

The Promise and Peril of Anti-Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Monoclonal Antibodies

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Over the past 2 years, monoclonal antibodies (mAbs) directed against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein have been a linchpin in our therapeutic toolbox for coronavirus disease 2019 (COVID-19). In November 2020, the US Food and Drug Administration (FDA) provided emergency authorization for the first mAb combination for the treatment of outpatients. Since then, 6 antibody regimens have been authorized [1] for either treatment or prevention. However, the promise of the anti-SARS-CoV-2 mAb class of therapies has also been tempered by its sensitivity to the ever-changing variant landscape. In this editorial, we discuss the Phase III Double-blind, Placebo-controlled Study of AZD7442 (Tixagevimab/Cilgavimab) for Post-exposure Prophylaxis of Symptomatic COVID-19 (STORM CHASER) trial that is published in this issue of *Clinical Infectious Diseases* and also the emergence of variants that represent a threat to all of the currently FDA-authorized mAb regimens.

Tixagevimab/cilgavimab, also known as AZD7442 or Evusheld, is a

combination neutralizing antibody against SARS-CoV-2 with an extended half-life. This regimen has been tested in phase 3 studies for 3 indications: pre-exposure prophylaxis (PROVENT trial), treatment of symptomatic COVID-19 (TACKLE trial), and post-exposure prophylaxis (STORM CHASER trial). In the PROVENT trial, a 300-mg intramuscular dose of tixagevimab/cilgavimab was found to be effective in preventing symptomatic COVID-19 infection in individuals who were at increased risk of poor response to vaccination and/or increased risk of exposure to SARS-CoV-2 [2]. Results from the TACKLE study also suggest that tixagevimab/cilgavimab may be efficacious in preventing progression to severe disease in unvaccinated individuals with SARS-CoV-2 infection [3]. However, at this time, tixagevimab/cilgavimab is currently approved only under emergency use authorization (EUA) by the FDA for pre-exposure prophylaxis for immunosuppressed individuals who are likely to have an impaired response to vaccination or for individuals in whom vaccination is contraindicated [4]. This regimen is not yet authorized for treatment of symptomatic COVID-19 or for post-exposure prophylaxis (in contrast, tixagevimab/cilgavimab is approved in other countries, including Canada, for COVID-19 treatment). In this issue of *Clinical Infectious Diseases*, Esser and colleagues report the results of the STORM CHASER trial for the use of tixagevimab/cilgavimab as post-exposure prophylaxis [5].

In the STORM CHASER trial, 1121 unvaccinated individuals aged ≥ 18 years who were exposed to SARS-CoV-2 within the previous 8 days and had no previous confirmed COVID-19 received either a 300-mg intramuscular injection of tixagevimab/cilgavimab (N = 749) or placebo (N = 372). The mean age of participants was 46 years, and 66% had at least 1 risk factor for severe COVID-19. A small proportion of participants were found to be SARS-CoV-2-seropositive at baseline: 34 (4.5%) in the intervention arm and 14 (3.8%) in the placebo arm. The primary efficacy analysis was performed shortly after the occurrence of the 25th primary end point, defined as the first incidence of post-dose SARS-CoV-2 reverse-transcription polymerase chain reaction (PCR)-positive symptomatic illness before study day 183. There was no significant difference between the 2 arms, as 3.1% of tixagevimab/cilgavimab-treated participants vs 4.6% of the placebo participants were found to have symptomatic COVID-19, representing a 33% relative risk reduction. An extended dataset with a longer duration of follow-up showed a marginally significant 43% reduction in symptomatic COVID-19.

However, the results of the study appeared to be substantially affected by the approximately 4% of participants who were already infected and SARS-CoV-2 PCR-positive at the time of study entry and before tixagevimab/cilgavimab infusion. If this group was excluded from the analysis, then individuals who

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Table 1. Monoclonal Antibody Efficacy Across Variants

	Bamlanivimab/ Etesevimab	Casirivimab/ Imdevimab	Sotrovimab	Bebtelovimab	Tixagevimab + cilgavimab
Alpha (B.1.1.7)	✓	✓	✓	✓	✓
Beta/Gamma (B.1.351/P.1)	X	✓	✓	✓	✓
Delta (B.1.617.2)	✓	✓	✓	✓	✓
Omicron (BA.1, BA.1.1)	X	X	✓	✓	?
Omicron (BA.2)	X	X	X	✓	✓
Omicron (BA.5)	X	X	X	✓	✓
Omicron (BA.4.6)	X	X	X	✓	X
Omicron (BQ.1.1)	X	X	X	X	X

