

Erika Keshishian, PhD, OMS IV, Elizabeth Kuge, OMS IV, Jordan Memmott, OMS IV, Phillip Hasenbalg, OMS IV, Nakiya Belford, OMS IV, Alexander Matlock, OMS IV, Sarah Schritter, RN, Geovar Agbayani, DO, Tyson Dietrich, PharmD, Anthony Santarelli, PhD and John Ashurst*, DO, MSc

Casirivimab/imdevimab treatment for outpatient COVID-19 during a SARS-CoV-2 B.1.617.2 (Delta) surge at a community hospital

<https://doi.org/10.1515/jom-2022-0070>

Received April 11, 2022; accepted July 11, 2022;
published online September 20, 2022

Abstract

Context: Vaccination status has been shown to be linked to patient-centered outcomes in those with COVID-19. However, minimal data have explored the relationship between vaccination status and representation rates after receiving monoclonal antibodies (MABs) the Delta strain of severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) in a community setting.

Objectives: The authors sought to determine if there was a difference in patient-centered outcomes between those who were vaccinated and unvaccinated after the administration of casirivimab/imdevimab for mild-to-moderate COVID-19 during the time when the Delta strain was most prevalent.

Methods: A convenience sample of consecutive adults given casirivimab/imdevimab at either an outpatient

infusion center or within the emergency department (ED) were included in analysis. Patient demographics, authorized-use qualifiers from the emergency use authorization (EUA), baseline vital signs at the time of infusion, representation rates to a healthcare provider within the hospital's network, and any admissions to the hospital following infusion were all collected from the patient's electronic medical record. Vaccination status was confirmed in both the patient's electronic medical record and the Arizona State Immunization Information System (ASIS). Analysis was conducted utilizing descriptive statistics, the Mann-Whitney U test for continuous data, and the chi-squared analysis for nominal data.

Results: In total, 743 patients were included in the study, with 585 being unvaccinated and 158 being vaccinated at the time of administration. Those in the vaccinated group were more likely to be older (60.0 vs. 55.0 years; $p<0.001$) and to have a history of diabetes (18.4% vs. 11.3%; $p=0.02$), hypertension (39.9% vs. 28.5%; $p=0.006$), immunosuppression (7.0% vs. 1.4%; $p<0.001$), and chronic kidney disease (7.0% vs. 3.4%; $p=0.05$). In the entire sample, 105 (14.1%) patients had an unexpected return visit to either the ED or urgent care at 28 days, with 17 (2.3%) requiring hospitalization. Patients who were vaccinated were more likely to represent for care after casirivimab/imdevimab infusion (20.3% vs. 12.5%; $p=0.01$), but no difference was noted in hospitalization rates between the two groups (18.8% vs. 15.1%; $p=0.15$).

Conclusions: MAB therapy with casirivimab/imdevimab for the outpatient treatment of mild-to-moderate COVID-19 was associated with a low rate of hospitalization. However, those who were vaccinated were more likely to present for unexpected return care at either the ED or urgent care within 28 days of the initial infusion.

Keywords: casirivimab/imdevimab; COVID-19; SARS-CoV-2 B.1.617.2.

*Corresponding author: John Ashurst, DO, MSc, Department of Graduate Medical Education, Kingman Regional Medical Center, 3269 Stockton Hill Road, 86409-3619, Kingman, AZ, USA, E-mail: ashurst.john.32.research@gmail.com

Erika Keshishian, PhD, OMS IV, Jordan Memmott, OMS IV, Phillip Hasenbalg, OMS IV, Nakiya Belford, OMS IV and Alexander Matlock, OMS IV, Pacific Northwest University of Health Sciences College of Osteopathic Medicine, Yakima, WA, USA

Elizabeth Kuge, OMS IV, Rocky Vista University College of Osteopathic Medicine, Parker, CO, USA

Sarah Schritter, RN, Department of Nursing, Kingman Regional Medical Center, Kingman, AZ, USA

Geovar Agbayani, DO and Anthony Santarelli, PhD, Department of Graduate Medical Education, Kingman Regional Medical Center, Kingman, AZ, USA

