RESEARCH ARTICLE

The Impact of COVID-19 Monoclonal Antibody Therapy on Progression to Hospitalization in A Population with a High Percentage of the SARS-CoV-2 Alpha Variant

Authors
Gabriel Johnson, PharmD[1]; Sarah Lim, MBBCh[2]; Daniel O Griffin, MD PhD[1,3,4]; Xiong Wang, PhD[2]; Lida R Etemad, PharmD[1]

Affiliation
[1]OptumLabs, UnitedHealth Group, Minnetonka, Minnesota
[2]Minnesota Department of Health
[3]ProHealth NY Lake Success, NY
[4]Department of Medicine, Division of Infectious Diseases, Columbia University, College of Physicians and Surgeons, New York, NY 10032

Author Contributions
GJ: protocol review, in-clinic testing, data analysis, manuscript writing; SL: protocol review, manuscript writing; DG: protocol authorship, manuscript writing and review; XW: lab analysis; LRE: protocol authorship, in-clinic testing, manuscript writing

Corresponding Authors:
Gabriel Johnson
UnitedHealthcare; 1581 Park Ave, White Bear Lake, MN 55110
Gabriel.johnson@uhg.com
952-219-4071

Abstract

Objective: Several investigational monoclonal antibody (mAb) therapies have Emergency Use Authorizations (EUA) for the treatment of mild to moderate coronavirus disease 2019 (COVID-19). In well-designed randomized clinical trials (RCTs), mAb therapies have demonstrated a reduction in the progression to hospitalization and death in high-risk individuals. This study assessed the real-world efficacy of treatment with mAb therapy during a time with a high percentage of the Alpha variant circulating.
Methods: We performed a prospective study looking at the progression to hospitalization in a high-risk treatment population that qualified for mAb therapy under the current EUA and that consented to have their viral isolates undergo whole genome sequencing (WGS) to assess for the presence of genetic variants. A total of 125 patients consented to participate and ultimately 81 participants that both had obtainable sequence data and completed follow-up were included in the final analysis. Based on the risk profile of these participants we anticipated a >10% hospitalization without therapy and a 70-80% reduction based on prior RCTs. Five of the 81 patients (6%) were hospitalized despite monoclonal antibody therapy. The most common variant was Alpha (n=66, 81%), followed by other unknown variants (n=6, 7%), Iota (n=3, 4%), Epsilon (n=2, 2%), Gamma (n=2, 2%), and no variant detected (n=2, 2%).
Conclusion: Monitoring of the local variants, proper procurement decisions regarding specific mAb treatment effective against circulating variants and following real world efficacy has the potential to positively impact the use of mAb therapies. Future studies are needed to assess the efficacy of different mAb treatment results in real world settings with various SARS-CoV-2 variants, various treatment delays and various populations.

Key Words: COVID-19, bamlanivimab-etesevimab, variants, antibodies, infusion

Introduction

In December 2019 the first cases of pneumonia due to a novel coronavirus were reported in Wuhan, China.[1] As this pathogen, SARS-CoV-2, spread throughout the world the various stages of the disease, COVID-19 and importance of timing for different therapeutics began to be appreciated.[2] During first week following symptom onset there is significant viral replication and high levels of viral RNA can be detected in the nasopharynx.[3] This viral replication stage is then followed by an early inflammatory phase that can result in clinical deterioration and hospitalization.[2] A number of medications with antiviral effect had minimal to no benefit when evaluated later in the course, during second week or early inflammatory phase but significant benefit if given during the first 7 days following symptom onset.[4-8]

Neutralizing monoclonal antibodies were shown to have significant impacts on the progression to hospitalization and death and the U.S. Food and Drug Administration (FDA) has issued Emergency Use Authorizations (EUA) for several investigational monoclonal antibody (mAb) therapies for the treatment of mild to moderate coronavirus disease 2019 (COVID-19), including bamlanivimab, bamlanivimab/etesevimab (BE), casirivimab/imdevimab (REGEN-CoV-2) and sotrovimab following the results of

investigations demonstrating reduction in hospitalization and death.[7]

