. Rigorous and reliable studies test one or two very focused questions. Nevertheless, the cocktail was also granted Emergency Use Authorization by the US FDA and and has been administered to thousands of patients based on virtually non-existent data, despite no clinically meaningful benefit for patients. One key finding did emerge from this study though: 45 percent of patients enrolled already had SARS-CoV-2 antibodies prior to the administration of the cocktail even though the researchers had gone out of their way to find patients who were still early in their disease course. Thus, the available evidence does not support the use of the REGN-CoV2 monoclonal antibody cocktail.

The past week, the complete dataset for the BLAZE-1 trial was published in *JAMA.* The study assessed bamlavinimab (LY-CoV555) as well as a dual monoclonal antibody therapy of bamlavinimab and another antibody, etesvimab. Interestingly, the benefit for the 2800 mg dose of bamlavinimab monotherapy reported in the BLAZE-1 interim report has disappeared in the final report. Thus, there is now *no* clinical trial data supporting bamlavinimab by itself with respect either to a clinical benefit, nor even for proxy outcomes like viral load reduction.

But what about the combination therapy? As before, there is evidence that viral load reductions occurred, albeit the reduction was smaller than the threshold that had been prespecified as meaningful by the researchers. The study also included a whopping 84 "secondary endpoints." Secondary endpoints are findings that trials were not designed to study but which were measured nonetheless—usually in an attempt to discover any hidden benefits or harms that a treatment may offer. One such finding was a reduction in hospitalization or emergency department visits. This finding was seen in two groups of test subjects who received bamlavinimab alone as well as in the group of patients who received that and etesvimab. However, there were wide confidence intervals (meaning that the range of possible outcomes was large), the number of ER visits and hospitalizations were low (meaning a small number of different outcomes could have had enormous impact on the findings), and no granular data on whether the reductions were in ER visits or in hospitalization (which, of course, are rather different). At best, this finding is hypothesis generating only.

It should also be noted that we have limited safety data for these drugs. Though none of the studies revealed a significant number of serious adverse events, the studies are not large enough to establish safety.

At this point, there is no convincing data that designed monoclonal antibodies that target SARS-CoV-2 improve meaningful outcomes in covid-19 patients, either alone or in a "cocktail" of antibodies. As mentioned, the idea of treating established covid-19 patients with monoclonal antibodies may itself be a flawed paradigm as even patients with early disease are likely to have already generated sufficient antibodies (as seen in the REGN-CoV2 study) that adding more to the body intravenously is like adding salt to an ocean. Additionally, we don't know the effect of monoclonal antibody infusions on vaccine efficacy. Despite emergency authorization for bamlavinimab and the Regeneron cocktail, at this time, these treatments should only be given in the setting of a randomized controlled clinical trial designed to evaluate outcomes that patients would notice. The BLAZE-2 trial currently underway is investigating the use of monoclonal antibodies for prophylaxis. This effort may be more promising, though vaccines are likely to be far more effective in this role.

While clinicians feel the need to do *something* for patients early in their disease process to prevent progression to more severe illness, this need does not justify giving a treatment with unproven benefits—and with mounting proof that there is little to none to be had.

–Anand Swaminathan MD

POLICY BRIEFING

Provider Relief Fund registration now open.

The Provider Relief Fund was established to compensate healthcare entities for lost revenue as part of the ongoing covid-19 pandemic. Renewed in three phases, the program to date has provided $178 billion to hospitals and healthcare providers to ensure the continuation of vital services. To avoid delays in payments, applicants for the allocated funding have not had to provide documentation or verification of claims until after receipt of disbursement, and so far, hard deadlines for any such requirements have not been established.

A recent policy from the US Department of Health and Human Services (HHS) requires any entity who received more than $10,000 to register via an online portal. While there is currently no deadline for registration or information submission, HHS is encouraging rapid adoption to allow participants to begin receiving updates and data requirements.

HHS has also issued a new document clarifying the steps required to calculate lost revenue in compliance with the Coronavirus Response and Relief Supplemental Appropriations Act of 2021.

The big takeaway here is that as the Provider Relief Fund has continued to expand—from what were initially more stringent rules requiring applicants to have received Phase I payments in order to be eligible for future disbursements and relying on net losses or prior years' data. There are now more methods to provide verification of revenue decline, opening the program to a larger group of healthcare-providing entities. *The Department of Health and Human Services*.

–Brief19 Policy Team

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