Check mark indicates likely efficacy, question mark indicates unknown efficacy, and X indicates unlikely efficacy.

received tixagevimab/cilgavimab had a statistically significant 73% reduction in symptomatic COVID-19 episodes compared with those who received placebo. The interpretation of the study results is also made challenging by the prolonged follow-up time period incorporated into the primary end point (events within 183 days of mAb infusion), an outcome that combines the efficacy of tixagevimab/cilgavimab for post-exposure prophylaxis and pre-exposure prophylaxis. This is highlighted by the fact that the Kaplan–Meier curves continued to separate after study day 11, when the protection conferred by the tixagevimab/cilgavimab infusion would be largely as pre-exposure prophylaxis, an effect that was previously demonstrated in the PROVENT study [2]. Another important limitation of this study is that enrollment of an unvaccinated population occurred during the pre-Omicron era, a factor that would likely affect the risk of symptomatic infection and mAb efficacy. While this study is unlikely to alter the FDA EUA indications for tixagevimab/cilgavimab, it should be highlighted that the idea behind the use of mAbs for post-exposure

prophylaxis of COVID-19 infection is sound, as a prior phase 3 trial of subcutaneously dosed casirivimab/imdevimab demonstrated an 81% reduction in the risk of SARS-CoV-2 infection in household contacts of infected individuals [6]. Unfortunately, casirivimab/imdevimab is not expected to have efficacy against the Omicron variant.

Over the past 2 years, anti-SARS-CoV-2 mAbs targeting the spike protein have represented a key class of therapeutics for the prevention and treatment COVID-19. However, the spike protein is also under intense immunologic pressure [7] and also represents a key site of viral evolution for new variants of concern. One of the first signs that the activity of mAb regimens may be dependent on the circulating variants was the emergence of bamlanivimab/etesevimab resistance with the Beta (B.1.351) variant [8]. While the Delta (B.1.617.2) variant was susceptible to all mAbs, the fragility of the mAb class of antiviral therapies has again been highlighted with the arrival of Omicron (BA.1) and its subvariants. With each successive Omicron variant, there

appears to be increasing resistance across the mAb class (Table 1). The BA.1 and BA.1.1 variants were resistant to both bamlanivimab/etesevimab and casirivimab/imdevimab regimens and necessitated an increased total dose of tixagevimab/cilgavimab to 600 mg based on modeling studies that showed the original 300 mg dose would have substantially reduced efficacy [9]. Next, the arrival of the BA.2 and BA.5 subvariants led to the loss of sotrovimab activity. In response, the FDA granted EUA for bebtelovimab with only phase 2 clinical trial results showing a reduction in SARS-CoV-2 RNA shedding and more rapid improvement in clinical symptoms [4]. However, we are now faced with emergent variants (eg, BQ.1.1, XBB) that are expected to be resistant to all mAbs, including bebtelovimab and tixagevimab/cilgavimab [10].

While treatment options that appear to retain efficacy against Omicron and its subvariants remain, these regimens have drawbacks, including drug–drug interactions (for nirmatrelvir/ritonavir), complicated intravenous dosing (for remdesivir), and both lower expected

efficacy and concerns surrounding mutagenesis (for molnupiravir). In addition, none of these regimens are authorized for pre-exposure prophylaxis. For these reasons, mAbs have continued to be widely used, especially tixagevimab/cilgavimab, for our immunocompromised patients who cannot effectively respond to vaccination. Now more than ever, we need nimble methods of designing and testing new mAbs that can keep pace with the changing landscape of variants. This may require the identification of mAb combinations that bind regions distinct from those commonly targeted by the immune system in response to vaccination or natural infection and would thus be under less evolutionary pressure for viral escape. Furthermore, we may need to dig deeper into our toolbox of antiviral strategies to further explore the use of therapies such as convalescent plasma [11], interferon lambda [12], and others that have shown promise in large-scale clinical trials. As we enter a new phase of the pandemic, we too will need to

adapt if we are to continue keeping our patients safe from severe COVID-19.

Notes

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