In addition to these small randomized controlled trials, evaluation of the susceptibility of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants to mAb therapy in real-world clinical settings is critical to assess the ongoing role of these resource intensive therapies for the early treatment of COVID-19. There is some concern that certain monoclonal antibody therapies will have less efficacy when used in the treatment of SARS-CoV-2 variants such as Omicron and other variants yet to be identified.[9] Our investigation looked at the real-world impact of neutralizing monoclonal therapies during the emergence of the alpha variant.

Methods

This study was performed at a COVID-19 BE infusion site in Eden Prairie, MN. While in observation after receiving a BE infusion, patients ≥ 18 years were educated on the study and invited to participate. Those who consented had a COVID-19 nasal swab either collected by a study staff member or self-collected. Swab samples were sent to the Minnesota Department of Health Public Health Laboratory (MDH-PHL) for reverse transcriptase polymerase chain reaction testing and whole genome sequencing (WGS). Nasal swabs were sent for whole genome sequencing on patients that had consented.

Trained nursing staff conducted follow-up telephone patient interviews to look for any association between infection with SARS-CoV-2 variants and adverse outcomes after treatment with BE. OptumLabs nurses made calls to the study participants at approximately days 4, 10, and 28 post-infusion.

We assessed 81 COVID-19-positive participants for whom we had sequencing data and follow-up data treated with BE for the association between infection with a SARS-CoV-2 variant and subsequent COVID-19 related hospitalization. Based on the risk profile of these patients we anticipated a >10% hospitalization without therapy and a 70-80% reduction based on prior RCTs.[6,10]

Data sources included the infusion site intake form, the nurse outreach calls, and the MDH-PHL results. The final study sample included participants who qualified under the EUA for BE, had MDH-PHL sequencing results, and had nurse call data spanning one month post infusion (≥ 27 days after BE infusion). An individual was considered high-risk and qualified under the EUA criteria for BE if they had one of the following:

- Criterion 1: are 18 years of age or older, AND have one of the following:
  - Have a body mass index (BMI) ≥ 35; OR
  - Have chronic kidney disease; OR
  - Have diabetes (type 1 or type 2); OR
  - Have immunosuppressive disease; OR
  - Are currently receiving immunosuppressive treatment (e.g., chemotherapy, transplant, immunosuppressants, immune modulators such as Rituximab, etc.)
- Criterion 2: are 55 years of age or older, AND have one of the following:
  - cardiovascular disease; OR
  - hypertension; OR
  - chronic obstructive pulmonary disease/other chronic respiratory disease
- Criterion 3: are ≥65 years of age

Descriptive statistics were reported on the study population. This study was reviewed and approved by the UnitedHealth Group (UHG) institutional review board.

Results

A total of 125 patients consented to participating in the study from April to May 2021. Seventeen patients did not have any

variant results from MDH-PHL (because of a failed sample, bad swab, etc.), and 27 did not have a complete follow-up period, so 81 patients with obtained sequence and a complete follow-up period were included in the final analysis. The mean age was 56 years, with 44% male (n=36) and 56% female (n=45) (Table 1). The median BMI was 32.1 (range 18.78–61.23). The most common race was white (n=72, 89%), followed by black (n=3, 4%). The most common referral sources were provider referrals (n=24, 30%); followed by the Minnesota Resource Allocation Platform for COVID-19 Treatment ("MNRAP"), a state-run, public-facing online platform for patient and provider mAb referrals (n=22, 27%); referrals from friends or family members who had received BE previously (n=7, 9%); self-referral following general MDH website information (n=7, 9%); and UHG employee outreach (n=7, 9%). Most participants were not vaccinated against COVID-19 (n=62, 77%), and of those with some vaccination, only 5 (6%) were fully vaccinated (defined as having ≥ 14 days between the completion of the vaccine course and the positive test). The mean number of days between the development of COVID-19 symptoms and the BE infusion was 5.2 (range 1–10, SD 2.1). On a 1–10 self-reported COVID-19 symptom severity scoring (10 being the most severe symptoms), the average symptom severity at infusion was 5.6. The most common infusion qualifications were BMI ≥ 35 (n=36, 41%), hypertension (n=27, 36%), and cardiovascular disease (n=23, 26%); the least common were an immunosuppressive disease (n=3, 3%), chronic kidney disease (n=5, 6%) and taking immunosuppressive therapy (n=8, 9%).

