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Breakthrough COVID-19 and casirivimab-imdevimab treatment during a SARS-CoV-2 B1.617.2 (Delta) surge

Dennis M. Bierle, Ravindra Ganesh, Raymund R. Razonable *

Divisions of General Internal Medicine and Infectious Diseases, Department of Medicine, Mayo Clinic, Rochester, Minnesota, United States

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ABSTRACT

Introduction: : The impact of vaccination and casirivimab-imdevimab monoclonal antibody treatment on the clinical outcome of COVID-19 during a period of SARS-CoV-2 Delta surge is not known.

Aim and Methods: : All patients with COVID-19 at our facilities in the US Midwest were enrolled to assess breakthrough cases among vaccinated individuals and to compare the rates of hospitalization between casirivimab-imdevimab treated versus untreated patients. The study period occurred in July 2021 during a period dominated by the Delta variant.

Results: : The majority (68.1%) of 630 COVID-19 cases occurred in unvaccinated individuals. Among 403 patients eligible for monoclonal antibody treatment, the 28-day hospitalization rate was 2.6% of 112 patients who received treatment with casirivimab-imdevimab, compared to 16.6% of 291 eligible high-risk patients who did not receive casirivimab-imdevimab (Odds Ratio [OR]: 0.138, 95% confidence interval (CI): 0.0426–0.4477, $p = 0.001$). Casirivimab-imdevimab treatment was associated with lower rates of hospitalization among the vaccinated and unvaccinated cohorts.

Conclusions: : During a SARS-CoV-2 Delta surge, breakthrough COVID-19 occurred among vaccinated persons, especially among those with multiple medical comorbidities. Casirivimab-imdevimab treatment was associated with significantly lower rates of hospitalization in vaccinated and unvaccinated persons.

1. Introduction

The United States is experiencing a surge of coronavirus disease-2019 (COVID-19) attributed to Severe Acute Respiratory Syndrome-coronavirus 2 (SARS-CoV-2) lineage B.1.617.2 (Delta). SARS-CoV-2 Delta became the dominant variant (88% for the two weeks ending 7/17/21, and currently at 99.1%) in Minnesota and upper Midwest in July 2021 [1]. Compared to the wild-type, Alpha and Beta variants of concern, the Delta variant has been associated with an increased severity of illness [2], although this has not translated to excess mortality among persons under the age of 50 [3]. There was also a higher rate of hospitalization among patients with the Delta COVID-19 when compared to the Alpha variant, especially among unvaccinated people [4].

COVID-19 vaccination is highly recommended as the primary strategy to reduce SARS-CoV-2 Delta outbreaks and its great burden to healthcare systems. However, with transmission of SARS-CoV-2 in communities, breakthrough COVID-19 have been reported among fully vaccinated individuals [3, 5]. Among patients with COVID-19, treatment with anti-spike monoclonal antibody has been suggested to further alleviate healthcare burden by reducing hospitalization [6, 7]. We have previously observed a 70% relative risk reduction in hospital admission among patients who received the monoclonal antibody combination of casirivimab-imdevimab compared to a propensity-matched untreated cohort with mild to moderate COVID-19 in December 2020 to April 2021 – a period *prior* to the Delta surge in US [8].

Casirivimab-imdevimab is a combination of 2 laboratory-developed monoclonal IgG antibodies that bind noncompetitively to the receptor binding domain of SARS-CoV-2 spike protein and prevent the virus from attaching to the human ACE2 receptor [8]. Casirivimab-imdevimab retains its activity against the SARS-CoV-2 Delta variant based on in vitro studies [9], but the clinical outcomes of its use during the period dominated by Delta has not been assessed. Whether persons who have been vaccinated against COVID-19 benefit from monoclonal antibody if they develop breakthrough COVID-19 is not known. In this communication, we assessed the outcomes of 630 patients with COVID-19 during the early period of the Delta surge in our community. We assessed the impact of vaccination and casirivimab-imdevimab treatment.

