

JPPT | Single Center Retrospective Study

Effectiveness and Safety of Outpatient Monoclonal Antibody Use for the Treatment of COVID-19 in Children and Adolescents: Single Center Study

Julia Cheng, BS; Emily Heideman, MD; Claudia Espinosa, MD, MSc; Kristen Zeitler, PharmD; Nicholas Piccicacco, PharmD; and Claudia Gaviria-Agudelo, MD, MSc

OBJECTIVE Monoclonal antibody therapy has been used to treat COVID-19, with paucity of literature about its use in children. This retrospective study sought to evaluate the effectiveness of preventing hospitalization and safety of monoclonal antibody (mAb) treatment (bamlanivimab-etesevimab and casirivimab-imdevimab) for COVID-19 in patients ≤ 18 years of age.

METHODS Between January 1 and December 31, 2021, patients were selected for mAb therapy, based on the referring provider's clinical assessment of high risk for progression to severe COVID-19. The choice of mAb was determined by drug availability, compounding feasibility, and documented *in vitro* activity against circulating SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) variants. All patients received a single-dose infusion. Primary outcomes included hospital readmissions and emergency department (ED) visits within 90 days of treatment. The secondary outcome was safety/adverse events.

RESULTS Of 141 patients who received mAbs in 2021, only 3 experienced ongoing COVID-19 symptoms. Only 1 patient necessitated escalated care owing to persistent COVID-19 symptoms post infusion. There were no infusion-related side effects or hospitalizations in the 90 days post infusion.

CONCLUSION Monoclonal antibodies appear to be safe and effective in preventing hospitalizations in COVID-19–positive children.

ABBREVIATIONS Bam-Ete, bamlanivimab-etesevimab; Cas-Imd, casirivimab-imdevimab; ED, emergency department; mAb, monoclonal antibody; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

KEYWORDS COVID-19; immunotherapy; monoclonal antibodies; pediatrics

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Introduction

The COVID-19 pandemic demanded the timely development of new therapeutics for prevention and treatment of COVID-19 infection. Aside from new vaccines, and few antivirals, monoclonal antibodies (mAbs) emerged as alternative treatment of COVID-19 in selected patients.¹ Monoclonal antibodies were approved for treatment of mild to moderate COVID-19 disease by the US Food and Drug Administration under emergency use authorization. The first mAb treatment to receive approval was bamlanivimab alone in November 2020 and later for the combination bamlanivimab-etesevimab (Bam-Ete) in February 2021. This was followed by authorization of casirivimab-imdevimab (Cas-Imd) months later.² Bamlanivimab is an immunoglobulin G1 antibody that binds to the receptor-binding domain of the spike protein of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2).³ The antibody was approved

for use in patients ≥ 12 years of age; however, the trials investigating bamlanivimab's efficacy included only patients ≥ 18 years of age at the time of randomization. Combination treatment with Bam-Ete (which also targets SARS-CoV-2 spike protein receptor-binding domain) was approved to treat younger pediatric patients including newborns in December 2021.⁴

Casirivimab and imdevimab (Cas-Imd), 2 additional mAbs targeting the spike protein of SARS-CoV-2, were also approved in November 2020. Again, the mAbs were approved for patients ≥ 12 years of age, because early investigations of Cas-Imd included only patients of this age group.^{5–7}

There has been scarcity of systematic studies reporting the safety and effectiveness of these treatments in the pediatric population. We aim to describe the safety and effectiveness of mAb use in patients aged 18 years and younger who had at least 1 risk factor for progression to severe COVID-19 disease.

Materials and Methods

Patients 18 years and younger who received bamlanivimab, Bam-Ete, or Cas-Imd for treatment of mild to moderate COVID-19 disease at Tampa General Hospital were identified retrospectively through pharmacy records and by electronic medical record review. Disease categorization was based on the Centers for Disease Control and Prevention classification of COVID-19 severity in children—mild: requiring no specific medical care or treatment; moderate: potentially needing outpatient care, oxygen, or other medical support; or severe: involving hospitalization, intensive care unit admission, or mechanical ventilation.⁸ Patients' medical records were reviewed from January 1, 2021, to December 31, 2021.

Examples of risk factors considered to increase the risk of progression to severe COVID-19 included obesity (body mass index >30), use of immunosuppression medications, immunodeficiency diseases, chronic kidney disease (estimated glomerular filtration rate <90 mL/min/1.73 m²), solid organ transplant, congenital heart disease, chronic respiratory disease (including asthma), neurodevelopmental disorder, and dependence on a gastrostomy or tracheostomy tube. Of note, owing to the high volume of patients infused with mAb at our site, as well as some patients being referred for mAb therapy from outside our hospital system, the high-risk indication for mAb was not readily documented for all patients. The specific mAb agent administered was dependent on drug inventory and allocation, ease of compounding to accommodate high-infusion clinic volumes, and documented pseudoviral, *in vitro* mAb activity against the predominant circulating variant at the time of each surge. Dosing was a single infusion provided at the infusion clinic within the hospital; the infusion would last 30 to 60 minutes. Patients were monitored for an hour post administration for any side effects.