During the follow-up, about half of participants (n=40, 46%) reported their COVID symptoms were fully resolved after a mean of 11 days (median 10, range 1–28). Five patients (6%) reported a hospitalization for COVID-19 after the infusion. Of note, infusion center staff recommended that all patients should schedule a routine follow-up with their primary care provider (PCP) within 30 days of the infusion. Hospitalizations occurred on average 9 days post-infusion.

Among the 5 hospitalized participants, 4 had a body mass index (BMI) ≥ 35 and 3 had hypertension, but there were no other widely shared comorbid conditions; uniquely, one had thyroid cancer and one had a gastric sleeve. For the hospitalized participants, the age range was 42–67 years, 3 were male and 2 were female, and all 5 identified as white. Two of the five hospitalized participants were given a course of remdesivir.

The most common variant was Alpha (n=66, 81%), followed by other unknown variants (n=6, 7%), Iota (n=3, 4%), Epsilon (n=2, 2%), Gamma (n=2, 2%), and no variant detected (n=2, 2%) (Table 2). Of the 5 participants hospitalized during follow-up, 3 had the Alpha variant (4.5% of the 66 Alpha variant participants), 1 had Gamma, and 1 had Iota. For those same 5 hospitalized participants, 2 were partially vaccinated (11% of the 19 participants who had some vaccination) and 3 were not vaccinated (5% of the non-vaccinated participants). Both participants with an ER visit during the follow-up had the Alpha variant, and 1 was partially vaccinated.

Discussion

As the criterial for selecting monoclonal antibodies for advancement to clinical trial is their ability to neutralize virus in invitro assays, there is a selection bias for identifying and advancing monoclonals that target the receptor binding domain (RBD) of the spike protein and a selection against antibodies with alternate functionality such as Fc mediated. Immune pressure on the viral evolution of SARS-CoV-2 may lead to changes in the RBD portion of spike potentially limited the impact

of certain neutralizing monoclonals. There are several studies demonstrating that changes in the amino acid sequence of the spike protein can result in decreased neutralization in lab-based assays.[5,11,12] This has been shown for systems using actual SARS-CoV-2 isolates as well as pseudotyped virus. While these findings are concerning it is critical to look at actual efficacy.

While the initial neutralizing monoclonals were developed and tested for efficacy in the context of widespread circulation of the ancestral Wuhan variant of SARS-CoV-2 it is not clear how well different monoclonal antibody therapies would impact the course of disease and risk of progression to hospitalization in a patient population with a high percentage of infections being due to the SARS-CoV-2 alpha variant. We observed important clinical trends in the local MN population seeking BE treatment for COVID-19 during the time when a high percentage of the infections were due to the SARS-CoV-2 alpha variant.

The overall progression to hospitalization following BE therapy in this population was 6%. This was higher than was anticipated based on RCTs. The higher failure rate could be due to several reasons. First, this analytic population had a higher mean age than those in the BLAZE-1 trial (53 years and 44 years, respectively). Second was that this population had a longer time to treatment after symptom onset than the BLAZE-1 trial (5 days and 3 days, respectively).[2] A third consideration was that as we were comparing rates of progression to hospitalization to RCTs conducted during the circulation of a a different variant, it is possible that the Alpha variant was associated with the higher-than-expected rate of progression to hospitalization.[11] Fourth and most concerning is the possibility that while vitro data suggest BE retains efficacy against the Alpha variant, this monoclonal cocktail may have less efficacy when used during infection with the SARS-CoV-2 alpha variant.

