SAFETY AND TOLERABILITY OF MONOCLONAL ANTIBODY THERAPIES FOR TREATMENT OF COVID-19 IN PEDIATRIC PATIENTS

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Abstract: There is a little data regarding safety or efficacy of monoclonal antibody treatment for mild-to-moderate COVID-19 in pediatric patients despite it being frequently used in adults. This retrospective study of 17 patients with mild-to-moderate COVID-19 who received monoclonal antibody therapy found that the treatment was well tolerated, safe, and may be effective in halting progression to severe disease.

Key Words: monoclonal antibody, pediatrics, COVID-19

The first reported case of COVID-19, a respiratory disease caused by a novel coronavirus SARS-CoV-2, occurred in December 2019. Since its discovery, the virus has caused a catastrophic pandemic, infected >155 million and resulted in >3 million deaths worldwide.[1] While the pediatric population has not been affected by primary COVID-19 to the same degree as adults, there is substantial morbidity for those with acute disease.[2] In addition to the acute presentation, a portion of pediatric patients also develop a newly described syndrome called multisystem inflammatory syndrome in children (MIS-C), particularly destructive inflammation that affects all organs including the heart.[3] The severity of the pandemic combined with its health and economic toll has made finding treatment and vaccines a pressing issue. This has prompted an unprecedented push for repurposed treatments such as dexamethasone in addition to novel medications and vaccines including remdesivir, convalescent plasma, and monoclonal antibodies.

Three monoclonal antibody treatments were developed for mild- to-moderate COVID-19 infection. Bamlanivimab, also known as LY-CoV555, is a monoclonal antibody developed with a partnership between AbCellera Biologics and Eli Lilly. It was found to be effective primarily in an outpatient setting whereby having received bamlanivimab reduced hospital admission or emergency room visits, while also decreasing the viral load faster than in patients who have not received treatment.[4] Bamlanivimab was later combined with etesevimab as a treatment, with additional randomized controlled trials showing this combination resulted in significant reduction in viral load compared with placebo.[5] Another monoclonal antibody developed for treatment of mild-to-moderate symptoms of COVID-19 infection was casirivimab/imdevimab, also known as REGEN-COV. Produced by Regeneron pharmaceuticals, it is an intravenous infusion of 2 monoclonal antibodies that are directed against the SARS-CoV-2 spike protein.[6] The promising results from early trials of monoclonal antibody treatments prompted the Food and Drug Administration (FDA) to issue an emergency use authorization (EUA) for bamlanivimab ± etesevimab and casirivimab/imdevimab for mild-to-moderate COVID-19 patients who are at risk for severe disease and/or hospitalization but not yet hospitalized.[7,8]

Despite the FDAs EUA regarding monoclonal antibody eligibility criteria, the use and administration in the pediatric population remains limited. This is likely due to a variety of factors including novelty of therapy, logistical limitations and lack of data in the pediatric population. In January 2021, a group of pediatric clinicians including infectious disease, critical care, pharmacy and hematology issued an expert opinion regarding its use in pediatric patients.[9] Based on the lack of pediatric data, their consensus did not recommend routine use of monoclonal antibodies in the pediatric population, even if patients meet the FDA criteria for high-risk of progression to hospitalization or severe disease.[9] This has led to individual centers taking a variety of approaches and also perpetuates the data gaps in the literature regarding tolerability and short-term outcomes of those who received treatment. As such this paper seeks to bridge this gap in monoclonal antibody therapy in pediatric patients and provide data for future use and studies.

METHODS

Patients who received monoclonal antibody infusions for the treatment of mild-moderate COVID-19 at Children's National Hospital located in Washington DC, from December 2020 to April 2021 were included in the review. The criteria for infusion at this institution were patients age 12 years old and older. Patients were referred to the Emergency Department/Infusion center for treatment if advised by their primary care provider and after eligibility and appropriateness of treatment were confirmed by an infectious disease provider. Pertinent patient information and demographics, type of infusion, adverse reactions and subsequent admissions from December 2020 to April 2021 were extracted from their charts. Monoclonal antibody infusion doses and rates were as follows: bamlanivimab 700 mg and casirivimab/imdevimab 2400 mg both infused over 60 minutes, and bamlanivimab 700 mg + etesevimab 1400 mg infused over 30 minutes. All patients were monitored for infusion-related reactions during and at least 60 minutes after infusion.

