COVID-19 Science Updates

CSU **25 June 2021**

1. Early evidence for the effectiveness of a third dose among immunocompromised

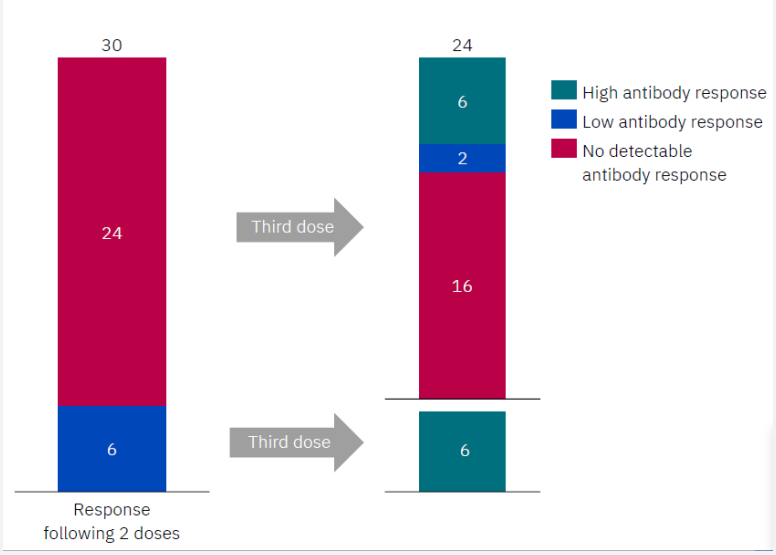
People with impaired immune function (immunocompromised) may not respond as well to vaccination as healthy individuals. This means that immunocompromised people can remain susceptible to infection with COVID-19 after vaccination. There are several classes of immune disorders, each with a variable degree of impact on humoral and/or cell-mediated responses. Humoral responses can be assessed by measuring antibody production and cell-mediated responses can be assessed by measuring the production of cytokines, such as interferon-gamma, from T cells. Although the immune correlates of protection have not been fully established for COVID-19, it is evident that both humoral and cell-mediated responses are required for short- and long-term vaccine efficacy. Over time, these tests are likely to be useful as an objective assessment of a person's response to vaccination. However, it is important to note that even individuals with a robust immune response may still become infected with SARS-CoV-2 following vaccination, as no vaccine is 100% effective at preventing infection.

People who have received a solid organ transplant are administered immunosuppressants to avoid organ rejection. These individuals have been shown to produce attenuated antibody responses after two doses of mRNA COVID-19 vaccines: the rate of seroconversion is 0-15% in solid organ transplant patients, based on handful of small studies, to date. Two trials, one reported in the Annals of Internal Medicine and one in the New England Journal of Medicine have been reported assessing the immunogenicity and safety of a third vaccine dose in this population.

The report from the Annals of Internal Medicine is summarised below.

- The cohort consisted of 30 patients who received solid organ transplants (23/30 were kidney transplant patients) on immunosuppression. The median age was 57 years. The most common therapies for immunosuppression were tacrolimus or cyclosporine plus mycophenalate. Corticosteroids were used in 24 patients.
- All patients received an initial course of two doses of the same mRNA vaccine, Pfizer or Moderna. The majority (24/30) of patients received a heterologous third dose, with 15/30 receiving the Janssen (Ad26.COV2.S) as the third dose.
- All patients had their antibody titres against spike protein assessed prior to the third dose. Third doses were administered at least 54 days after the second dose. Antibody testing was repeated at least 14 days after the third dose.
- After the second dose, 6 patients (20%) had low-positive antibody titres, and the remaining 24 patients (80%) were negative for antibody titres.
- The immune response improved after the third dose, with 12 patients (40%) reporting high-positive titres and 2 reporting low-positive titres (7%), for an overall response rate of 47%. The remaining 16 transplant recipiants (53%) remained negative (see figure below).

- One patient developed a rejection episode after the third dose. However, this individual did not develop an increase in antibody titres in response to the third dose of vaccine which raises doubt about the relationship between the vaccine and rejection event. No other serious adverse events were reported.



The second study, reported in NEJM, included 101 patients with solid organ transplants.

