

## EDITORIAL

# Is There Any Advantage of Using Polyclonal vs. Monoclonal Antibodies for Passive Enhancement of Immunity in Patients with COVID-19?

On November 08, 2020, the US Food & Drug Administration (FDA) approved the use of first monoclonal antibody – Bamlanivimab (LY-CoV555; Eli Lilly & Company) for the treatment of high-risk patients with mild-moderate SARS-CoV-2 infection (1). Subsequently, on November 23, 2020, FDA approved another cocktail of monoclonal antibodies – Casirivimab + Imdevimab (REGEN-COV; Regeneron Pharmaceuticals) for use in a similar cohort of high-risk patients with mild-moderate COVID-19. Since the initial Emergency Use Authorizations (EUA), FDA has made numerous modifications/amendments including revoking the authorization for monotherapy with Bamlanivimab (3); addition of Etesevimab to Bamlanivimab monotherapy; and authorization of another monoclonal antibody – Sotrovimab (Xevudy; Glaxo, Smith & Kline) (4). The primary objective of these emergency authorizations was to treat patients early in the course of the disease in a non-hospitalized setting thus mitigating the progression of COVID-19 to a more severe stage that would necessitate hospitalization.

With the availability of these monoclonal antibodies, we at DHR Health proceeded to obtain approval of a prospective study from the DHR Health Institute for Research & Development Institutional Review Board to treat high-risk patients with mild-moderate COVID-19. The first patient was treated on November 25, 2020, and since then, we have infused anti-SARS-CoV-2 monoclonal antibodies in over 580 patients with very satisfactory outcomes. This included both patients who had mild-moderate SARS-CoV-2 infection as well for post-exposure prophylaxis in COVID-19 negative subjects.

While effective, monoclonal antibodies have inherent advantages and disadvantages when used for therapeutic purposes. Produced *in vitro* from

immortalized plasma cells, monoclonal antibodies have single specificity and affinity which, reduces the probability of cross reactivity (Figure 1). Due to batch-to-batch homogeneity, effectiveness of monoclonal antibodies is much more predictable, and they serve as an ideal candidate for use in diagnostic immunoassays. **A distinct disadvantage of monoclonal antibodies is the fact that due to its high specificity and affinity, a minor mutation in the epitope often renders the antibody ineffective in neutralizing the target.** This is a serious limitation since observed mutations in SARS-CoV-2 with generations of numerous variants may render the available monoclonal antibodies less effective in mitigating the progression of COVID-19. On the contrary, polyclonal antibodies are a mixture of monoclonal antibodies that are products of multiple B cell clones. Generated in animals, polyclonal antibodies recognize with reasonably high affinity multiple epitopes on a single antigen (Figure 1). **This affords polyclonal antibodies a distinct advantage over monoclonal antibodies when used as therapeutic agents particularly in patients infected with rapidly mutating SARS-CoV-2 virus.**

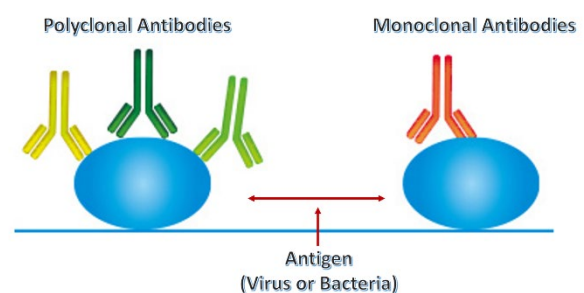


Figure 1: Monoclonal antibody have affinity for a single epitope on the antigen (i.e., the virus or the bacteria). On the contrary, polyclonal antibodies are a mixture of monoclonal antibodies with affinity for various epitopes on the antigen.

On April 17, 2020, the National Institutes of Health (NIH) announced the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) public-private partnership to develop a coordinated research strategy for prioritizing and speeding development of the most promising treatments and vaccines. ACTIV was based on Bayesian adaptive clinical trial design which allows for frequent “looks” at the data and permits data-driven modifications during the course of the study (5). DHR Health Institute for Research and Development is part of the ACTIV collaborative and have initiated numerous studies in an attempt to find the most promising therapeutic agent to prevent and/or treat patients with COVID-19.

As part of ACTIV-2, DHR Health Institute for Research & Development has initiated a prospective Phase 2/3 clinical trial to evaluate the efficacy of fully human anti-SARS-CoV-2 polyclonal antibody (SAB-185; SAB Pharmaceuticals, Inc.) to treat unvaccinated non-hospitalized high-risk patients with mild-moderate COVID-19. SAB-185 is a fully human, anti-SARS-CoV-2 immunoglobulin produced in transchromosomal bovines (Tc-hIgG-SARS-CoV-2) hyperimmunized with two doses of plasmid DNA encoding the SARS-CoV-2 Wuhan strain S gene, followed by repeated immunization with S protein purified from insect cells (6,7). The resulting Tc-hIgG-SARS-CoV-2, termed SAB-185, efficiently neutralizes SARS-CoV-2, and vesicular stomatitis virus (VSV) SARS-CoV-2 chimeras in vitro. This fully human polyclonal antibody that potently inhibits SARS-CoV-2 infection may provide an effective therapeutic agent to combat COVID-19. **This is not a placebo-controlled study as the patients in the comparator arm will be treated with REGEN-COV monoclonal antibody.**

In conclusion, the use of available anti-SARS-CoV-2 monoclonal antibodies has been effective in mitigating the progression of disease in high-risk patients with mild-moderate COVID-19. However, it could be argued that the use of fully human polyclonal antibodies with affinity for multiple epitopes on SARS-CoV-2 may be more effective in eliminating the virus and its variants which exhibit

higher transmissibility, infectivity, and the potential to “escape” from the neutralizing effects of existing experimental agents.

## References

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