Impact of a subcutaneous casirivimab and imdevimab clinic in outpatients with symptomatic COVID-19: A single-center, propensity-matched cohort study

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Purpose: To evaluate the success of a clinic for subcutaneous administration of casirivimab and imdevimab (REGEN-COV; Regeneron) for treatment of patients with symptomatic mild to moderate coronavirus disease 2019 (COVID-19) in terms of preventing disease progression and healthcare utilization.

Methods: This retrospective single-center, propensity-matched cohort study examined healthcare utilization outcomes for patients who received subcutaneous casirivimab and imdevimab at a pharmacist-led clinic of an academic health system. Eligible patients were treated between August 1, 2021, and January 5, 2022, and were at high risk for COVID-19 disease progression. Treatment patients were propensity matched with high-risk control patients with a diagnosis of COVID-19 in the same timeframe who did not receive casirivimab and imdevimab. Patients were followed for 30 days for collection of data on inpatient admissions, emergency department visits, and mortality. Risk of a 30-day healthcare utilization event was assessed and tested for statistical significance utilizing McNemar's test.

Results: A total of 585 patients who received treatment with subcutaneous casirivimab and imdevimab were matched with 585 patients who did not receive casirivimab and imdevimab therapy. Patients who received casirivimab and imdevimab had significantly lower risk of a 30-day all-cause inpatient admission event than untreated patients (relative risk reduction, 61.2%; $P < 0.0001$). Treated patients also had a significantly lower risk of 30-day all-cause emergency department visit than untreated subjects (relative risk reduction, 36.6%; $P = 0.0021$). There were 6 mortality events in the untreated group and no mortality events in the treatment group.

Conclusion. This study provides evidence for the effectiveness of a subcutaneous casirivimab and imdevimab clinic in preventing progression of symptomatic mild to moderate COVID-19.

Keywords: casirivimab and imdevimab, COVID-19, monoclonal antibodies, real-world outcomes

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As of March 2022, more than 79 million cases of coronavirus disease 2019 (COVID-19) had been reported in the United States, with these cases resulting in over 4.5 million hospital admissions and nearly 1 million deaths.[1] An emerging therapeutic class for preexposure prophylaxis and treatment of patients with COVID-19 is SARS-CoV-2 spike protein–neutralizing monoclonal antibodies. Combination regimens of the monoclonal antibodies casirivimab and imdevimab (REGEN-COV [Regeneron], first available as a coformulated product and since made available in copackaged separate-vial products) received emergency use authorization (EUA) from the Food and Drug Administration (in November 2020) for use in prevention and treatment of mild to moderate COVID-19 in patients with a high risk of progression.[2] Casirivimab and imdevimab therapy was shown to reduce viral load, healthcare utilization, and death in clinical trials.[3,4] Initial clinical trials focused on intravenous infusion of casirivimab and imdevimab; however, subcutaneous administration has also been studied for prophylaxis and treatment of asymptomatic COVID-19 positivity, with significant reductions in the development of symptomatic COVID-19.[5,6]

Due to the immediate need for therapeutics to respond to the COVID-19 pandemic, as well as the rapid mutation and emerging variants of SARS-CoV-2 with potentially greater virulence and infectiousness, real-world evidence and monitoring has been crucial in determining the role of casirivimab and imdevimab in therapy. Previous real-world observations support the findings of randomized controlled trials showing reduced all-cause and COVID-19–related hospitalizations in patients with mild to moderate COVID-19.[7,8] Reductions in healthcare utilization and disease progression with use of casirivimab and imdevimab combination therapy also have been reported in immunocompromised

subpopulations, suggesting those most vulnerable to COVID-19 progression may benefit most from the treatment.[9,10]

However, several questions regarding the role of casirivimab and imdevimab in therapy for COVID-19 remain. In June 2021, the EUA for casirivimab and imdevimab was updated to allow for subcutaneous administration as an alternative for patients who cannot receive intravenous (IV) infusion. Subcutaneous administration of casirivimab and imdevimab remains somewhat controversial, with demonstrated benefit over placebo but unclear evidence for noninferiority to intravenously administered casirivimab and imdevimab therapy.[11] Additionally, the emergence of SARS-CoV-2 variants of concern, including the B.1.617.2 and B.1.529 variants (commonly known as the Delta and Omicron variants, respectively) have raised concerns about the continued effectiveness of monoclonal antibodies. It has previously been documented that the Delta variant is less susceptible to antibody neutralization[12,13]; however, preliminary evidence regarding use of casirivimab and imdevimab for the Delta variant appears to demonstrate continued effectiveness.[14] More concerning is the Omicron variant, which does not appear to be significantly neutralized by casirivimab and imdevimab in vitro.[15,16] This has led to a recommendation against the use of casirivimab and imdevimab for the Omicron variant and a revision of the EUA on January 24, 2022, preventing use in geographic regions where infection is likely to have been caused by a nonsusceptible SARS-CoV-2 variant.[2,17] As a result of these unknowns, further real-world investigations into the effectiveness of subcutaneous casirivimab and imdevimab for COVID-19 variants of concern is warranted.