Because the Alpha variant was the most common variant in the United States during study enrollment, it is not surprising and was expected that Alpha variant was the most common variant identified in our population. This high prevalence and our small sample size limit the ability to draw conclusions regarding the impact of this variant as we could not directly compare success in treatment of the Alpha variant with treatment of the ancestral Wuhan variant or other variants. We also were looking at a treatment population and did perform a randomized placebo control trial based on the demonstrated efficacy from RCTs. Future studies would benefit from a larger analytic population and a large enough number of different variants to determine the impact of the viral variant on treatment.

Conclusion

We saw a higher-than-expected rate of progression to hospitalization in a population with acute COVID-19 following treatment with bamlanivimab/etesevimab when there was widespread circulation of the SARS-CoV-2 alpha variant. These findings suggest that with each new variant, in addition to lab-based assessment of in vitro neutralization, monitory of real-world efficacy is an important and critical step in determining the continued efficacy of different monoclonal antibody therapies.

Acknowledgements

OptumLabs funded study personnel and test supplies. The Minnesota Department of Health paid for the processing of the tests. No grants were used to fund this research.

References

1. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA*. Feb 7 2020;doi:10.1001/jama.2020.1585
2. Griffin DO, Brennan-Rieder D, Ngo B, et al. The Importance of Understanding the Stages of COVID-19 in Treatment and Trials. *AIDS Rev*. Feb 8 2021;doi:10.24875/AIDSRev.200001261
3. Kim SE, Jeong HS, Yu Y, et al. Viral kinetics of SARS-CoV-2 in asymptomatic carriers and presymptomatic patients. *Int J Infect Dis*. Jun 2020;95:441-443. doi:10.1016/j.ijid.2020.04.083
4. Gottlieb RL, Vaca CE, Paredes R, et al. Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients. *N Engl J Med*. Dec 22 2021;doi:10.1056/NEJMoa2116846
5. Weinreich DM, Sivapalasingam S, Norton T, et al. REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19. *N Engl J Med*. Jan 21 2021;384(3):238-251. doi:10.1056/NEJMoa2035002
6. Falcone M, Tiseo G, Valoriani B, et al. Efficacy of Bamlanivimab/Etesevimab and Casirivimab/Imdevimab in Preventing Progression to Severe COVID-19 and Role of Variants of Concern. *Infectious diseases and therapy*. Dec 2021;10(4):2479-2488. doi:10.1007/s40121-021-00525-4
7. Dougan M, Nirula A, Azizad M, et al. Bamlanivimab plus Etesevimab in Mild or Moderate Covid-19. *N Engl J Med*. Oct 7 2021;385(15):1382-1392. doi:10.1056/NEJMoa2102685
8. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Early Treatment for Covid-19 with SARS-CoV-2 Neutralizing Antibody Sotrovimab. *N Engl J Med*. Nov 18 2021;385(21):1941-1950. doi:10.1056/NEJMoa2107934
9. Chen RE, Winkler ES, Case JB, et al. In vivo monoclonal antibody efficacy against SARS-CoV-2 variant strains. *Nature*. Aug 2021;596(7870):103-108. doi:10.1038/s41586-021-03720-y
10. Khunti K, Griffiths A, Majeed A, Nagpaul C, Rao M. Assessing risk for healthcare workers during the covid-19 pandemic. *Bmj*. Mar 15 2021;372:n602. doi:10.1136/bmj.n602
11. Planas D, Veyer D, Baidaliuk A, et al. Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization. *Nature*. Aug 2021;596(7871):276-280. doi:10.1038/s41586-021-03777-9
12. Ho D, Wang P, Liu L, et al. Increased Resistance of SARS-CoV-2 Variants B.1.351 and B.1.1.7 to Antibody Neutralization. *Res Sq*. Jan 29 2021;doi:10.21203/rs.3.rs-155394/v1