Data on age, sex, race, underlying condition, and COVID-19 screening were collected. Our primary outcomes were readmission rates and emergency department (ED) visits within 90 days. The secondary outcome was safety. Descriptive statistics were used to analyze the population demographics and outcomes.

Results

A total of 141 pediatric patients received a single infusion of mAb during the study period. Five patients (3.6%) received bamlanivimab, 9 (6.4%) received Bam-Ete, and 127 (90.1%) received Cas-Imd. The mean age was 15 years and ranged between 10 months and 18 years (IQR = 13.6-17; SD = 2.3). More than half of the patients self-identified as White (n = 82; 58.2%), 16 (11.4%) as African American, 16 (11.4%) as Hispanic, 8 (5.7%) as other race, and 19 (13.5%) declined to disclose their race. Two patients below age 12 years received mAb under compassionate use. The majority (n = 103; 73.0%)

had antigen-confirmed COVID-19 infection, while 38 subjects (27.0%) underwent SARS-CoV-2 polymerase chain reaction testing. The most common underlying condition was asthma (n = 38; 27.0%), followed by obesity (n = 29; 20.6%), and immunocompromised state (n = 9; 6.4%) (Table 1).

None of the patients were hospitalized for 90 days post infusion. There were no significant variations identified in clinical response according to race/ethnicity. Within 90 days of receiving mAb, only 3 patients (2.1%) experienced ongoing COVID-19 symptoms (Table 2). All 3 received Cas-Imd. Two patients phoned in to report symptoms: one experienced continuous vomiting for 3 days post infusion and the second experienced nausea and vomiting. The third patient visited the ED 1 day after infusion with worsening COVID-19 symptoms. Chest x-ray was performed, leading to a diagnosis of bacterial pneumonia, and the patient was treated with amoxicillin-clavulanate. No infusion-related side effects, including rashes, urticaria, or anaphylaxis, were observed in any of the patients during infusion or after standard observation period. The 2 patients receiving mAbs under compassionate use were hospitalized. The 8-year-old patient receiving chronic immunosuppression therapy (prednisone, mycophenolate, and cyclosporine) owing to kidney transplant was admitted for the infusion, had no adverse infusion-related events, and required no escalation of care. The 10-month-old with ornithine transcarbamylase deficiency was admitted for treatment of hyperammonemia and COVID-19. He had no adverse infusion-related events and needed no escalation of care for COVID-19 symptoms but was hospitalized for 13 days owing to hyperammonemia.

Discussion

Our study found that no patients were hospitalized within 90 days of single-dose mAb administration and that mAbs were safe for treatment of COVID-19 in pediatric patients. Overall, patients in our study tolerated mAb infusions with less side effects than other authors have reported in the literature and had a lower rate of escalation of care. This may be due to healthier starting population.

Santos et al⁹ reported that of 44 pediatric patients with risk factors of obesity and/or asthma who received bamlanivimab, Bam-Ete, or Cas-Imd, 38 experienced improvement of COVID-19 symptoms, 2 did not improve clinically, 3 did not keep their follow-up appointment, and 1 did not complete infusion owing to infusion-related adverse events. Two patients were evaluated at the ED within 28 days of infusion. One had shortness of breath and received treatment with albuterol and the other had cervical lymphadenitis. Both were discharged home. The patient who had infusion-related adverse events had shortness of breath and flushing that resolved after administration

Table 1. Demographics and Clinical Characteristics

Patient Characteristics	n (%)		
	Cas/Imd (n = 127)	Bam/Ete (n = 9)	Bam (n = 5)
Age, mean $\pm$ SD, yr	15.25 $\pm$ 2.0	16.15 $\pm$ 1.0	15.32 $\pm$ 1.5
Sex			
Male	69 (54.3)	6 (66.7)	2 (40)
Female	58 (45.7)	3 (33.3)	3 (60)
Race			
White	76 (59.8)	3 (33.3)	2 (40)
African American	13 (10.2)	2 (22.2)	0
Hispanic	12 (9.4)	2 (22.2)	2 (40)
Other	4 (3.1)	1 (11.1)	1 (20)
Unknown	18 (14.2)	1 (11.1)	0
No underlying condition	75 (59.1)	5 (55.6)	0
Underlying condition(s)	52 (40.1)	4 (44.4)	5 (100)
Asthma	24 (18.9)	2 (22.2)	3 (60)
Obesity (BMI >30)	13 (10.2)	3 (33.3)	1 (20)
Immunocompromised	7 (5.5)	0	2 (40)
Chronic kidney disease	1 (0.8)	0	0
COVID-19 screening			
Antigen-confirmed COVID-19	95 (74.8)	5 (55.6)	1 (20)
PCR-confirmed COVID-19	30 (23.6)	4 (44.4)	4 (80)
No test done	1 (0.8)	0	0