At our academic health system, patients with mild to moderate COVID-19 at high risk for disease progression were eligible for monoclonal antibody treatment. Treatment with subcutaneous casirivimab and imdevimab was provided beginning in August 2021 and

continuing into early January 2022. This timeframe included multiple COVID-19 case surges at the health system involving the Delta and Omicron variants of concern. These cases provided an opportunity to examine the effectiveness of a subcutaneous casirivimab and imdevimab clinic in preventing progression of mild to moderate COVID-19 variants of concern and, subsequently, to alleviate the burden on healthcare resources in terms of additional hospital admissions and emergency department visits.

Methods

Study design. This retrospective study followed a single-center cohort design. All subjects who received subcutaneous casirivimab and imdevimab treatment at the health-system specialty pharmacy (HSSP) between August 1, 2021, and January 5, 2022, were included in the treatment cohort. In order to be eligible for casirivimab and imdevimab treatment, patients must have met the following inclusion criteria: (1) a positive COVID-19 polymerase chain reaction (PCR) or antigen test; (2) age of ≥18 years; (3) reported symptoms of COVID-19 including fever, cough, sore throat, malaise, headache, myalgia, gastrointestinal distress, and/or shortness of breath on exertion; (4) receipt of casirivimab and imdevimab treatment within 10 days of symptom onset; and (5) criteria for high risk of disease progression as described in the casirivimab and imdevimab EUA.[2] These eligibility requirements for treatment were unchanged throughout the study period at our institution. International Classification of Diseases 10th Revision (ICD-10) diagnosis code definitions of EUA high-risk conditions used for study identification purposes are listed in eTable 1 and were created through use of Healthcare Cost Utilization Project's Clinical Classifications Software as well as selected literature.[18,19] Patients were excluded from treatment eligibility if they were admitted at the time of their initial diagnosis or required oxygen therapy for

COVID-19 treatment. A control cohort was created by identifying patients at the health system who met treatment inclusion/exclusion criteria but did not receive casirivimab and imdevimab, then applying 1:1 propensity score matching to obtain the final control cohort. The study design was reviewed and approved by the the health system's medical institutional review board.

Casirivimab and imdevimab treatment at the health system. Our academic health system serves its patient population with a combined 749 inpatient beds across 2 hospital sites. To provide context for the COVID-19 pandemic at the health system during the study period, at the beginning of the study period (ie, in August 2021) approximately 77 beds were utilized to treat COVID-19–positive patients, with a maximum peak of 159 beds in September 2022 (approximately 20% of bed capacity). At the end of the study period (ie, in January 2022), 110 beds were occupied by COVID-19–positive patients.

In order to relieve strain on our inpatient infrastructure, the health system provided casirivimab and imdevimab through subcutaneous administration at the ambulatory infusion center associated with the HSSP. This location was chosen because it allowed for rapid administration with minimal risk of exposure to other patients and providers, as the infusion center is located separately from the main medical campus. Subcutaneous administration of casirivimab and imdevimab was chosen to minimize compounding and administration time and allow for utilization of providers (primarily pharmacists) on-site. To perform patient administration of casirivimab and imdevimab, a single full-time pharmacist role was created, with 3 as-needed pharmacists and 1 as-need nurse role to support the position. Treatment was performed during normal ambulatory infusion center hours from Monday through Friday. Alongside these roles, a preexisting call center team of 5 pharmacy technicians and 3 pharmacists who ordinarily support the HSSP infusion center was utilized

for scheduling, referral processing/authorization, and performing follow-up for patients treated with casirivimab and imdevimab.

The process for providing casirivimab and imdevimab treatment is outlined in Figure 1. Health-system providers were responsible for identifying patients who met treatment eligibility criteria, offering treatment under the EUA, and subsequently creating the therapy plan and sending a referral to the HSSP. HSSP call center pharmacists subsequently contacted patients to schedule a treatment appointment and confirm they could receive treatment within the 10-day treatment window. Patients were typically scheduled for treatment on the same day or day after HSSP contact, with a mean time from first positive COVID-19 test to treatment of 2.5 days.