Tyson Dietrich, PharmD, Department of Pharmacology, Kingman Regional Medical Center, Kingman, AZ, USA

First identified in May 2021, the Delta (B.1.617.2) variant of the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) virus quickly swept the globe and became the predominant strain seen in the majority of locations within months of its discovery [1]. The Delta variant was found to be 60% more transmissible than the Alpha strain and has a basic reproduction rate of between 5 and 8 [1]. Not only was the transmissibility higher than other strains encountered but also healthcare providers from around the globe saw increased numbers of hospitalizations and deaths in the unvaccinated populations [2, 3].

COVID-19 vaccination is highly recommended as the primary strategy to slow the spread of disease and eventually curtail the current pandemic [1]. Data from Iceland, which has vaccinated nearly all eligible patients, showed that there was decreased rates of hospitalization and mortality in those with breakthrough infections due to the Delta variant of SARS-CoV-2 [1]. However, a significant number of patients within the United States remain unvaccinated for a variety of reasons [4].

Since receiving emergency use authorization (EUA), the usage of monoclonal antibodies (MABs) has become the mainstay of treatment for those outpatients at risk of progression to severe COVID-19. Several studies have shown a decrease in the rate of healthcare utilization, hospitalization, and mortality in those who receive the therapy as compared to those who do not [5, 6]. Casirivimab/imdevimab is a MAB cocktail that consists of two noncompeting neutralizing antibodies that noncompetitively binds to the receptor binding domain of the SARS-CoV-2 spike protein and prevents it from attaching to human angiotensin-converting enzyme-2 (ACE2) receptors [7]. Data from *in vitro* studies has shown that casirivimab/imdevimab has retained activity against the Delta strain, but little real-world data are available on its usage during the Delta surge, especially between those with varying vaccination statuses [8]. Due to the lack of evidence, the authors sought to determine the rate of healthcare utilization and admission following the administration of casirivimab/imdevimab for mild-to-moderate COVID-19 between those who were vaccinated and unvaccinated for COVID-19.

Methods

Setting

Kingman Regional Medical Center (KRMC) is a 235-bed community hospital located in northern Arizona with an annual emergency department (ED) volume of approximately 50,000 patient visits per

year. During the study period, a total of 3794 SARS-CoV-2 tests were positive. The prevalence of the Delta strain was estimated through genomic sequencing to be the most prevalent strain from June 2021 through at least December 2021, with the Omicron variant becoming the most prevalent in January 2022 [8].

Protocol

Following Kingman Healthcare Incorporated institutional review board (IRB) approval (KHI-0227), a convenience sample of consecutive adults aged 18 and above who received casirivimab/imdevimab for the outpatient treatment of mild-to-moderate COVID-19 from June 23, 2021 to December 31, 2021 were included in analysis. Healthcare staff screened patients on a daily basis who had positive results from a direct SARS-CoV-2 viral test for those who met one of the criteria for the administration of casirivimab/imdevimab specified by the EUA. A physician then spoke with each patient to discuss the risks and benefits of casirivimab/imdevimab infusion. Following patient agreement, casirivimab/imdevimab was administered by nursing staff at either an outpatient infusion center or the ED. Each patient received a combination dose of 1,200 mg of casirivimab and 1,200 mg of imdevimab as a single intravenous infusion within 10 days of symptom onset. Patients were monitored for 1 h following infusion to assess for any adverse infusion reactions.

All clinical data reported was abstracted from patient charts housed in the MEDITECH Expanse Platform (Medical Information Technology Inc, Westwood, MA), and vaccination data were abstracted from the Arizona State Immunization Information System (ASIIS) web application by trained research staff. The ASIIS an immunization registry designed to capture immunization data on individuals within the state. Clinical data collected from the MEDITECH Expanse Platform included: patient demographics, authorized use qualifiers from the EUA, baseline vital signs at the time of infusion, representation rates to a healthcare provider within the hospital's network, and any admissions to the hospital following infusion. Data collected from ASIIS included vaccination status prior to infusion. Patients were considered fully vaccinated at the time of infusion if they had completed either two doses of a Pfizer or Moderna vaccine or a single dose of the Johnson & Johnson vaccine.