* Corresponding author.
E-mail address: Razonable.raymund@mayo.edu (R.R. Razonable).

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2. Methods

2.1. Patients

After approval by the Mayo Clinic Institutional Review Board, this retrospective study enrolled patients with COVID-19 and were screened for eligibility for treatment with casirivimab-imdevimab in July 2021. Eligibility for treatment was guided by the US Food and Drug Administration (FDA) Emergency Use Authorization (EUA) criteria. Vaccination status was not part of criteria. All patients were tested at the Mayo Clinic Laboratories. All were screened by the Mayo Clinic Monoclonal Antibody Treatment Program, as previously described [10].

The demographic and clinical characteristics of the patients, as well as the COVID-19 vaccination status, were collected by a review of their Electronic Health Records. The risk of severe outcomes and hospitalization was assessed using Monoclonal Antibody Screening Score (MASS), as described [7, 11].

The conduct of this study was in compliance with the aims of Strengthening the Reporting of Observational Studies in Epidemiology (STROBE). All patients had authorization for the use of their medical records for research purposes.

2.2. Outcomes

The outcome of interest is the rate of hospitalization by day 28 after diagnosis of COVID-19. All 630 patients had ≥28 days of follow up by the end of this study on August 30, 2021. The differences in the outcomes between subgroups of patients, such as vaccinated versus unvaccinated and those treated versus not treated with monoclonal antibodies, were compared using descriptive statistics.

3. Results

The population consisted of 630 patients (average age, 46.5 years; 47% male) with COVID-19 and were screened for casirivimab-imdevimab therapy, under US FDA EUA guidance, in July 2021. The most common comorbidities were obesity (39.8%), hypertension (24.3%), cardiovascular disease (11.6%), chronic pulmonary disease (10.3%) and chronic kidney disease (5.9%). A total of 112 patients received casirivimab-imdevimab combination at a median 5.7 days after symptom onset, 291 were eligible but did not receive treatment, while 227 were ineligible based on the FDA EUA criteria.

Among 403 patients eligible for monoclonal antibody treatment, the 28-day hospitalization rate was 2.6% of 112 patients who received treatment with casirivimab-imdevimab, compared to 16.6% of 291 eligible high-risk patients who did not receive casirivimab-imdevimab (Odds Ratio [OR]: 0.138, 95% confidence interval (CI): 0.0426–0.4477, $p = 0.001$). The proportion of patients who developed hypoxia, defined as SpO2 <93% on room air, was lower among patients who received casirivimab-imdevimab compared to those who did not receive the antibody treatment (OR: 0.141, 95% CI: 0.0337–0.5907, $p = 0.008$).

The majority (68.1%) of 630 COVID-19 cases occurred in unvaccinated individuals. However, breakthrough COVID-19 was observed in 201 patients who had completed COVID-19 vaccination (mostly with two doses of an mRNA vaccine) at least 14 days prior to onset of symptoms. Notably, breakthrough COVID-19 occurred among vaccinated patients with significantly higher number of comorbidities (mean number, 3.0 vs 1.8, $p < 0.0001$). As shown in Table 1, treatment with casirivimab-imdevimab significantly reduced the hospitalization rates among the vaccinated and unvaccinated patients.

Table 1
Crude hospitalization rates at day 28 among 630 patients with coronavirus disease-19 at the Mayo Clinic in the Midwest, July 2021, stratified according to vaccination status and casirivimab-imdevimab treatment.

