Single Site Experience of the use of Monoclonal Antibodies for the Treatment of COVID-19 in High-risk Pediatric and Young Adult Patients

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Background: Effective therapeutic agents for the treatment of COVID-19 have been investigated since the onset of the pandemic. Monoclonal antibodies targeting the spike protein of SARS-CoV-2 have been developed for the treatment of mild or moderate COVID disease in high-risk populations. Despite widespread use in the adult population, data are limited on the safety and efficacy of monoclonal antibody infusions in the adolescent and young adult population.

Methods: Patients who received bamlanivimab, bamlanivimab-etesevimab, casirivimab-imdevimab, or sotrovimab for treatment of mild-to-moderate COVID-19 disease at Cincinnati Children's Hospital Medical Center from 5/1/2020 to 3/1/2022 were identified retrospectively. Patient data including demographics, adverse events, and outcomes were extracted from patients' charts and summarized by standard descriptive summaries.

Results: Ninety-four patients received monoclonal antibody therapy, of which 14 (14.9%) received either bamlanivimab or bamlanivimab-etesevimab, 54 (57.4%) received casirivimab-imdevimab, and 26 (27.6%) received sotrovimab. Ten patients (10.6%) experienced one or more infusion-related adverse event. Of the patients who experienced adverse events, all resolved with cessation of infusion. No life-threatening events or deaths occurred. Within 90 days of receiving a monoclonal antibody, 12 patients (12.7%) required additional medical care for ongoing COVID symptoms. Five of these were either hospitalized or received escalation of care while already in the hospital. All subsequently fully recovered. Neither infusion-related adverse events nor progression to hospitalization for ongoing COVID-19 symptoms following monoclonal antibody administration were associated with any particular underlying condition.

Conclusions: Overall, monoclonal antibodies are reasonably well-tolerated COVID-19 therapies in high-risk adolescent and young adult populations.

Key Words: COVID-19, pediatrics, monoclonal antibodies

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SARS-CoV-2, a novel coronavirus responsible for COVID-19 disease, has spread rapidly world-wide and led to a devastating pandemic.[1] Effective therapeutic agents for the treatment and prevention of COVID-19 have been investigated since the onset of the pandemic. Four neutralizing monoclonal antibodies targeting the spike protein of SARS-CoV-2 have been developed and provided emergency use authorization (EUA) status by the U.S. Food and Drug Administration (FDA) for the treatment of mild or moderate COVID-19 disease in high-risk patients aged 12 years and older.[2,3] While there are numerous published reports of the safety and effectiveness of COVID-19 monoclonal antibodies in adults, scant information exists regarding use of the products in the adolescent or young adult population.[4,5] Due to the paucity of pediatric-specific evidence and absence of clinical trials, comprehensive guidelines for the usage of monoclonal antibodies are not available. Therefore, we describe the experience using monoclonal antibodies in high-risk pediatric and young adults to treat COVID-19.

METHODS

Patients who received monoclonal antibody infusions for the treatment of mild-to-moderate COVID-19 disease or as post-exposure prophylaxis as permitted by EUA at Cincinnati Children's Hospital Medical Center (CCHMC) from 5/1/2020 to 3/1/2022 were included in this retrospective chart review. In accordance with the FDA EUA directive, patients were eligible for monoclonal antibody administration if they were >12 years of age, weighed >40 kg, and were at high risk of progressing to severe disease or hospitalization. Patients were considered high risk if at least one of the following comorbidities were present: elevated BMI (>85th percentile for their age/gender based on CDC growth charts), chronic kidney disease, diabetes, immunosuppressive disease or currently receiving immunosuppressive treatment, sickle cell disease, congenital or acquired heart disease, neurodevelopmental disorders (e.g. cerebral palsy), dependency on medical-related technology (e.g. tracheostomy or positive pressure ventilation), asthma or other chronic respiratory disease. To ensure judicious use of the limited supply of monoclonal antibodies, requests for use were screened by a multidisciplinary group of health care practitioners (the COVID-19 Treatment Team) composed of infectious diseases physicians, oncologists, rheumatologists, as well as an infectious diseases-trained pharmacist. Patients who were unvaccinated with at least one risk factor and those who were vaccinated with 2 or more risk factors were prioritized due to intermittent limitations in product availability.