All data were abstracted by trained research staff who were blinded to the study's objectives. Research staff was trained on proper data abstraction prior to the collection of data by the study team. This was completed by a member of the study team abstracting data with each research assistant. With adherence to a quality-controlled protocol and structured abstraction tool, research assistants manually collected all data points. Patients with incomplete data were removed from the final analysis.

Statistical analysis

Data were analyzed utilizing Statistical Product and Service Solutions (SPSS), v. 27 (IBM Corp., Armonk, NY). Continuous variables were presented as descriptive statistics and analyzed with the Mann-Whitney U Test. Differences between the frequency of cases were analyzed utilizing chi-squared analysis. Statistical significance was defined as $p \leq 0.05$.

Table 1: Patient demographics.

	Total (n=743)	Not vaccinated (n=585)	Vaccinated (n=158)	Significance
Age	57.0 (43.0–66.0)	55.0 (43.0–66.0)	60.0 (50.0–73.0)	<0.001
Age over 55	223 (30.0%)	164 (28.0%)	59 (37.3%)	0.02
Sex				0.92
Female	416 (56.0%)	327 (55.9%)	69 (43.7%)	
Male	327 (44.0%)	258 (78.9%)	69 (21.1%)	
Diabetes mellitus	95 (12.8%)	66 (11.3%)	29 (18.4%)	0.02
Chronic kidney disease	31 (4.2%)	20 (3.4%)	22 (7.0%)	0.05
Immunosuppression	19 (2.6%)	8 (1.4%)	11 (7.0%)	<0.001
Hypertension	230 (31.0%)	167 (28.5%)	63 (39.9%)	0.006
Congestive heart failure	28 (3.8%)	22 (3.8%)	6 (3.8%)	0.98
Chronic lung disease	98 (13.2%)	72 (12.3%)	26 (16.5%)	0.17
Smoker	215 (28.9%)	166 (28.4%)	49 (31.0%)	0.52

Table 2: Intake vital signs of those given casirivimab/imdevimab.

	Total (n=743)	Not vaccinated (n=585)	Vaccinated (n=158)	Significance
BMI (n=547)	30.1 (25.6–35.2)	30.2 (25.5–35.5)	29.2 (25.7–34.8)	0.59
Respiratory rate	18.0 (16.0–18.0)	18.0 (16.0–18.0)	18.0 (17.8–18.0)	0.49
Pulse	80.0 (69.0–90.0)	80.0 (70.0–91.0)	77.0 (68.0–87.0)	0.01
Systolic pressure	130.0 (117.0–143.0)	129.0 (116.0–143.0)	132.0 (119.0–146.3)	0.06
Diastolic pressure	76.0 (68.0–83.0)	76.0 (68.0–84.0)	75.0 (68.0–83.0)	0.93
Oxygen saturation	96.0 (94.0–97.0)	96.0 (94.0–97.0)	96.0 (94.0–97.0)	0.14
Temperature	97.4 (97.1–98.2)	97.5 (97.0–98.3)	97.3 (97.1–97.9)	0.28

Results

Overall, 743 patients were abstracted for inclusion in the study. Of the patients included in the final analysis, patients had a median age of 57.0 (43.0–66.0) years, and 416 (56.0%) were female (Table 1). Those in the vaccinated group were older (60.0 vs. 55.0 years; $p < 0.001$) and more likely to have chronic kidney disease (7.0%, $n = 22$ vs. 3.4%, $n = 20$; $p = 0.05$), a history of immunosuppression (7.0%, $n = 11$ vs. 1.4%, $n = 8$; $p < 0.001$), hypertension (39.9%, $n = 63$ vs. 28.5%, $n = 167$; $p = 0.006$) and diabetes (18.4%, $n = 29$ vs. 11.3%, $n = 66$; $p = 0.02$) as compared to their unvaccinated counterparts. Pulse rate was noted to be lower in those who were vaccinated as compared to those unvaccinated at the time of medication administration (77 vs. 80 beats per minute; $p = 0.01$). No other differences in intake vital signs at the time of medication administration was observed between those who were vaccinated and unvaccinated (Table 2).

