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BRIEF REPORT

Effect of Monoclonal Antibody Treatment on Clinical Outcomes in Ambulatory Patients With Coronavirus Disease 2019

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We compared rates of emergency department visits or hospitalizations among ambulatory coronavirus disease 2019 (COVID-19) patients treated with monoclonal antibody (mAb) therapy (n = 305) vs untreated patients (n = 6354). Treatment was associated with decreased encounters within 30 days (adjusted odds ratio, 0.23 [95% confidence interval, .15–.36]). Our findings support treatment of acute COVID-19 with mAbs.

Keywords. COVID-19; monoclonal antibodies; SARS-CoV-2; therapeutics.

In November 2020, the US Food and Drug Administration (FDA) issued emergency use authorizations (EUAs) for the investigational monoclonal antibody (mAb) therapies bamlanivimab (Eli Lilly and Company, Indianapolis, Indiana) and casirivimab-imdevimab (Regeneron Pharmaceuticals, Inc, Tarrytown, New York) for treatment of mild to moderate coronavirus disease 2019 (COVID-19) in ambulatory patients [1, 2]. The EUAs were issued based on clinical trials that suggested these treatments reduced emergency department (ED) encounters or hospitalizations [3–5].

Despite the surge of COVID-19 cases experienced in the United States during the 2020–2021 winter season, several barriers to implementation of mAb treatment and uptake have prevented its widespread use [6]. Given the continued challenges in mAb treatment and uncertainties about the clinical benefits, studies regarding its clinical impact when used under the EUA guidance are needed. We evaluated the effects of mAb treatment on 30-day clinical outcomes in COVID-19 patients treated at Emory Healthcare (EHC; Atlanta, Georgia).

METHODS

On 25 November 2020, EHC began offering outpatient COVID-19 mAb infusion therapy at a dedicated outpatient COVID-19 clinic [7]. Ambulatory patients who tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by polymerase chain reaction or rapid antigen detection were screened and offered treatment if they met treatment criteria under the EUA. EUA criteria for bamlanivimab and casirivimab-imdevimab are identical in regard to age and medical risk factor requirements, as well as confirmed mild to moderate COVID-19 illness within 10 days of symptom onset [8, 9].

For this study, the EHC clinical data warehouse (CDW) was queried for all patients with a positive SARS-CoV-2 test from internal or external testing sites from 1 November 2020 to 26 February 2021. The index date was defined as the date of collection of the positive test. For patients with multiple positive results, the date of the first positive test was used. Baseline data were collected, including demographics, body mass index (BMI), testing location (specimen collected at an EHC ED vs other sites), and chronic health conditions relevant to the mAb EUA, including hypertension, history of coronary artery disease, diabetes mellitus, chronic obstructive pulmonary disease (COPD), chronic kidney disease, history of malignancy, and immunocompromising conditions. The presence of chronic health conditions was determined using *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes from outpatient visits from the 3 years before COVID-19 diagnosis, using codes validated for Charlson Comorbidity Index calculation [10]. This was supplemented by searching outpatient problem lists with relevant Systemized Nomenclature of Medicine (SNOMED) clinical terms. Receipt of mAb treatment was determined based on a scheduled clinic appointment and an order for bamlanivimab or casirivimab-imdevimab. The CDW was queried for ED encounters or hospitalization at 30 days after the index date at any of the 6 EHC hospitals. Intensive care unit (ICU) admission and death within 30 days of the index date were also assessed. Patients with missing race or BMI data were excluded. All patients who were hospitalized 2 days or less from the index date were excluded since they were unlikely to have had an opportunity for mAb infusion. Patients who were treated with mAb but admitted to the ED within 6 hours after the infusion time were also excluded, since these events were likely due to a rapid progression of illness (unlikely to have been affected by infusion) or reaction to the mAb.

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Patient data were analyzed with standard descriptive statistics. Baseline characteristics of treated and untreated patients were compared with χ^2 test for categorical variables and *t* test for continuous variables. The effect of specific variables on the odds of ED encounters or hospitalization 30 days after the index date was analyzed with a multivariate logistic regression model. Modeled variables were chosen a priori and included patient demographics (age, sex, African American race), medical history considered in the mAb treatment criteria, and testing location (EHC ED or other site). Age and BMI were evaluated as continuous variables. The effects of these variables on other clinical outcomes were also evaluated. All analysis was performed using Python (Anaconda 3, Austin, Texas) and SAS version 9.4 software (SAS Institute, Cary, North Carolina). This study was approved by the Institutional Review Board of Emory University with a waiver of informed consent.