RESULTS

A total of 17 pediatric patients received monoclonal antibody treatment for SARS-CoV-2. All infusions were administered in the emergency department. The youngest patient was 12 and oldest 20 years old, with the most common comorbidities in this patient population were diabetes and obesity (Table 1). Twelve patients received bamlanivimab, 3 patients received the combination casirivimab/imdevimab and 2 patients received bamlanivimab + etesevimab (Table 2). There were no significant adverse effects or reactions that required cessation of infusion such as anaphylaxis, hypotension or dyspnea (Table 2). Two patients (12%) developed a potential infusion reaction, one having fever and the other a headache. However, these symptoms are difficult to differentiate between medication reaction and COVID-19 symptoms as both are a part of the known symptomology (Table 2). Supportive measures were taken with medications leading to symptom resolution and continuance of transfusion. One of 17 patients (6%), who received bamlanivimab, was readmitted to the hospital 6 days after transfusion and diagnosed with severe COVID-19 pneumonia requiring treatment with remdesivir and dexamethasone. No other patient was readmitted for reasons related to COVID-19 or MIS-C within 30 days after receiving treatment.

TABLE 1. Patient Demographics and COVID-19 Symptomology

Subjects	Age	Sex	Race	Comorbid Conditions	COVID Symptoms
Patient 1	20	M	Caucasian	T1DM	Headache, cough, congestion
Patient 2	15	F	Black	T1DM	Anosmia, ageusia, fatigue, pharyngitis, rhinorrhea
Patient 3	13	F	Other	chronic neutropenia, asthma, obesity	Cough, myalgia, headache, fatigue, fever
Patient 4	20	F	Black	Addison's disease, asthma, GI dysfunction, migraine, obesity, POTS, visceral hyperalgesia	Cough, fever, headache
Patient 5	15	F	Caucasian	Celiac, T1DM	Headache, pharyngitis, myalgia
Patient 6	12	F	Hispanic	T1DM	Fever, pharyngitis, myalgia
Patient 7	13	M	Black	Stickler syndrome, asthma, hypertension, obesity	Cough, dyspnea
Patient 8	17	M	Caucasian	T1DM	Anosmia, ageusia, headache, fatigue, myalgia
Patient 9	17	M	Black	Asthma, hypertension, obesity	Anosmia, pharyngitis, chest pain, headache, fatigue, myalgia
Patient 10	17	M	Black	Obesity, T2DM	Abdominal pain, fatigue
Patient 11	17	F	Black	Trisomy 21, ASD, VSD, pHTN, OSA, asthma, obesity	Cough
Patient 12	17	F	Black	Asthma, obesity	Pharyngitis
Patient 13	17	F	Black	Obesity, T2DM	None—symptoms not recorded
Patient 14	15	M	Black	Obesity, T2DM	None—symptoms not recorded
Patient 15	19	M	Black	Asthma, obesity	Headache, cough, diarrhea, dyspnea,
Patient 16	13	M	Black	Asthma, obesity	Chest pain, congestion, cough, dyspnea, fever, headaches, myalgias, pharyngitis
Patient 17	14	M	Black	Corpus callosum agenesis, obesity	Fever, myalgias

F indicates female; M, male; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