When a patient receiving casirivimab and imdevimab arrived for the treatment appointment, the treating pharmacist escorted the patient to the infusion chairs designated for monoclonal antibody treatments. The pharmacist collected vital signs on arrival and provided additional medication counseling, including distribution of the applicable EUA fact sheet to patients. After counseling, 600 mg of casirivimab and 600 mg of imdevimab were administered as 4 subcutaneous injections. This dosage was utilized for all patients. After administration, vital signs were collected again by the treating pharmacist, and the patient was monitored for 1 hour for hypersensitivity or other adverse drug reactions. The patient was subsequently escorted out of the building by the pharmacist. The HSSP call center pharmacists followed up with all patients treated via phone 5 days post treatment to assess for any additional adverse drug reactions.

Data collection and outcomes. All demographics and outcomes data were extracted from the institution's Epic electronic medical record (Epic Systems Corporation, Verona, WI) data repository with support from the University of Kentucky Center for Clinical and

Translational Science. The treatment cohort was identified in the data set by applying a list of subjects who were documented as receiving casirivimab and imdevimab in HSSP clinical documentation software (Therigy, LLC, Maitland, FL). The remaining subjects who did not receive casirivimab and imdevimab were considered for the control cohort. The date of receipt of casirivimab and imdevimab was used as the study index date for the treatment cohort, whereas the date of the initial positive COVID-19 test was used as the index date for the control cohort. For both cohorts, all subject data within the institution's electronic medical record regarding healthcare service utilization for 30 days post index date was collected.

The primary outcome of interest was all-cause hospitalization within the 30-day posttreatment period. Secondary outcomes included all-cause emergency department (ED) visits and all-cause mortality within the 30-day posttreatment period. A 30-day period was selected based upon existing evidence that hospitalizations for acute COVID-19 occur within 10 days or less of symptom onset.[20,21] In addition to the outcomes, demographic data including age, gender, and race/ethnicity, as well as ICD-10 diagnosis codes corresponding to EUA-qualifying high-risk conditions, were collected for all subjects. Additional relevant covariables, including history of any COVID-19 vaccination and whether the patient presented before or after the Omicron variant was classified as a variant of concern (VOC) in the United States by the Centers for Disease Control and Prevention were also collected.[22] For study purposes, the cases prior to and including November 30, 2021, were classified as "pre-Omicron VOC" cases, while those occurring on December 1, 2021, and after were considered "post-Omicron VOC" cases. These covariables were hypothesized to have a significant effect on the primary and secondary outcomes based upon prior studies and

were used in the propensity matching process to control for the confounding bias of their influence.[23,24]

Propensity score matching and statistical analysis. All propensity score matching and statistical analysis were carried out in SAS 9.4 (SAS Institute Inc., Cary, NC). Propensity scores were estimated for all treatment and potential control cohort subjects utilizing a logistic regression model.[25] Variables used in the creation of propensity scores included all collected demographics (age, race, and gender); ICD-10 diagnosis codes corresponding to EUA-qualifying high-risk conditions; relevant disease-modifying criteria, including history of a COVID-19 vaccination and whether the patient presented during the designated pre- or post-Omicron VOC periods. Propensity score matching was conducted in a 1:1 treatment:control ratio utilizing a publicly available SAS macro, %psmatch_multi.[26] Matches were made by identifying all controls within a maximum score radius between treated and controlled subjects (0.25 times the standard deviation of the propensity scores) and randomly selecting a match. Matches were made without optimization (ie, "greedy" matching) or replacement.[26] Treatment effect on healthcare utilization outcomes was assessed for statistical significance utilizing McNemar's test to evaluate the difference between the matched cohorts.[27]

Results

Overview. A total of 585 patients received treatment with subcutaneous casirivimab and imdevimab during the study period. A matching control cohort of 585 patients was drawn from a sample of 835 patients who met inclusion and exclusion criteria for casirivimab and imdevimab therapy but did not receive the treatment. Summary statistics regarding demographic data, vaccination status, presentation during pre- or post-Omicron

VOC period, and treatment-qualifying high-risk conditions are contained in Table 1. The median age of the study population was 51 years, with a range of 18 to 94 years. Subjects were predominantly female (56.2%) and white (78.7%), and the majority (63.9%) had received at least one dose of a COVID-19 vaccination series. Most study subjects (70.4%) were diagnosed during the pre-Omicron VOC period. The most common treatment-qualifying high-risk conditions were a body mass index (BMI) greater than or equal to 25 kg/m^2 (66.8% of patients), cardiovascular disease/hypertension (36.5%), receipt of immunosuppressing drug regimens (29.9%), and an age greater than or equal to 65 years (22.2%).