RESULTS

During the study period, 6996 patients tested positive for SARS-CoV-2, of which 308 (4.4%) received mAb treatment for COVID-19. After excluding patients who were admitted to the hospital within 2 days of the index date (n = 334 [4.8%]) and those who were admitted to the ED within 6 hours of mAb infusion (n = 3 [1.0% of treated patients]), 6659 patients were included in this study, of whom 305 (4.6%) received treatment (Table 1). Compared to untreated patients, treated patients had significantly higher mean age, lower likelihood of being African American, and higher prevalence of several comorbid conditions. Treated patients were less likely to have been tested at an EHC ED (12.8% vs 34.6%, $P < .001$). Most treated patients received bamlanivimab (76.3%). Among treated patients, there were no severe adverse infusion-related events. An ED encounter or hospital admission within 30 days of the index date occurred in 21 (6.9%) mAb-treated patients vs 1198 (18.9%) untreated patients ($P < .001$). When adjusted for patient age, medical conditions, testing site, and race, mAb treatment was associated with a decreased odds of ED visits or hospitalization within 30 days of the index date (odds ratio [OR], 0.23 [95% confidence interval {CI}, .15–.36]; Table 2). Similar effects of infusion were observed in other clinical outcomes, including ICU admission at 30 days (OR, 0.07 [95% CI, .01–.25]) and death at 30 days (OR, 0.12 [95% CI, .03–.51]). Increased odds of ED visits or hospitalization in 30 days were independently associated with older age, higher BMI, male sex, non–African American race, diabetes mellitus, COPD, chronic kidney disease, and immunocompromised conditions (Table 2).

DISCUSSION

In our health system we found that mAb therapy of COVID-19 infection in ambulatory patients was associated with a 77% decreased odds of ED encounters or hospitalizations in the 30 days after diagnosis. While most of our patients were treated with bamlanivimab, our findings are similar to the results of the clinical trials of all currently authorized mAb treatments [3,

Table 1. Patient Characteristics and Outcomes Among Ambulatory Patients With Coronavirus Disease 2019 Untreated and Treated With Monoclonal Antibodies

	All Patients (N = 6659)				
	Not Treated		Treated		
Characteristics	(n = 6354)		(n = 305)		*P* Value
Age, y, mean (IQR)	54.5	(42–67)	62.9	(54–72)	**<.001**
Male sex	2704	(42.6)	141	(46.2)	.205
Non–African American race	3424	(53.9)	213	(69.8)	**<.001**
BMI, kg/m^2, mean (IQR)	30.8	(25.3–34.8)	31.3	(25.7–35.7)	.317
Past medical history					
Hypertension	3566	(56.12)	235	(77.05)	**<.001**
Coronary artery disease	1081	(17.01)	83	(27.21)	**<.001**
Diabetes	1931	(30.39)	125	(40.98)	**<.001**
Obstructive lung disease	1507	(23.72)	105	(34.43)	**<.001**
Chronic kidney disease	1005	(15.82)	51	(16.72)	.673
Cancer	934	(14.7)	68	(22.3)	**<.001**
Immunocompromised	316	(5.0)	34	(11.15)	<.001
Specimen collection in ED	2201	(34.6)	39	(12.8)	**<.001**
Outcomes					
ED visit or hospitalization within 30 d	1198	(18.9)	21	(6.9)	**<.001**
ICU admission at 30 d	484	(7.6)	2	(0.66)	**<.001**
Death	148	(2.3)	1	(0.33)	**.021**

Bold text indicates $P < .05$. Categorical variables are expressed as No. (%), and continuous variables are reported as mean (IQR).

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; ED, emergency department (Emory Healthcare); ICU, intensive care unit; IQR, interquartile range.