During the period of review covered by this report, depending on availability and the circulating variant of SARS-CoV-2, patients received bamlanivumab, bamlanivumab-etesevimab, casirivimab-imdevimab, or sotrovimab. Bamlanivumab alone was used from the time of authorization until the emergence of new variants that led to the revocation of the EUA for bamlanivimab alone on November 9, 2020. At that time, treatment was transitioned to bamlanivimab in combination with etesivamb until the

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emergence of the Delta variant, which became the dominant strain worldwide by July 2021.[6] During the Delta variant surge, casirivimab-imdevimab retained efficacy and was the primary monoclonal antibody used for the outpatient treatment of COVID-19.[7] In November 2021, the B1.1.529 Omicron variant was first reported and led to treatment failure with casirivimab-imdevimab; thus, in December 2021, sotrovimab became the predominant monoclonal antibody administered.

Patient data including demographics, comorbid conditions, onset and severity of symptoms, diagnostics, and infusion-related adverse events and outcomes were extracted from the patients' charts and summarized by standard descriptive summaries. Adverse events were independently graded by 2 investigators using the Common Terminology Criteria for Adverse Events.[8] Discrepancies were adjudicated by a third independent reviewer. Categorical variables were summarized by frequencies while continuous variables were summarized using mean, standard deviation and/or median, 25th and 75th percentiles, minimum, and maximum. The protocol was reviewed and approved by CCHMC's Institutional Review Board and a waiver of consent was provided.

RESULTS

Patient Demographics and Clinical Characteristics

During the study period, the COVID-19 Treatment Team approved the use of monoclonal antibodies in 104 adolescents and young adults. Patients ranged in age from 12 years to 25-years old and were composed of 60 females (57.7%). The most common presenting symptoms were fever, cough, congestion/rhinorrhea, and headache. Comorbidities of the study population are shown in Table 1. The most common comorbidity was "immunocompromised status" (n = 76, 73%), followed by congenital heart disease (n = 9, 8%) and diabetes mellitus (n = 6, 5.7%). Thirty-three patients (31.7%) had more than one comorbid condition. On average, patients in this report were symptomatic 2.5 days at the time of COVID-19 diagnosis, and another 1.6 days elapsed between COVID-19 diagnosis and infusion of monoclonal antibody therapy. Ten families elected not to proceed with the approved treatment resulting in 94 patients receiving an infusion of monoclonal antibodies. The most commonly infused product was casirivimab-imdevimab (n = 54, 57% of patients) followed by sotrovimab (n = 26, 28%) and either bamlanivimab monotherapy or the combination of bamlanivimab-etesevimab (n = 14, 15%).

TABLE 1. Study Population Demographics

Characteristics	Number of Patients (Percentage), Unless Otherwise Specified (N = 104)
Age in years, mean + SD	17.5 + 3.2
Male sex	44 (42.3%)
Race or ethnic group	
Native American/Alaska Native	1 (0.96%)
Asian	2 (1.9%)
Black	12 (11.5%)
Middle Eastern	2 (1.9%)
White	86 (82.7%)
Mixed Race	1 (0.96%)
Hispanic	2 (1.9%)
Body mass index, mean + SD	28.8 + 19.9
Immunocompromised	76 (73%)
Cardiac disease	9 (8%)
Diabetes mellitus	6 (5.7%)
Obesity	28 (26.9%)
Pulmonary disease	8 (7.7%)
>1 co-morbid condition	33 (31.7%)
Time between COVID diagnosis and MAB treatment in days; mean ± SD	1.6 + 1.3 7 (6.7%)
Vaccinated (at least 2 doses of vaccine received)	43 (41.3%)
Received for post-exposure prophylaxis	7 (6.7%)
Monoclonal antibody treatment	94 (90.4%)
Bamlanivimab or bamlanivimab-etesivimab	14 (13.5%)
Casirivimab-imdevimab	54 (51.9%)
Sotrovimab	26 (25%)