Bam/Ete, bamlanivimab-etesivimab; BMI, body mass index; Cas/Imd, casirivimab-imdevimab; PCR, polymerase chain reaction

of diphenhydramine and dexamethasone, and infusion was stopped. In comparison, our study had a lower percentage of participants with obesity (80% vs 20.6%) and asthma (43% vs 27.0%).⁹

Compared with our study, other published studies that included higher proportions of immunocompromised pediatric patients suggest that mAbs were less effective and safe for these populations. Despite this, most of their patients experienced improvement of COVID-19 symptoms with mAb infusion. Bahakel et al¹⁰ reported a study of 94 patients ranging in age from 12 to 25 years with a higher percentage of immunocompromised patients than in our study (73% vs 5.7%). However, the percentage of patients with obesity was similar in both studies (26.9% and 20.6%). Of note, mAb therapy had greater efficacy in our population, with escalation of care necessary for only 1.4% of our population, compared with 12.7% of their patients. Patients in our cohort did not experience infusion-related adverse events, compared with a reported 10.1% of patients in their study.¹⁰

Another study, by Sherman et al,¹¹ included 142 patients, with 32% classified as immunosuppressed and 39% classified as obese. They had a higher rate in escalation of care than in our study (6% vs 0.7%). In the study of Sherman et al,¹¹ 4 of the 8 patients admitted in the 30 days post infusion were immunocompromised, while the other 4 had other underlying conditions. None of these patients went to the intensive care unit or died.

Our population did not experience infusion-related adverse events as previously mentioned.

Blind et al¹² included 182 patients ranging in age from 10 months to 21 years with a higher proportion of participants (25%) classified with “severe immunosuppression,” while our study had 5.7% of participants with immunocompromised status. In their cohort, 15 patients experienced ongoing COVID-19 symptoms in the 30 days after infusion—13 sought medical attention (2 went to their primary care provider, 3 received care in the ED, and 8 were hospitalized). One patient died from COVID-19 complications 23 days post infusion. This patient was actively receiving chemotherapy and was severely immunosuppressed. Blind et al¹² also reported 7 patients (4%) with infusion-related adverse events, but all completed their infusion therapy.

The evolution of the pandemic necessitated changes in the guidelines for mAb use. At the time of this writing, mAbs are no longer recommended for treatment of COVID-19 owing to the high mutability of later viral variants. However, these data remain valuable as a bridge in the knowledge gap of how children and adolescents respond to mAb treatment for this viral illness.

Limitations

Limitations of our study include its retrospective design, single center, small sample size, and lack of information regarding subjects' COVID-19 vaccination status. The analysis did not take into consideration

Table 2. Treatment-Related Adverse Events and Escalation of Care			
Age, yr	mAb Received	Primary Underlying Condition	Event
17	Casirivimab-imdevimab	None	Severe vomiting × 3 days post infusion; reported via telephone
12	Casirivimab-imdevimab	Asthma	Nausea and vomiting; reported via telephone within 1 wk after infusion
12	Casirivimab-imdevimab	Asthma, immunocompromised due to azathioprine (taken for Behcet syndrome)	Emergency department visit; diagnosed with bacterial pneumonia 1 day post infusion

mAb, monoclonal antibody

circulating variants of SARS-CoV-2. Additionally, we did not include sotrovimab, an additional mAb approved for treatment of COVID-19.

Conclusions

In summary, single doses of mAb infusion included in our study were well-tolerated therapies for children and adolescents infected with COVID-19 who have at least 1 risk factor for progression to severe disease in our population. Our data suggest that mAbs are safe for use in children and adolescents, as demonstrated through the low rate of adverse events and absence of hospitalizations. It also demonstrates that mAb therapy is effective in preventing hospitalizations and progression of the disease, as only 1 patient required escalation of care due to unresolved COVID-19 symptoms after infusion. It is important to continue surveillance and data collection to monitor the long-term safety and effectiveness of mAb therapies in pediatric patients with COVID-19, particularly in the context of evolving viral variants and treatment guidelines.

Article Information

Affiliations. University of South Florida Morsani College of Medicine (JC, EH), Tampa, FL; Pediatric Infectious Diseases (CE, CG-A), University of South Florida Morsani College of Medicine, Tampa, FL; Department of Pharmacy (NP, KZ), Tampa General Hospital, Tampa, FL.

Correspondence. Claudia Gaviria-Agudelo, MD, MSc; Claudiag13@usf.edu

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Ethical Approval and Informed Consent. The authors assert that all procedures contributing to this work comply with the ethical standards of relevant international guidelines on human

experimentation and have been approved by the appropriate committees at the University of South Florida Morsani College of Medicine and Tampa General Hospital. However, given the nature of this study, informed consent was not required by our institution.

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