DISCUSSION

Monoclonal antibodies may be an important tool in the struggle against COVID-19 in pediatrics as timing of vaccine eligibility, vaccine uptake in the younger age groups and vaccine responses in immunocompromised population remains unknown. Despite EUA approval on November 2020, our literature review found no documentation of monoclonal antibody treatment for mild-to-moderate SARS-CoV-2 infection in pediatric patients. The data from Children's National Hospital at the height of the pandemic in March through April 2020 calculated a hospitalization rate of approximately 25% of all positive tests in our pediatric community with 80% of the patients hospitalized for COVID-19 pneumonia or MIS-C requiring critical care.[2] Despite the lower morbidity and mortality compared with adult patients, this still involves significant healthcare resources and may entail unknown long-term consequences. Our limited number of 17 patients shows that monoclonal antibody treatment for mild-to-moderate SARS-CoV-2 infection was well tolerated and may be effective in halting progression to severe disease and prevention of hospitalization. Only one patient (6%) in our cohort of high-risk patients required admission. This particular patient had significant congenital cardiac disease and multiple comorbidities such as pulmonary hypertension and obesity and ultimately led to prolonged hospitalization with a significant portion requiring intensive care. However, these results should be interpreted with caution as there are significant limitations in this case series. Sample size is small and there are several potential confounders including variation in viral strain, utilization of different monoclonal antibodies given changing EUA's, and possibility that patients were admitted to a different institution than where they received the infusion. Long-term follow up data are also needed, particularly in evaluation for subsequent impact on development of MIS-C. Despite these limitations, these cases do provide information and data in the pediatric literature and will support pediatric specific trials.

Since pediatric clinical trials on novel medications and interventions are lacking, formal guidelines and recommendations are unable to provide any guidance citing the lack of data. The lack of formal guidance generates little enthusiasm for providers to justify use of these medications and treatment which in turn perpetuates the lack of data. This creates a continuous cycle of sparse data and lack of guidelines

TABLE 2. Monoclonal Antibody Treatment Information

	Days of Symptoms	Days From Positive Test to Treatment	Medication Received	Infusion Reactions	30-d Admission
Patient 1	3	3	Bamlanivimab	None	N
Patient 2	Not reported	0	Bamlanivimab	None	N
Patient 3	2	0	Bamlanivimab	Headache	N
Patient 4	3	0	Bamlanivimab	Fever	N
Patient 5	3	0	Bamlanivimab	None	N
Patient 6	2	0	Bamlanivimab	None	N
Patient 7	Not reported	1	Bamlanivimab	None	N
Patient 8	2	1	Bamlanivimab	None	N
Patient 9	2	2	Bamlanivimab	None	N
Patient 10	5	0	Bamlanivimab	None	N
Patient 11	1	0	Bamlanivimab	None	Y
Patient 12	1	1	Bamlanivimab	None	N
Patient 13	0	0	Casirivimab/imdevimab	None	N
Patient 14	0	0	Casirivimab/imdevimab	None	N
Patient 15	7	2	Casirivimab/imdevimab	None	N
Patient 16	3	1	Bamlanivimab/etesevimab	None	N
Patient 17	1	1	Bamlanivimab/etesevimab	None	N

N, No; Y, Yes.

for frontline providers. While our data is limited, this article provides preliminary information for future studies of antibody treatment for a disease that carries a significant morbidity in the pediatric population.

REFERENCES

1. CDC. COVID Data Tracker 2021. Available at: https://covid.cdc.gov/covid-data-tracker/#datatracker-home2021. Accessed April 20, 2021.

2. DeBiasi RL, Song X, Delaney M, et al. Severe coronavirus disease-2019 in children and young adults in the Washington, DC, metropolitan region. *J Pediatr*. 2020;223:199-203 e191.

3. Feldstein LR, Tenforde MW, Friedman KG, et al; Overcoming COVID-19 Investigators. Characteristics and outcomes of US children and adolescents with multisystem inflammatory syndrome in children (MIS-C) compared with severe acute COVID-19. *JAMA*. 2021;325:1074–1087.

4. 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;384:229–237.

5. 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;325:632–644.

6. 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;384:238–251.

7. An EUA for bamlanivimab and etesevimab for COVID-19. *Med Lett Drugs Ther*. 2021;63:49–50.

8. An EUA for casirivimab and imdevimab for COVID-19. *Med Lett Drugs Ther*. 2020;62:201–202.

9. Wolf J, Abzug MJ, Wattier RL, et al. Initial guidance on use of monoclonal antibody therapy for treatment of coronavirus disease 2019 in children and adolescents. *J Pediatric Infect Dis Soc*. 2021;10:629–634.