Outcomes Post-Monoclonal Antibody Infusion

At the time of monoclonal antibody infusion, 89 patients were in the outpatient setting while 5 were hospitalized for reasons unrelated to COVID-19 infection. Due to hospital policy, all patients in our report received their monoclonal antibody infusion at our inpatient infusion center. After completion of the infusion, all 89 outpatients were discharged to home. Within 90 days after infusion, 12 (13.5%) of the patients in the outpatient setting had persistence or worsening of their COVID-19 symptoms, which led to re-access of the medical system (Table 2). Seven of the 12 were evaluated in the clinic or Emergency Department and discharged home while 5 required hospitalization with subsequent full recovery. The range of time between monoclonal antibody administration and subsequent admission for ongoing COVID-19 symptoms was 3 days to 3 weeks. Four of the 5 patients were admitted 3–7 days following monoclonal antibody administration. Of the patients who required escalation in care or re-access of the medical system following monoclonal antibody administration, 2 received bamlanivimab or bamlanivimab-etesivimab (13.3%), 8 received casirivimab-imdevimab (53.3%), and 5 received sotrovimab (33.3%). No specific underlying conditions were found to be associated with progression to hospitalization following monoclonal antibody administration, and no specific monoclonal antibody conferred a higher risk for breakthrough need for care.

Of the patients who received monoclonal antibody infusion while admitted for reasons unrelated to COVID infection, 3 required escalation of care post infusion, 2 of whom required transfer to the pediatric intensive care unit (PICU). Of these 3 patients, 2 required escalation of care due to side effects of monoclonal antibody, and one required escalation of care involving transfer to the PICU several days following infusion for progression of COVID-19 symptoms. The patient who required transfer to the PICU for progression of COVID-19 symptoms was additionally treated with 2 doses of remdesivir 17 days after bamlanivumab infusion and another dose of remdesivir 45 days after bamlanivimab infusion. In

TABLE 2. Frequency and Severity of Adverse Events and Subsequent Events Requiring Medical Attention

Adverse Events (Anaphylaxis, Infusion Reactions)	10 (10.6%)
Grade I	6 (60%)
Grade II	3 (30%)
Grade III	1 (10%)
Adverse events with bamlanivimab or bamlanivimab-etesivimab	2 (14.3%)
Adverse events with casirivimab-imdevimab	7 (12.9%)
Adverse events with sotrovimab	1 (3.8%)
Subsequent event requiring medical attention	15 (15.9%)
ED/urgent care	4 (4.2%)
Primary care provider	3 (3.2%)
Escalation of care in patient already admitted	3 (3.2%)
Subsequent hospitalization related to ongoing COVID symptoms	5 (5.3%)

both instances, remdesivir was discontinued due to elevated liver enzymes. One patient received hydrocortisone for an infusion-related reaction and was able to remain on the inpatient floor.

Of the 10 patients who declined therapy, 3 sought further medical care for COVID-related symptoms. Two were evaluated in an urgent care or emergency department and discharged home with supportive care, one was evaluated on 2 subsequent occasions by their primary care physician and was also managed symptomatically.

Seven patients received casirivimab-imdevimab for post-exposure prophylaxis. One patient of the 7 who received monoclonal antibody for prophylaxis subsequently developed acute COVID infection 2 months after antibody infusion.

Adverse Events

Ten of the 94 patients (10.6%) experienced some form of an infusion-related adverse event (Table 2). The frequency of infusion-related adverse events ranged from 1 of 26 (3.8%) for sotrovimab to 2 of 14 (12.9%) for bamlanivimab (comprising bamlanivimab or bamlanivimab-etesivimab) and 7 of 54 (12.9%) who received casirivimab-imdevimab. Due to the small sample size, statistical comparison of frequency of infusion-related reactions between the groups was not performed. The most common infusion-related reactions were rash, nausea, and throat irritation. Six of the reactions were graded as Grade 1 (mild), 3 as Grade 2 (moderate), and only one as Grade 3 (severe) due to severe abdominal pain requiring morphine and hypoxia requiring supplemental oxygen (Table 2). No deaths or life-threatening events occurred with monoclonal antibody administration. All infusion-related adverse events resulted in early cessation of monoclonal antibody infusion. Regardless of the severity, there was rapid resolution of the event with cessation of infusion.

Neither the likelihood nor the severity of an infusion-related reaction appeared to be related to obesity, diabetes, immunocompromised status, sickle cell disease, congenital or acquired heart disease, neurodevelopmental disorders, asthma, or other chronic respiratory disorders.