- In this study, all patients received three doses of the Pfizer vaccine. Otherwise, the cohort and immunosuppressive therapies were similar between the two studies.
- The paper reported whether antibodies were detected, but did not classify response as 'low' or 'high'.
- The prevalence of anti-SARS-CoV-2 antibodies was 40% after the second dose and 68% four weeks after the third dose.
- Among the 59 patients who had been seronegative before the third dose, 44% (26) were seropositive at 4 weeks after the third dose.
- Those who did not respond after the third dose were older, had a higher degree of immunosuppression and had poorer renal function than those who did respond.
- There were no cases of acute rejection in this cohort.

Comment: These case series provide evidence that a third dose of COVID-19 vaccination can increase the titre of antibodies against SARS-CoV-2, particularly in those individuals who do respond, albeit poorly, to an initial standard course. The safety of a third dose, particularly the risk of organ rejection, cannot be thoroughly assessed from these studies and it is important to note that only humoral response was assessed in these studies. Although antibody concentration has been reported to correlate well with efficacy (link), the degree to which the development of antibodies confers protection from infection or disease is not yet well established.

There was considerable heterogeneity between the vaccine regimens. The use of a different vaccine for non-responders to that which was used for the initial course (as was used in the first study) seems a sound

strategy, but it is also appears that a third dose of the same mRNA vaccine may also induce an improved antibody response.

Vaccination is a key part of the global response to COVID-19, but there will always be groups of individuals who cannot be vaccinated or do not respond to vaccination well. These studies provide some evidence for a method of providing protection to some of the individuals who may not respond to a standard course of vaccination. However, a substantial number of patients (approximately 30-60%) showed little or no improvement in antibody response after the third dose. Therefore, it is likely that existing interventions, such as distancing, masking, and continued emphasis on hygiene will continue to be required for some time. Therapeutic options, such as monoclonal antibody cocktails, may also be beneficial, particularly for some at-risk individuals.

2. Preliminary results of a Phase 3 trial for an antibody cocktail in treating COVID-19 outpatients

There is an urgent need globally for effective therapeutics to treat COVID-19, particularly for those who may not respond to vaccination. To date, there are a few therapies that have some demonstrated benefit in treating COVID-19 including tocilizumab (an interleukin-6 inhibitor) and dexamethasone (a steroid), although the effect sizes are often small and have quite specific indications e.g., only for use in people with severe disease.

The REGEN-COV monoclonal antibody cocktail (casirivimab and imdevimab) was issued an emergency use authorisation (EUA) by the Food and Drug Administration (FDA) on November 21, 2020, for the treatment of mild to moderate COVID-19 in adults and paediatric patients with positive results of direct SARS-CoV-2 viral testing, and who are at elevated risk for progressing to severe COVID-19 and/or hospitalisation. The two monoclonal antibodies within the REGEN-COV cocktail work by targeting different parts of the SARs-CoV-2 spike protein, neutralising the viral particle and preventing viral entry into cells. The EUA was based on Phase 1/2 data that demonstrated a reduced viral load, less medical intervention, and potentially a reduced risk of hospitalisation.

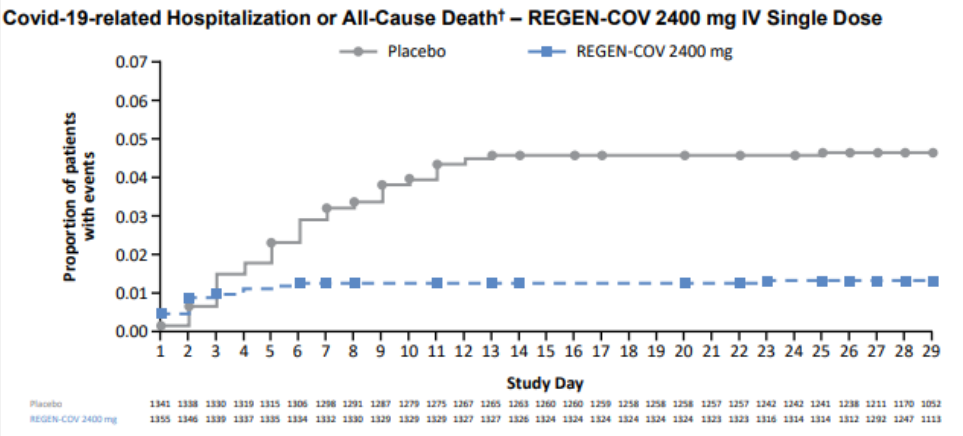
A Phase 3 trial has recently evaluated the efficacy of REGEN-COV in 4,057 outpatients (pre-print):

- All participants were 18 years and older, non-hospitalised, symptomatic, had a SARS-CoV-2-positive diagnostic test, and at least one risk factor for severe disease.
- Two doses of REGEN-COV (1200 mg and 2400 mg) were administered intravenously and compared to placebo.
- 736 participants received the 1200 mg dose and 1,355 the 2400 mg dose. Participants were followed up for 28 days.
- There were no major differences in demographic and baseline medical characteristics of each group.