	Vaccinated patients($n = 201$)		Unvaccinated patients($n = 429$)	
	Casirivimab-imdevimab ($n = 55$)	No antibody treatment ($n = 146$)	Casirivimab-imdevimab ($n = 57$)	No antibody treatment ($n = 372$)
Number of hospitalized patients (percentage)	1 (1·8%)	22 (15·1%)	2 (3·5%)	51 (13·7%)
Number of patients with hypoxia (percentage)	0 (0%)	11 (7·5%)	2 (3·5%)	36 (9·7%)

4. Discussion

This short communication provides several observations that are relevant in the current era of the SARS-CoV-2 pandemic dominated by the Delta variant. First, this study observed that the majority of COVID-19 cases in the era of the Delta surge occurred in unvaccinated individuals. This emphasizes the need to aggressively promote COVID-19 vaccination as a public health strategy to reduce transmission and clinical disease due to SARS-CoV-2 Delta [2, 4].

Second, this study reinforced the occurrence of breakthrough COVID-19 among vaccinated individuals [5]. Previous studies have shown that the viral load (as measured by Ct values) of patients with breakthrough COVID-19 can be high, and may be similar to those who were not vaccinated [3, 12, 13]. In our cohort, the occurrence of breakthrough COVID-19 was higher among patients with multiple comorbidities. The number of comorbidities were significantly higher among vaccinated patients with breakthrough COVID-19 when compared to the unvaccinated lower-comorbidity patients. Obesity, hypertension, chronic lung, kidney and cardiac conditions accounted for majority of these comorbidities. Whether this heightened risk of COVID-19 among multi-comorbid vaccinated persons is due to waning immunity over time [14, 15], or suboptimal response to the vaccination remains unclear. Administration of third dose of mRNA vaccine or booster vaccination has been suggested as strategies to address these concerns. Moreover, the occurrence of breakthrough COVID-19 among fully-vaccinated highly-comorbid persons, which led to hospitalization in some of the patients, emphasizes the need for other public health strategies (e.g., use of face mask and avoidance of large gatherings) for all individuals during periods of high community SARS-CoV-2 Delta transmission.

Third, this study observed that the subgroup of high-risk patients who received casirivimab-imdevimab were much less likely to develop severe illness that would require hospitalization, when compared to the untreated cohort. This observation is true for both the vaccinated and unvaccinated persons. This finding is consistent with our previous report that associated monoclonal antibody treatment with reduced rates of hospitalization compared to those who did not receive treatment [8]. This finding also provides the clinical correlate to experimental studies that suggested that casirivimab-imdevimab combination retains efficacy against SARS-CoV-2 B1.617.2 [9].

Our study was limited by a relatively small cohort of 630 mostly Caucasian patients during a defined short study period in July 2021 when the SARS-CoV-2 Delta emerged in our community. The infecting SARS-CoV-2 variants were not sequenced routinely in clinical practice hence we do not have objective data to indicate that all the cases were indeed Delta. However, the CDC and public health departments that monitor circulating variants in the communities reported that the Delta variant was predominantly circulating in Minnesota and upper Midwest at the time of this study [1]. The findings should also be interpreted in the context that it was performed in a cohort of patients proactively screened and treated in a single healthcare system. While the treatment-eligible population was standardized by the US FDA

eligibility, patients who consented for monoclonal antibody treatment often possessed more medical comorbidities [11], thereby potentially underestimating the true effect of treatment.

5. Conclusion

During the Delta surge, prior vaccination may not fully protect highly co-morbid patients from developing severe COVID-19 illness that requires hospitalization. Early treatment with casirivimab-imdevimab of both the vaccinated and unvaccinated patients was associated with significantly lower rates of hospitalization.

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Author contributions

Drs. Bierle, Ganesh and Razonable participated in all aspects of the study from study connect, design, analysis, drafting and final revision for submission.

Ethical statement

This study was approved by the Mayo Clinic Institutional Review Board.

Declaration of Competing Interest

Dr. Bierle and Dr. Ganesh have nothing to disclose. Dr. Razonable is principal investigator of research funded by Regeneron, Roche, Gilead (all funds provided to his institution), and is a member of Data Safety Monitoring Board of Novartis, on projects not directly related to this submission. Dr. Razonable received research funds from the Mayo Clinic for studies on monoclonal antibodies for COVID-19.

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