DISCUSSION

To our knowledge, this is the first report of a large series of adolescents and young adults who received monoclonal antibody infusion for the prevention/treatment of COVID-19 and thus contributes much needed data regarding the safety and tolerability of these novel therapeutics in this vulnerable population. Our single-center retrospective study suggests that monoclonal antibodies were generally well tolerated. We noted a higher incidence of infusion-related events than has been reported in the adult literature. Of the 10 events in our population, 6 were mild and only one was classified as severe.[9–11] All of the events resolved soon after the infusion was discontinued. The reason for our higher incidence of infusion-related adverse events is unclear, as no particular underlying risk factor was identified that was associated with a higher risk of infusion-related reactions.

As COVID-19-specific antiviral therapy is extremely limited, and vaccines require weeks to achieve full efficacy, monoclonal antibody therapy has played an important role in the prevention and treatment of COVID-19 in high-risk patients. However, unlike vaccines that stimulate a polyclonal response of both B- and T-cells, monoclonal antibodies, as their name indicates, focus on a single target.[12] SARS-CoV-2 is an RNA virus and similar to other RNA viruses, commonly mutates.[13] Mutation within the region of monoclonal antibody binding could translate to decreased effectiveness of the monoclonal antibody formulation. This possibility unfortunately became reality as new variants of SARS-CoV-2 arose. Initially, the monoclonal antibody preparations bamlanivimab and etesevimab demonstrated benefit; however, this waned as variants arose requiring a shift to utilization of casirivimab-imdevimab.[6,14] While casirivimab-imdevimab remained an effective therapy for high-risk outpatients with mild-to-moderate infection with the SARS-CoV-2 delta variant, it too lost effectiveness with the emergence of B.1.1.529 (Omicron variant). Although the mutations in the Omicron variant had proven resistant to most available monoclonal antibodies, sotrovimab retained efficacy until the arrival of the COVID-19 omicron BA.2 subvariants.[7,15] The emergence of these variants continues to negatively affect therapeutic use of available monoclonal antibodies; however, Ly-CoV1404, also known as bebtelovimab, is a fully human monoclonal antibody that, to date, potently neutralizes all currently known variants of concern of SARS-CoV-2.[16] Additionally, the combination of 2 monoclonal antibodies (tixagevimab co-packaged with cilgavimab) was recently approved for pre-exposure prophylaxis for COVID-19 in high-risk patients and appears to be a promising preventative option for pediatric and adult populations who are unable to mount an immune response to vaccination and remain at an increased risk of severe COVID-19 disease.[17] Unfortunately, this product only became available for use at our institution as our study period was concluding, thus only 3 of the patients in our cohort received tixagevimab-cilgavimab for pre-exposure prophylaxis during the study period.

While monoclonal antibody administration has been demonstrated in adult outpatients to be efficacious in preventing disease progression leading to hospitalization, our findings suggest the same may not be true for adolescents and young adults.[9–11] As compared to hospitalization rates of 1–3% for worsening COVID-19 symptomatology post-monoclonal antibody infusion in adults, 5 (5.3%) of the patient in our report subsequently were hospitalized for ongoing or worsening COVID-19 symptoms.[9–11] While our findings may not be generalizable, at the minimum they demonstrate that further studies are needed to fully define the safety and efficacy of monoclonal antibody therapy in the pediatric population.

Limitations and potential confounders of this report include a small sample size, emergence of SARS-CoV-2 variants, which may have resulted in administration of less effective products, under-reporting of access of medical care postinfusion and minimal racial and ethnic diversity (reflective of the demographics of the treating institution). As the molecular epidemiology of SARS-CoV-2 was followed closely by the COVID-19 Treatment Team and product administration adjusted as variants arose, we think our results closely mirror monoclonal antibody use in the U.S. Because the overwhelming majority of patients in the study had a long-term relationship with the treating hospital, as well as the hospital being the primary pediatric treatment facility within a 100-mile radius, we believe very few, if any, medical visits (particularly hospitalizations) were missed.

In summary, we have shown that monoclonal antibody administration to adolescents and young adults for the prevention/treatment of COVID-19 is generally safe and may be effective to decrease the progression of COVID-19 disease.

