# Update: Eli Lilly Neutralizing Antibodies—Innovative Approach Needs Stewardship

October 8, 2020
Kevin Kavanagh, MD

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Finally, we have some good news in our fight against COVID-19. Eli Lilly announced preliminary findings of their SARS-CoV-2 neutralizing monoclonal antibody product, LY-CoV555, and a combination product composed of LY-CoV555 and LY-CoV016 antibodies. Both products are reported to have spectacular results. In an investor news release, the company stated that in a phase 2 randomized double-blind controlled trial it observed a 72% decrease in hospitalizations and ER visits with LY-CoV555 and an 85.5% decrease using the combination product.

This is excellent news after the mediocre results for the recent randomized trial of remdesivir which found outcome differences of "uncertain clinical importance".

Eli Lilly stated the combination product had no drug related serious adverse events. The LY-CoV555 monoclonal antibody was "well tolerated" without the observation of any drug-related serious events. But it did have "isolated drug-related infusion reactions or hypersensitivity," two of which were reported as "serious reactions" with all patients recovering. Both products had adverse events were similar to placebo.

However, the exact incidence of milder drug reactions which could affect patient acceptance were not given in the news release.

Eli Lilly has also observed that most hospitalizations occurred in patients who had an increased age or BMI. Underscoring the importance of the co-morbidities of age and obesity in COVID-19 disease.

A related product, convalescent serum, was found to have clinical efficacy when it was given within three days of diagnosis and in high concentration. And although given an FDA emergency authorization, its overall benefit has since been panned in the news media.

One may ask, why are the Eli Lilly results different from the positive but somewhat disappointing results of convalescent serum? The short answer is, they are not. Both monoclonal

antibodies target the same clinical sweet spot where convalescent serum was found to be most effective.

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In the Eli Lilly trial, both products were given to patients with mild to moderate symptoms and within three days of their diagnosis. In other words, similar to convalescent serum, initial results demonstrate that the products are effective if given in the early stages of the disease, soon after diagnosis. In addition, Eli Lilly's product is designed to be composed of highly effective neutralizing antibodies.

Meeting these patient administration requirements on a mass scale is almost an impossible task with convalescent serum. There just is not enough to have it in everyone's urgent treatment center.

The Eli Lilly product is composed of a high concentration of highly effective neutralizing antibodies, which hopefully can be manufactured in great enough quantities to become a bridge to a vaccine.

One cautionary note was a statement: "Viral RNA sequencing revealed putative LY-CoV555-resistance variants in placebo and all treatment arms. The rate of resistance variants was numerically higher in treated patients (8 percent) versus placebo (6 percent)."

Thus, as with any anti-viral agent, viral resistance might possibly develop. This is to be expected. Nature adapts and RNA viruses are known to have a proclivity to mutate. This is often observed in phage therapy where there is described a dance of mutations between the bacteria and attacking virus. However, in this instance, the viral mutations are beneficial when you are wanting to kill an evolving bacteria, but are detrimental when targeting the virus itself.

LY-CoV555 targets an "epitope in the SARS-CoV-2 spike region." This is the same region many vaccines are targeting. So far, SARS-CoV-2 has not appeared to mutate at a very fast rate regarding its spike protein region. However, the development of resistance to LY-CoV555 will still need to be carefully monitored, since the emergence of a new resistant viral strain could impact the efficacy of not only monoclonal antibodies but also of future vaccines.

The combination product, having two different antibodies, would be expected to be less susceptible to the development of resistance. So far, Eli Lilli has not observed the development of resistant variants using the combination product.

Resistance would be less of a concern if these products were targeted and effective in the few who were severely sick, but it appears their administration is most beneficial when given early and possibly to the masses.

No SARS-CoV-2 product to date has been able to achieve mass production of a product. However, Eli Lilly has requested an emergency use authorization or its monoclonal antibody product and expect to submit application for its combination product in November. Eli Lilly expects 100,000 doses of their monoclonal product to be available in October and 1 million doses by the end of the year. Fifty thousand doses of the combination product will be available by the end of the year, with a planned increase in production in 2021.

As observed in Eli Lilly's research, those newly diagnosed patients who are obese or have advanced age are the most likely to become hospitalized, and I feel initially this innovative product should be targeted toward these high-risk patients.