Following administration of casirivimab/imdevimab, 105 (14.1%) patients represented to either the ED or urgent care following infusion (Table 3). Vaccinated patients were

more likely to represent after infusion as compared to those who were unvaccinated (32 vs. 73 patients; $p = 0.01$). No difference was noted for the length of time since casirivimab/imdevimab administration and representation for further care between the two groups (3 vs. 3 days; $p = 0.92$). Of those who represented for further care after casirivimab/imdevimab administration, 17 patients were admitted to the hospital with no difference between those who vaccinated and unvaccinated (6 vs. 11 patients; $p = 0.15$). No difference was noted in the length of hospitalization between vaccinated and unvaccinated patients after receiving casirivimab/imdevimab (2 vs. 5 days; $p = 0.22$).

Discussion

Overall, the rate of hospitalization due to severe COVID-19 after receiving casirivimab/imdevimab at a community hospital during the Delta variant surge was low. This finding was similar to previous literature describing hospitalization rates when other variants were predominant in the community [10–14]. Unlike several other MABs utilized previously, casirivimab/imdevimab is a dual MAB

Table 3: Patient outcomes following casirivimab/imdevimab infusion.

	Total (n=743)	Not vaccinated (n=585)	Vaccinated (n=158)	Significance
Representation within 28 days	105 (14.1%)	73 (12.5%)	32 (20.3%)	0.01
Hospitalization after infusion	17 (2.3%)	11 (1.9%)	6 (3.8%)	0.15
Time to representation	3.0 (2.0–9.0)	3.0 (2.0–9.0)	3.0 (1.0–8.8)	0.92
Duration hospitalized following infusion	4.0 (1.5–8.0)	5.0 (1.0–8.0)	2.0 (1.5–3.5)	0.22

cocktail that targets nonoverlapping epitopes on the spike protein [7]. Due to this, casirivimab/imdevimab was found to be able to maintain its treatment effect between circulating variants seen within the different surges [15]. The current results further correlate with experimental data that showed that casirivimab/imdevimab retained efficacy against SARS-CoV-2 B.1.617.2 and was a viable treatment option for those at risk of disease progression [9].

Once becoming ill with COVID-19, the unvaccinated have been shown to have worse outcomes than those who were fully vaccinated against COVID-19 [16]. In the current study, the majority of those seeking MAB therapy for the treatment of COVID-19 were unvaccinated. This data is similar to prior studies from other locations within the United States in which those who were unvaccinated were more likely to receive monoclonal therapy as compared to those who were vaccinated [11, 12]. This data not only further emphasizes the need for vaccination as a primary means to reduce transmission and minimize the burden of disease on healthcare facilities but also shows the willingness of those who are unvaccinated to receive treatment with MABs.

Although data have shown that those who are fully vaccinated are less likely to require ED care or hospitalization for breakthrough COVID-19 infection, the data from the current study showed that those who were fully vaccinated were more likely to represent unexpectedly to the ED for further care following casirivimab/imdevimab infusion as compared to those who were unvaccinated [17]. Although it is difficult to ascertain the exact mechanism behind these findings, it is postulated that it could be related to the differences seen between the groups in the study. Those who were vaccinated were more likely to be older and have underlying comorbidities such as immunosuppression, chronic kidney disease, hypertension, and diabetes mellitus. Previous data have shown that those with breakthrough COVID-19 were more likely to be at advanced age and have multiple comorbidities [11]. Data have also shown that the viral load in these individuals can be as high as those who are unvaccinated [18, 19]. The possibility of a high viral load coupled with multiple

underlying health issues may have exacerbated symptoms and caused a large number of vaccinated individuals to seek further care.