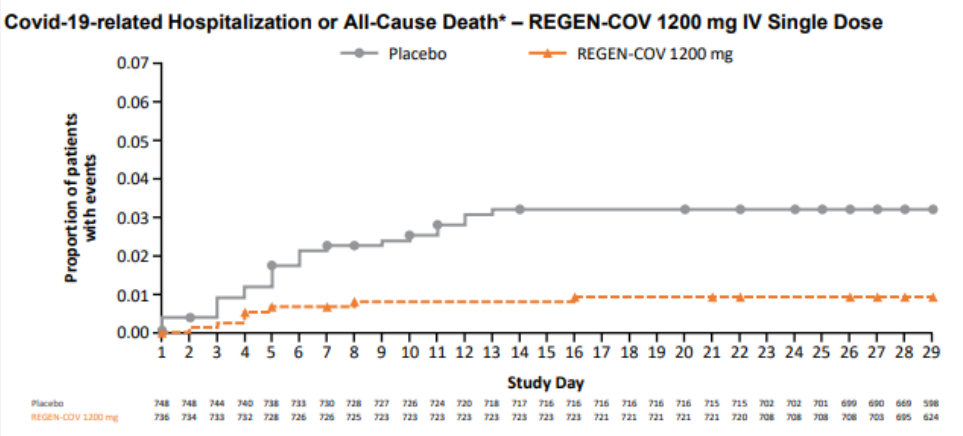
Efficacy:

- REGEN-COV 2400 mg reduced COVID-19-related hospitalisation or all-cause mortality in the 28 days after treatment by 71.3% (95%CI: 51.7% to 82.9%); absolute risk reduction (ARR) was 3.3%.

- Hospitalisation alone was reduced by 71.5% (95%CI: 51.3% to 83.3%); ARR was 3.1%.



- REGEN-COV 1200 mg reduced COVD-19-related hospitalisation or all-cause mortality by 70.4% (95%CI: 31.6% to 87.1%); ARR was 2.2%.
- Hospitalisation alone was reduced by 73.5% (95%CI: 35.3% to 89.1%); ARR was 2.3%.



- Similar reductions were observed across subgroups, including those with viral load >10^6 copies/ml and those who were antibody negative at baseline.
- Median time to symptom resolution was 4 days earlier for both REGEN-COV doses compared to placebo (10 days vs. 14 days; p<0.000 1).
- Both doses were associated with similar improvements in symptom resolution across subgroups and faster declines in viral load compared to placebo.
- Those participants who received REGEN-COV and who were admitted to hospital had a shorter stay and were less likely to be admitted to ICU.

Safety:

- A similar safety profile was observed between REGEN-COV doses, with no discernible imbalance in safety events.

- More participants in the placebo group experienced serious adverse events (4.0%) compared to the REGEN-COV groups (1.1% to 1.7% across the two different doses).
- More participants in the placebo group (n=6, 0.3%) experienced a serious adverse event of interest (hypersensitivity reactions (grade ≥2), infusion-related reactions (grade ≥2), or medical attention at a healthcare facility, regardless of relation to COVID-19) compared to the REGEN-COV groups: 1 (0.1%) in the 1200 mg group and 1 (<0.1%) in the 2400 mg group.

Comment: This phase 3 study provides more evidence that the REGEN-COV monoclonal antibody cocktail reduces hospitalisation and all-cause mortality, in addition to having a good safety profile. Moreover, the treatment improves the time to resolution of symptoms and if a participant was admitted to hospital, they had shorter stays. In absolute terms (using the GRADE approach), this treatment could result in 33 fewer people per 1,000 being hospitalised or dying.

REGEN-COV may play an important role in treating people who have mild/moderate symptoms and are at risk of developing severe disease. It could also have a role for the people who are not or cannot be vaccinated; taken together, providing a potentially meaningful reduction in the burden of COVID-19 on the healthcare system.