Primary outcome. The overall frequency of patients experiencing the primary outcome of a 30-day all-cause inpatient admission was lower in the cohort that received subcutaneous casirivimab and imdevimab treatment (n = 35) than in the control group (n = 92): 6% versus 15.7% ($P < 0.0001$). The observed absolute risk reduction was 9.7%, and the relative risk reduction was 61.8%, with a number needed to treat to avoid one inpatient admission of 11 (Table 2).

Secondary outcomes. The secondary outcome of occurrence of a 30-day all-cause ED visit was lower in the treatment cohort (n = 61) than in the control cohort (n = 96): 10.4% versus 16.4% ($P = 0.0021$). The observed absolute risk reduction was 6%, with a relative risk reduction of 36.6% and a number needed to treat to avoid one ED visit of 17. No subjects in the treatment cohort had a 30-day mortality event, whereas 6 subjects (1%) in the control cohort died. Due to the low number of mortality events and lack of sufficient statistical power to evaluate a rare event, risk reductions and statistical significance testing is not reported for the 30-day all-cause mortality outcome.

Discussion

This study provided evidence that administering subcutaneous casirivimab and imdevimab to patients with mild to moderate COVID-19 and a high-risk of disease progression significantly reduced 30-day healthcare utilization relative to no intervention. In treatment and control cohorts that were propensity matched on relevant covariables, the frequencies of 30-day inpatient admissions, ED visits, and mortality were observed to be lower in the treatment group. Significantly lower risks of 30-day inpatient admissions and ED visits were observed in the treatment cohort after controlling for relevant confounding variables.

While there was no comparison of subcutaneous therapy with IV administration, these results support a growing body of clinical trial results and real-world evidence suggesting that subcutaneous casirivimab and imdevimab is superior to no intervention in patients with COVID-19.[6,11] Furthermore, there are no randomized controlled trial data on use of subcutaneous casirivimab and imdevimab therapy in patients who are symptomatic, increasing the need for real-world studies to assess its effectiveness. Notable about these results are that the risks of inpatient admission and ED visits appeared to be higher in both treatment and control cohorts than risks reported in other studies examining casirivimab and imdevimab therapy for COVID-19. The authors suspect that this is attributable to the health system's patient population, which has a high case mix index and significant socioeconomic barriers to care, which can affect COVID-19 outcomes negatively.[28] Other real-world preliminary analyses of subcutaneous casirivimab and imdevimab therapy appear to have demonstrated similar relative risk reductions, suggesting that the observed treatment effectiveness in our study is still comparable to that in other populations.[11]

Administration of casirivimab and imdevimab subcutaneously can offer several benefits to the health system, including a reduction in time spent in the infusion clinic, a reduction in the number of staff needed to run a successful clinic, and elimination of the need for sterile compounding. Patients receiving subcutaneous casirivimab and imdevimab spend less time waiting in an infusion chair to obtain IV access or for sterile medication compounding. Subcutaneous administration may be performed more quickly and utilizing fewer staff, freeing up time to treat additional patients. Additionally, subcutaneous administration may be performed by pharmacists, which may be especially important during future pandemic surges and for health systems with limited nursing and provider resources. Without the requirement for sterile compounding, a subcutaneous monoclonal antibody clinic does not need to be located in close proximity to a sterile compounding site, allowing treatment to occur in lower traffic areas and decreasing risk of COVID-19 exposure to other patients.

The limitations of this study include a single-center design that may not have fully eliminated all confounding variables found in the study population. Due to the single-center design, results may not be generalizable to the greater population. Additionally, without a placebo control, this study could not account for the effect of additional healthcare contact related to administration of casirivimab and imdevimab, and subsequently the true risk reduction observed in a randomized controlled trial may be lower. Similarly, without a group receiving IV therapy, no conclusions can be made about the optimal route of administration for casirivimab and imdevimab. Another limitation of this study is that whether or not control cohort subjects presented with symptomatic COVID-19 could not be assessed retrospectively, introducing a potential confounding variable for cohort comparisons. Disease-specific outcomes in the patient population could not be assessed, so

the true disease-specific treatment effect may be greater or less than the values reported here. An additional limitation is the lack of exclusion criteria for oral COVID-19 antiviral treatment in our treatment and control groups; those criteria (specified in the EUA of December 22, 2021[29]) became available shortly before the end of the study period. While this variable was not accounted for in the control group, to the knowledge of the investigators, no patient in the treatment group received oral COVID-19 antiviral treatment. Finally, this study is limited by collection of data from a single health system and cannot account for healthcare utilization events occurring at other institutions outside our health system. The strengths of this study include the provision of positive evidence in terms of reduced healthcare utilization associated with subcutaneous casirivimab and imdevimab therapy, which has thus far not been fully characterized in prior literature. Further strengths include the utilization of propensity matching and logistic regression methods, which reduce bias to a minimum in observational studies by adjusting for baseline variations in the patient population.