LONG COVID IN CHILDREN

Observations From A Designated Pediatric Clinic

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Abstract: Systematic data are lacking on pediatric long COVID. This study prospectively assessed 90 children with persistent symptoms who presented to a designated multidisciplinary clinic for long COVID. In nearly 60%, symptoms were associated with functional impairment at 1–7 months after the onset of infection. A comprehensive structured evaluation revealed mild abnormal findings in approximately half the patients, mainly in the respiratory aspect.

Key Words: bronchodilator, lung function, postacute sequelae of severe acute respiratory syndrome coronavirus 2 infection, respiratory

Long-term follow-up of adults diagnosed with acute coronavirus disease 2019 (COVID-19) has shown that a substantial proportion experience persisting symptoms months after the initial diagnosis.[1,2] To date, systematic data are lacking on long COVID or postacute sequelae of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children.[3] We prospectively analyzed persistent symptoms in children who recovered from COVID-19, and described the diagnostic yield of a comprehensive clinical evaluation.

METHODS

This study prospectively assessed children ≤18 years of age who presented to a designated multidisciplinary clinic for long COVID, at a tertiary pediatric center, from November 2020 to April 2021, following referral by their general practitioner. SARS-CoV-2 infection was microbiologically confirmed by real-time quantitative reverse transcription polymerase chain reaction during acute infection or by subsequent serology using an in-house enzyme-linked immunosorbent assay (The Central Virology Laboratory of the Ministry of Health at Sheba Medical Center, Tel Hashomer) until mid-March and Abbot ARCHITECT SARS-CoV-2 IgG Immunoassay, thereafter. All the patients underwent a structured evaluation >4 weeks from diagnosis. This included assessment of symptoms and their impact on daily activities by means of a structured interview conducted by a senior pediatrician with >10 years' experience; a physical examination, blood tests, electrocardiograph and a chest radiograph. In the event of cardiorespiratory symptoms, a pulmonary function test (for children older than 6 years) and echocardiography were performed. Further testing, such as bronchodilator response testing and cardiac magnetic resonance imaging (MRI), was done following abnormal findings on the initial evaluation. Additionally, data on background illnesses and on acute COVID-19 disease were retrieved from patients' electronic files. Severity of the acute COVID-19 disease was classified according to the National Institute of Health symptom severity criteria.[4]

Persistent symptoms were stratified by age (≤11 versus >11 years) and compared by χ^2 (IBM SPSS Statistics, Version 22.0). Written informed consent was obtained from parent or legal guardian; the study was approved by the institutional review board (RMC-20-0885).

RESULTS

Ninety children, mean age 12 ± 5 years, were assessed at a median of 112 days (range: 33–410) after COVID-19 diagnosis. One adolescent who tested positive for COVID-19 was excluded from the analysis because during the initial evaluation, diabetic ketoacidosis was diagnosed; following medical care, his symptoms of fatigue and weight loss resolved. The cohort comprised mainly previously healthy children who exhibited a mild symptomatic acute disease (Table 1). The sex ratio showed a minor male predominance. Twenty-five percent were overweight, with a body mass index >85th percentile for age, in accordance with national published rates.[5] The most common reason for patient referral was dyspnea (30, 33.3%), followed by myalgia (12, 13.3%) and headache (8, 8.8%).

The median number of reported symptoms was 4 (range: 1–14). Fatigue (64, 71.1%), dyspnea (45, 50.0%) and myalgia (41, 45.6%) were the most frequently reported symptoms, and were significantly associated with older age >11 years (Table 1, Supplemental Digital Content 1, http://links.lww.com/INF/E492). Additional persistent symptoms included sleep disturbances (30, 33.3%), chest pain (28, 31.1%), paresthesia (26, 28.9%), headache (26, 28.9%), hair loss (24, 26.7%), anosmia-ageusia or parosmia/euosmia (23,25.6%), gastrointestinal symptoms (18, 20.0%), dizziness (17, 18.9%), weight loss of >5% of body weight (17, 18.9%), memory impairment (16, 17.8%), vasomotor complaints