Another reason for the difference in representation found between those who were vaccinated and unvaccinated could be related to the behavioral differences, willingness to accept medical advice, and levels of medical mistrust between the two groups [20]. Medical mistrust has been defined as “distrust of healthcare providers, the healthcare system, medical treatments, and the government as a steward of public health” and has been conceptualized as a form of coping during a time of threat or uncertainty [21, 22]. Although those who were unvaccinated showed a willingness to accept treatment both in the current and previous studies, it could be postulated that patients with MAB treatment failure may have decided to not follow up with the institution that provided the treatment and sought care elsewhere.

Although those who were vaccinated were more likely to represent for unexpected care, no difference in hospitalization rates or length of stay was noted between those who were vaccinated and unvaccinated 28 days post-casirivimab/post-imdevimab infusion. This suggests that in the community setting, post-infection monoclonal therapies may prove effective for patients independent of their previous health decisions regarding COVID-19. Based upon these data, the authors suggest continued administration of monoclonal therapies to patients meeting EUA qualifiers irrespective of their previous vaccination status, and that vaccination status should not be utilized as a rule out for monoclonal therapy. Active surveillance of the variants of interest/concern is also needed to monitor the efficacy of each monoclonal therapy over time in order to minimize representations and hospitalizations of those receiving therapy.

From an osteopathic standpoint, this article highlights the need to assess and treat the whole person regardless of prior healthcare choices. Many individuals have shown vaccine hesitancy due to either mistrust of healthcare professionals, short-/long-term safety of the vaccine,

religious reasons, and sociopolitical views. Given the fact that many individuals who sought care were unvaccinated, healthcare providers should not judge individuals based upon a subset of life choices and instead treat individuals with compassion and empathy based upon established guidelines and evidence-based medicine.

Limitations

The data collected were from a single institution in northern Arizona, and results may not be applicable to all communities across the nation. Given the availability of MABs during different times of the study, patients may have presented for treatment outside of the typical catchment area for KRMC. Only medical records for representation and admission were tracked within the KRMC electronic medical records. If a patient from outside of the usual catchment area were to receive treatment and present to an outside facility for follow-up care, it could not be tracked by the study team and may have altered the results. A large number of patients were removed from final analysis due to incomplete documentation of past medical history within the electronic medical record.

Conclusions

Although the rate of representation and hospitalization was low after receiving casirivimab/imdevimab for the outpatient treatment of mild-to-moderate COVID-19, those who were vaccinated were more likely to represent to either an ED or urgent care for unexpected care following medication administration. This is most likely due to the underlying risk factors associated with those choosing to receive a vaccine and not necessarily due to a treatment effect of the medication being administered.

Research funding: None reported.

Author contributions: All authors provided substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; A.S., S.S., T.D., and J.A. drafted the article or revised it critically for important intellectual content; all authors gave final approval of the version of the article to be published; all authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing interests: John Ashurst, DO, MSc is part of the speaker's bureau for AstraZeneca.

Ethical approval: The study was approved by the Kingman Healthcare Incorporated Institutional Review Board (KHI-0227).