Table 2. Association of Baseline Conditions and Monoclonal Antibody Treatment on Adverse Clinical Outcomes Within 30 Days of Test Confirmation of Coronavirus Disease 2019

	ED Visit or Hospitalization		ICU Admission		Death	
Characteristic	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Age	**1.01**	**(1.01–1.02)**	**1.02**	**(1.01–1.03)**	**1.06**	**(1.04–1.07)**
Male sex	**1.43**	**(1.26–1.63)**	**1.50**	**(1.27–1.89)**	**1.56**	**(1.15–2.11)**
Non–African American race	**1.39**	**(1.21–1.59)**	**1.34**	**(1.01–1.54)**	**1.60**	**(1.16–2.22)**
BMI	**1.02**	**(1.01–1.03)**	**1.02**	**(1.00–1.03)**	1.00	(.98–1.03)
Past medical history						
Hypertension	1.04	(.89–1.23)	1.04	(.79–1.37)	1.02	(.64–1.64)
Coronary artery disease	1.03	(.86–1.23)	0.95	(.75–1.21)	0.97	(.69–1.36)
Diabetes	**1.18**	**(1.09–1.29)**	**1.48**	**(1.31–1.67)**	1.17	(.98–1.40)
COPD	**1.33**	**(1.15–1.53)**	**2.12**	**(1.67–2.71)**	**2.45**	**(1.73–3.46)**
Chronic kidney disease	**1.14**	**(1.05–1.23)**	**1.52**	**(1.23–1.86)**	**2.07**	**(1.53–2.81)**
Cancer	1.02	(.97–1.08)	**1.17**	**(1.05–1.30)**	**1.32**	**(1.14–1.53)**
Immunocompromised	**1.43**	**(1.10–1.89)**	1.02	(.95–1.10)	1.09	(.99–1.21)
Specimen collection in ED	1.39	(.96–1.26)	**1.83**	**(1.51–2.22)**	1.31	(.96–1.77)
mAb treatment	**0.23**	**(.15–.36)**	**0.06**	**(.01–.25)**	**0.12**	**(.03–.51)**

Bold text indicates odds ratios with 95% confidence intervals that do not include 1.

Abbreviations: BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ED, emergency department; ICU, intensive care unit; mAb, monoclonal antibody; OR, odds ratio.

5, 11]. Positive effects of mAb therapy in real-world use have also recently been reported in the unrefereed preprint literature [12–14]. These results support current recommendations for mAb therapy for outpatient treatment of mild to moderate COVID-19 [15]. Our study population had high rates of comorbid conditions, including a mean BMI >30 kg/m^2, so our findings might not be representative of patient populations with fewer comorbidities. African American persons in our study had a small but significantly decreased odds of adverse events, which is not consistent with most studies [16]. This most likely reflects variation in health care access and other social determinants of health among different patient populations.

Our study considered all outpatients who tested positive for SARS-CoV-2, and because untreated patients did not necessarily meet treatment criteria, we are unable to calculate the number needed to treat (NNT). However, an alternate analysis of propensity-matched treated and untreated patients demonstrated decreased rates of 30-day ED or hospital admission with mAb treatment (25.2% to 6.9%; OR, 0.3; $P < .01$) and an NNT of 5.4 (data not shown). It is possible that unaccounted confounders such as those related to health care access or quality of care may bias our findings [17]. Insurance status was not included in our analysis due to initial challenges in data collection; however, subsequent models including this did not alter our findings (results not shown). COVID-19 serology was not performed in most patients and not considered in the analysis.

Since we did not consider symptoms and used test date as the index date, it is likely that some of our untreated patients were asymptomatic infections or presented later in illness compared to the treated patients. However, untreated patients who had asymptomatic infection or were beyond the acute phase of illness would probably be less likely to progress to severe illness, biasing the results against treatment. Other limitations of our study largely stem from the inherent constraints of retrospective studies based on data warehouse queries. Misclassification of outcomes including ED encounters, hospitalizations, and deaths is possible if the patient received care outside of EHC. Since the majority of treated patients were established EHC patients, we believe that the number of misclassified outcomes in treated patients is probably low and unlikely to bias our results in favor of treatment. We did not assess the reasons for the ED encounters and hospitalizations, since nonspecific diagnoses might not indicate if an encounter was the result of COVID-19 infection. However, this is unlikely to bias the results for or against treatment in models adjusted for age and comorbid conditions.