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Current Abstracts

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Increased Incidence of Invasive Pneumococcal Disease among Children after COVID-19 Pandemic, England

Bertran M, Amin-Chowdhury Z, Sheppard CL, et al. Emerg Infect Dis 2022;28:1669–1672

The Coronavirus disease 2019 (COVID-19) pandemic and its associated lockdowns, social isolation and other interventions led to large declines in respiratory infections, including invasive pneumococcal disease (IPD). In England, IPD cases declined by 30% after the first lockdown in March 2020 and remained low during the subsequent winter until February 2021, when cases increased by 8% above the 3-year pre-pandemic mean incidence for February. As the country ended its third national lockdown in March 2021, after the emergence of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Alpha variant, IPD cases started to gradually increase. By June 2021, case numbers remained 25% lower than prepandemic levels, but a proportionately higher increase in cases among children <15 years of age was observed. IPD trends during July–December 2021, after England removed all COVID-19 control measures on July 19, 2021 are described.

IPD cases during July–December 2021 were compared to July–December 2020 and July–December in 3 pre-pandemic years (2017–2019) by using national enhanced surveillance data for England. During July–December 2021, a total of 1632 IPD cases were reported to the United Kingdom Health Security Agency, compared with a mean of 2403 during July–December of 3 pre-pandemic years, 2017-2019. Among children <15 years of age, the number of IPD cases and incidence (cases per 100,000 children) declined by 50% (n = 71) during July–December 2020 but gradually increased in February 2021 and remained above the 3-year pre-pandemic mean of 145 cases (incidence 1.43, 95% CI: 1.21–1.68) during July–December 2021 (n = 200; 1.96, 95% CI: 1.70–2.25). Case rates rose earlier in younger age groups among whom incidence was highest during this period: 10.63 (95% CI: 8.19–13.58) among <1-year olds; 3.22 (95% CI: 2.57–3.98) among 1–4 year-olds; 1.02 (95% CI: 0.71–1.41) among 5–9-year-olds; and 0.44 (95% CI: 0.24–0.72) among 10–14 year-olds. Cases also increased (n = 1432) among persons >15 years old during February–December 2021, but the incidence during July–December 2021 remained lower (2.60, 95% CI: 2.47–2.74) than the prepandemic mean during July–December in 2017–2019 (4.14, 95% CI: 3.97–4.32).

Age distribution of childhood IPD cases resembled the prepandemic period ($p = 0.08$): 32% of cases were among <1-year-olds, 42.5% among 1–4 year-olds, 18% among 5–9 year-olds, and 7.5% among 10–14 year-olds. Of 172 (86%) pneumococcal isolates serotyped, no difference in serotype distribution between years or within age groups was noted. The most frequent serotypes among childhood cases remained similar in 2021 to those in pre-pandemic years.

More IPD cases in 2021 involved bacteremia (50/125, 40%) compared with the prepandemic period (105/422, 25%). The proportion of cases with meningitis (22%), pneumonia (31%) and other clinical manifestations (7%) were not substantially different. The prepandemic and postpandemic 30-day fatality rates were also similar (5% vs. 4%, $p = 0.6$)

Comment: After lifting COVID-19 social restrictions, England experienced an increase in childhood IPD cases that exceeded prepandemic levels. England's pandemic social restrictions led to large declines in many infectious diseases, including IPD. Reduced social contact and exposure to respiratory pathogens have led to concerns of immunity debt and risk for higher infection rates as restrictions are lifted globally. Immunity debt is typified in the emergence of respiratory viruses outside their typical season, as observed with the respiratory syncytial virus. Of note, respiratory virus infections that usually peak in winter (eg, influenza and rhinovirus) remained low during winter 2021–2022.

In the United Kingdom, the 13-valent pneumococcal conjugate vaccine (PCV13) vaccination schedule for infants born after January 1, 2020, was changed from a 2 + 1 schedule (8 weeks, 16 weeks and 1 year) that had been in place since 2010 to a reduced 1 + 1 schedule (12 weeks and 1 year). This change was made on the basis that most protection is through the indirect herd or population protection offered by preventing carriage among toddlers, thus interrupting transmission to others. However, the program relies on maintaining high vaccine coverage in infants to provide adequate population protection.

In England, PCV13 coverage data for the 12-month dose were not available 2020–2021 during this study, but uptake of other childhood vaccines was lower after the pandemic started and improved during August–December 2021. Because of the COVID-19 pandemic restrictions, evaluation of the effect of the 1 + 1 schedule is not yet possible. Maintaining high PCV13 uptake is critical for ongoing population protection.