References

1. Del Rio C, Malani PN, Omer SB. Confronting the Delta variant of SARS-CoV-2, summer 2021. *JAMA* 2021;326:1001–2.
2. Twohig KA, Nyberg T, Zaidi A, Thelwall S, Sinnathamby MA, Aliabadi S, et al. Hospital admission and emergency care attendance risk for SARS-CoV-2 delta (B.1.617.2) compared with alpha (B.1.1.7) variants of concern: a cohort study. *Lancet Infect Dis* 2022;22:35–42.
3. Lin L, Liu Y, Tang X, He D. The disease severity and clinical outcomes of the SARS-CoV-2 variants of concern. *Front Public Health* 2021;9:9775224.
4. Centers for Disease Control and Prevention. COVID data tracker. 2022. Available from: https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-total-admin-rate-total.
5. Kow CS, Ramachandram DS, Hasan SS. The use of neutralizing monoclonal antibodies and risk of hospital admission and mortality in patients with COVID-19: a systematic review and meta-analysis of randomized trials. *Immunopharmacol Immunotoxicol* 2022;44:28–34.
6. Lin WT, Hung SH, Lai CC, Wang CY, Chen CH. The impact of neutralizing monoclonal antibodies on the outcomes of COVID-19 outpatients: a systematic review and meta-analysis of randomized controlled trials. *J Med Virol* 2022;94:2222–9.
7. Weinreich D, Sivapalasingman S, Norton T, Ali S, Gao H, Bhore R, et al. REGN-COV2, a neutralizing antibody cocktail, in outpatients with COVID-19. *N Engl J Med* 2021;384:238–51.
8. Translational Genomics Research Institute. The Arizona COVID-19 sequencing dashboard. 2022. Available from: https://pathogen.tgen.org/covidseq-tracker/arizona_trends.html [Accessed 21 Jun 2022].
9. Wilhelm A, Toptan T, Pallas C, Wolf T, Goetsch U, Gottschalk R, et al. Antibody-mediated neutralization of authentic SARS-CoV-2 B.1.617 variants harboring L452R and T478K/E484Q. *Viruses* 2021;13:1693.
10. Bierle DM, Ganesh R, Tulledge-Scheitel S, Hanson SN, Arndt LL, Wilker CG, et al. Monoclonal antibody treatment of breakthrough COVID-19 in fully vaccinated individual with high-risk comorbidities. *J Infect Dis* 2022;225:598–602.
11. Bierle DM, Ganesh R, Razonable RR. Breakthrough COVID-19 and casirivimab-imdevimab treatment during a SARS-CoV-2 B.1.617.2 (Delta) surge. *J Clin Virol* 2021;145:105026.
12. Zitek T, Jodoin K, Kheradia T, Napolillo R, Dalley MT, Quenzer F, et al. Vaccinated patients have reduced rates of hospitalization after receiving casirivimab and imdevimab for COVID-19. *Am J Emerg Med* 2022;56:370–1.
13. Ash J, Leavitt R, Dietrich T, Schritter S, Wells J, Santarelli A, et al. Real world utilization of REGN-COV2 at a community hospital. *Am J Emerg Med* 2021;50:129–31.

14. Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. REGEN-COV antibody combination and outcomes in outpatients with COVID-19. *N Engl J Med* 2021;385:e81.
15. Copin R, Baum A, Wloga E, Pascal KE, Giordano S, Fulton BO, et al. The monoclonal antibody combination REGEN-COV protects against SARS-CoV-2 mutational escape in preclinical and human studies. *Cell* 2021;184:3949–61.
16. Johnson AG, Amin AB, Ali AR, Hoots B, Cadwell BL, Arora S, et al. COVID-19 incidence and death rates among unvaccinated and fully vaccinated adults with and without booster doses during periods of delta and omicron variant emergence – 25 U.S. Jurisdictions, April 4 – December 25, 2021. *MMWR. Morb Mortal Wkly Rep* 2022;71:132–8.
17. Bahl A, Johnson S, Maine G, Garcia MH, Nimmagadda S, Qu L, et al. Vaccination reduces need for emergency care in breakthrough COVID-19 infections: a multicenter cohort study. *Lancet Reg Health Am* 2021;4:100065.
18. Bergwerk M, Gonen T, Lustig Y, Amit S, Lipsitch M, Cohen C, et al. Covid-19 breakthrough infections in vaccinated health care workers. *N Engl J Med* 2021;385:1474–84.
19. Chau NVV, Ngoc NM, Nguyet LA, Quang VM, Ny NTH, Khoa DB, et al. An observational study of breakthrough SARS-CoV-2 Delta variant infections among vaccinated healthcare workers in Vietnam. *EclinicalMedicine* 2021;41:101143.
20. Bogart LM, Ojikutu BO, Tyagi K, Klein DJ, Mutchler MG, Dong L, et al. COVID-19 related medical mistrust, health impacts, and potential vaccine hesitancy among black Americans living with HIV. *J Acquir Immune Defic Syndr* 2021;86:200–7.
21. LaVeist T, Isaac L, Williams K. Mistrust of healthcare organizations is associated with underutilization of health services. *Health Serv Res* 2009;44:2093–105.
22. Jaiswal J, Halkitis P. Towards a more inclusive and dynamic understanding of medical mistrust informed by science. *Behav Med* 2019;45:79–85.