Given the limited treatment options for ambulatory COVID-19 patients, our findings of reduced ED encounters and hospitalizations strongly support the continued use of mAb treatments. Efforts to educate physicians and patients about the treatments are appropriate. After the completion of this study, increasing concern of decreased in vitro activity of bamlanivimab on certain SARS-CoV-2 variants resulted in discontinuation of its release as a single mAb treatment [18]. Although genomic sequencing was not performed on specimens in this study, it would be prudent to assume that SARS-CoV-2 variants of concern were unlikely to be highly prevalent during the study period. Given the uncertainties about emerging variants, continued monitoring of mAb treatment outcomes is warranted.

Notes

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References

1. US Food and Drug Administration. Coronavirus (COVID-19) Update: FDA Authorizes Monoclonal Antibodies for Treatment of COVID-19. **2020**. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibodies-treatment-covid-19. Accessed 21 June 2021.
2. US Food and Drug Administration. FDA News Release Coronavirus (COVID-19) Update: November 9, 2020. **2020**. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-november-9-2020. Accessed 21 June 2021.
3. Chen P, Nirula A, Heller B, et al; BLAZE-1 Investigators. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with Covid-19. N Engl J Med **2021**; 384:229–37.
4. Regeneron. Clinical trial results and supporting data for EUA. **2021**. https://www.regencov.com/hcp/clinical-information. Accessed 15 April 2021.
5. Weinreich DM, Sivapalasingam S, Norton T, et al; Trial Investigators. REGN-COV2, a neutralizing antibody cocktail, in outpatients with Covid-19. N Engl J Med **2021**; 384:238–51.
6. National Academies of Sciences, Engineering, and Medicine. Rapid Expert Consultation on Allocating COVID-19 Monoclonal Antibody Therapies and Other Novel Therapeutics (January 29, 2021). Washington, DC: The National Academies Press; **2021**.
7. Ramakrishnan A, Zreloff J, Moore MA, et al. Prolonged symptoms after COVID-19 infection in outpatients. Open Forum Infect Dis **2021**; 8:ofab060.
8. Regeneron. Fact sheet for health care providers: emergency use authorization (EUA) of REGEN-COV (casirivimab with imdevimab). **2021**. https://www.regeneron.com/downloads/treatment-covid19-eua-fact-sheet-for-hcp.pdf. Accessed 15 April 2021.
9. Eli Lilly and Company. Emergency use authorization (EUA) for the treatment of COVID-19. https://www.covid19.lilly.com/bamlanivimab/hcp. Accessed 15 April 2021.
10. Glasheen WP, Cordier T, Gumpina R, et al. Charlson comorbidity index: *ICD-9* update and *ICD-10* translation. Am Health Drug Benefits **2019**; 12:188–97.
11. Gottlieb RL, Nirula A, Chen P, et al. Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19: a randomized clinical trial. JAMA **2021**; 325:632–44.
12. Rainwater-Lovett K, Redd JT, Stewart MA, et al. Real-world effect of monoclonal antibody treatment in COVID-19 patients in a diverse population in the United States. *medRxiv* [Preprint]. Posted online 10 April **2021**. doi:10.1101/2021.04.08.21254705.
13. Bariola JR, McCreary EK, Wadas RJ, et al. Impact of monoclonal antibody treatment on hospitalization and mortality among non-hospitalized adults with SARS-CoV-2 infection. *medRxiv* [Preprint]. Posted online 30 March **2021**. doi:10.1101/2021.03.25.21254322.
14. Webb BJ, Buckel W, Vento T, et al. Real-world effectiveness and tolerability of monoclonal antibodies for ambulatory patients with early COVID-19. *medRxiv* [Preprint]. Posted online 17 March **2021**. doi:10.1101/2021.03.15.21253646.
15. Infectious Diseases Society of America. IDSA guidelines on the treatment and management of patients with COVID-19. **2021**. https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Accessed 15 April 2021.
16. Mackey K, Ayers CK, Kondo KK, et al. Racial and ethnic disparities in COVID-19-related infections, hospitalizations, and deaths: a systematic review. *Ann Intern Med* **2021**; 174:362–73.
17. Busby J, Purdy S, Hollingworth W. A systematic review of the magnitude and cause of geographic variation in unplanned hospital admission rates and length of stay for ambulatory care sensitive conditions. BMC Health Serv Res **2015**; 15:324.
18. US Food and Drug Administration. Coronavirus (COVID-19) Update: FDA Revokes Emergency Use Authorization for Monoclonal Antibody Bamlanivimab. **2021**. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-monoclonal-antibody-bamlanivimab. Accessed 21 June 2021.