Conclusion

This study provides evidence for the effectiveness of a subcutaneous casirivimab and imdevimab clinic in preventing progression of mild to moderate COVID-19 due to viral VOCs in terms of healthcare utilization. The evidence presented suggests that administration of subcutaneous casirivimab and imdevimab therapy lowers the risks of 30-day inpatient admission, ED visits, and mortality in a real-world setting. Health systems should consider utilizing subcutaneous monoclonal antibody therapy, which can be administered by pharmacists to improve patient outcomes and prevent utilization of emergent healthcare resources.

Figure 1. Process for provision of casirivimab and imdevimab within the health system. EMR indicates electronic medical record; EUA, emergency use authorization; HSSP, health-system specialty pharmacy.

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Key Points

- Casirivimab and imdevimab, monoclonal antibodies used to treat mild to moderate COVID-19 in the outpatient setting, may be administered intravenously or subcutaneously, but there is less evidence for the effectiveness of subcutaneous administration.
- In a propensity-matched cohort study, patients treated with subcutaneous casirivimab and imdevimab a had significantly lower risk of healthcare utilization or death within 30 days than patients who received no treatment.
- Subcutaneous monoclonal antibody clinics can improve patient outcomes and reduce healthcare utilization during the COVID-19 pandemic.

Table 1. Demographics and Treatment-Qualifying High-Risk Conditions by Study Group[a]

	Casirivimab and imdevimab (n = 585)	**Control (n = 585)**
Age, y		
Mean (SD)	50.9 (16)	50.7 (16.5)
Median	51	51
Range	18-94	18-89
Sex (female)	331 (56.6)	326 (55.7)
Race/ethnicity		
White	463 (79.2)	458 (78.3)
Black or African American	58 (9.9)	64 (10.9)
Hispanic/Latinx	36 (6.2)	36 (6.2)
Asian or Pacific Islander	11 (1.9)	10 (1.7)
Multiracial or unknown	17 (2.9)	17 (2.9)
COVID-19 vaccination status		
One or more dose of any COVID-19 vaccine	380 (65)	368 (62.9)
Presentation while omicron considered a VOC		
Diagnosis in pre-omicron VOC period	412 (70.4)	409 (69.9)
Diagnosis in post-omicron VOC period	173 (29.6)	176 (30.1)
Treatment-qualifying high-risk conditions		
Age ≥65 years	128 (22.9)	132 (22.6)
BMI ≥25 kg/m^2	391 (66.8)	391 (66.8)
Cardiovascular disease or hypertension	218 (37.3)	209 (35.7)
Chronic kidney disease	37 (6.3)	28 (4.8)
Chronic lung disease	113 (19.3)	103 (17.6)
Diabetes mellitus	104 (17.8)	106 (18.1)
Immunosuppressive disease	67 (11.5)	57 (9.7)
Immunosuppressive drug regimen	169 (29.9)	179 (30.6)
Medical-related technological dependence	5 (0.9)	9 (1.5)
Neurodevelopmental disorders	12 (2.1)	15 (2.6)
Pregnancy	21 (3.6)	15 (2.6)
Sickle cell anemia	1 (0.2)	1 (0.2)

Abbreviations: BMI, body mass index; ED, emergency department; VOC, variant of concern.
[a]All data are No. (%) unless otherwise indicated.

Table 2. Frequency of Healthcare Utilization Outcomes by Study Group[a]

Outcome	Casirivimab and imdevimab (n = 585)	Control (n = 585)	Relative risk reduction	Absolute risk reduction	Number needed to treat	*P* value
30-day all-cause inpatient admission	35 (6)	92 (15.7)	61.2	9.7	11	<0.0001[a]
30-day all-cause ED visit	61 (10.4)	96 (16.4)	36.6	6.0	17	0.0021[a]
30-day all-cause mortality	0 (0)	6 (1)				

Abbreviation: ED, emergency department.
Significance at $P \leq 0.05$ level.
[a]Data for study groups are No. (%); risk reduction data are %.

Figure 1