THE BEST OF THE WEEK (10 apr – 16 apr 2023)

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The Promise and Peril of Anti–Severe Acute Respiratory Syndrome Coronavirus 2 Monoclonal Antibodies

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Abstract

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/cilgavimabis 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.

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

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.

HaogaoGu et al.

Within-host genetic diversity of SARS-CoV-2 lineages in unvaccinated and vaccinated individuals

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Abstract

Viral and host factors can shape SARS-CoV-2 evolution. However, little is known about lineage-specific and vaccination-specific mutations that occur within individuals. Here, we analysed deep sequencing data from 2,820 SARS-CoV-2 respiratory samples with different viral lineages to describe the patterns of within-host diversity under different conditions, including vaccine-breakthrough infections. In unvaccinated individuals, variant of Concern (VOC) Alpha, Delta, and Omicron respiratory samples were found to have higher within-host diversity and were under neutral to purifying selection at the full genome level compared to non-VOC SARS-CoV-2. Breakthrough infections in 2-dose or 3-dose Comirnaty and CoronaVac vaccinated individuals did not increase levels of non-synonymous mutations and did not change the direction of selection pressure. Vaccine-induced antibody or T cell responses did not appear to have significant impact on within-host SARS-CoV-2 sequence diversification. Our findings suggest that vaccination does not increase exploration of SARS-CoV-2 protein sequence space and may not facilitate emergence of viral variants.

YanXie et al.

Risk of Death in Patients Hospitalized for COVID-19vs Seasonal Influenza in Fall-Winter 2022-2023

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Abstract

In the first year of the COVID-19 pandemic, 2 US studies suggested that people hospitalized for COVID-19 had nearly 5 times the risk of 30-day mortality compared with those hospitalized for seasonal influenza.1,2 Since then, much has changed, including SARS-CoV-2 itself, clinical care, and population-level immunity; mortality from influenza may have also changed. This study assessed whether COVID-19 remains associated with higher risk of death compared with seasonal influenza in fall-winter 2022-2023.

Methods

We used the electronic health databases of the US Department of Veterans Affairs (VA). Between October 1, 2022, and January 31, 2023, we enrolled all individuals with at least 1 hospital admission record between 2 days before and 10 days after a positive test result for SARS-CoV-2 or influenza and an admission diagnosis for COVID-19 or seasonal influenza. We removed 143 participants hospitalized with both infections. The cohort was followed up until the first occurrence of death, 30 days after hospital admission, or March 2, 2023. Differences in baseline characteristics between the groups were evaluated through absolute standardized differences (<0.1 indicating good balance).

Results

There were 8996 hospitalizations (538 deaths [5.98%] within 30 days) for COVID-19 and 2403 hospitalizations (76 deaths [3.16%]) for seasonal influenza (Table). After propensity score weighting, the 2 groups were well balanced (mean age, 73 years; 95% male).

The death rate at 30 days was 5.97% for COVID-19 and 3.75% for influenza, with an excess death rate of 2.23% (95% CI, 1.32%-3.13%) (Figure). Compared with hospitalization for influenza, hospitalization for COVID-19 was associated with a higher risk of death (hazard ratio, 1.61 [95% CI, 1.29-2.02]).

The risk of death decreased with the number of COVID-19 vaccinations (P = .009 for interaction between unvaccinated and vaccinated; P < .001 for interaction between unvaccinated and boosted). No statistically significant interactions were observed across other subgroups (Figure).

Discussion

This study found that, in a VA population in fall-winter 2022-2023, being hospitalized for COVID-19 vs seasonal influenza was associated with an increased risk of death. This finding should be interpreted in the context of a 2 to 3 times greater number of people being hospitalized for COVID-19 vs influenza in the US in this period.3,4 However, the difference in mortality rates between COVID-19 and influenza appears to have decreased since early in the pandemic; death rates among people hospitalized for COVID-19 were 17% to 21% in 2020 vs 6% in this study, while death rates for those hospitalized for influenza were 3.8% in 2020 vs 3.7% in this study.1,2 The decline in death rates among people hospitalized for COVID-19 may be due to changes in SARS-CoV-2 variants, increased immunity levels (from vaccination and prior infection), and improved clinical care.5

The increased risk of death was greater among unvaccinated individuals compared with those vaccinated or boosted—findings that highlight the importance of vaccination in reducing risk of COVID-19 death.

Study limitations include that the older and predominantly male VA population may limit generalizability to broader populations. The results may not reflect risk in nonhospitalized individuals. The analyses did not examine causes of death, and residual confounding cannot be ruled out