Treatment of Infants and Children With SARS-CoV-2 Monoclonal Antibodies: A European Case Series

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Background: Although severe COVID-19 in children is rare, those with certain pre-existing health conditions are more prone to severe disease. Monoclonal antibodies (mAbs) against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are potent antiviral agents that reduce adverse clinical outcomes in adults, but are commonly not approved for use in pediatric patients.

Methods: We retrospectively evaluated mAb treatment in children <12 years of age or <40kg with SARS-CoV-2 infection between January 1, 2021, and March 7, 2022, in 12 tertiary care centers in 3 European countries.

Results: We received data from 53 patients from Austria, Denmark and Germany. Median age was 5.4 years [0–13.8, interquartile range (IQR) = 6.2], and median body weight was 20 kg (3–50.1, IQR = 13). The most frequent SARS-CoV-2 variant in this study, if known, was Omicron, followed by Delta and Alpha. Pre-existing conditions included immunodeficiency, malignancy, hematologic disease, cardiac disease, chronic lung disease, chronic liver disease, kidney disease and diabetes. Forty-two patients received sotrovimab (79%), 9 casirivimab/imdevimab (17%) and 2 bamlanivimab (4%). All but 1 patient survived. Median duration of hospital stay was 3 days (0–56, IQR = 6). Seven patients required treatment in an intensive care unit, and 5 required high-flow nasal cannula treatment. Potential side effects included neutropenia (6/53, 11%), lymphopenia (3/53, 6%), nausea or vomiting (2/53, 4%), rise of alanine transaminase (1/53, 2%) and hypotonia (1/53, 2%).

Conclusions: MAb treatment was well tolerated by children in this cohort.

Key Words: SARS-CoV-2, COVID-19, children, treatment, monoclonal antibodies

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Following reports from China of an unusual cluster of pneumonia in the late 2019, a previously unknown beta coronavirus was discovered, later named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for a disease known as coronavirus disease 2019 (COVID-19). In March 2020, the World Health Organization declared a global pandemic. Since then, reported COVID-19 cases have exceeded 590 million globally, causing >6.4 million deaths.[1] Most severe cases and deaths occur in older age groups, while most children and young people (CYP) only develop mild disease, and approximately one-third of cases stay asymptomatic.[2,3] In adults, several underlying health conditions are associated with a high risk for severe COVID-19. In contrast, no definite risk factors have been defined in children. Nonetheless, immunodeficiency, chronic lung disease, including severe asthma, and heart disease have been described as potential risk factors in CYP.[4] With the emergence of more transmissible virus variants of concern, pediatricians face increasing case numbers and hospitalizations worldwide.[5–8] In addition to antiviral drugs, treatment with monoclonal antibodies (mAbs) against SARS-CoV-2 key protein structures play an important role in immune naïve high-risk individuals. The European Medicines Agency authorized the use of casirivimab/imdevimab, sotrovimab and regdanvimab to treat mild-to-moderate SARS-CoV-2 infections in an outpatient setting.[9] Among various antibodies, bamlanivimab, bamlanivimab/etesevimab and sotrovimab were cleared for usage in patients above 12 years of age and 40 kg of body weight. To date, there are no valid data on the use of these mAbs in younger children who have not been vaccinated against SARS-CoV-2 or were unable to mount immune response

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and could potentially benefit from passive immune therapy.[9,10] The main concern of mAb treatment in children is that the risks of potential side effects, unknown due to data scarcity, or side effects seen in adults (eg, hypotension, drug-related anaphylaxis, etc.) may outweigh the marginal benefit of its application in children who show lower mortality and morbidity associated with COVID-19 compared with adults.[11] In adults, mAB treatment has been studied more extensively and there exists higher quality evidence on drug safety, indications and dosage regimens, especially in patients prone to severe disease.[12] This study aimed to synthesize the experience with providing mAbs against SARS-CoV-2 to children infected with SARS-CoV-2 below 12 years of age or CYP below 40 kg of body weight in Europe, focusing on safety.

MATERIALS AND METHODS

Study Design

We conducted a retrospective, observational cohort study in pediatric patients with SARS-CoV-2 infection in tertiary care centers in Europe who received mAbs against SARS-CoV-2. Building on partnerships established through the Paediatric Tuberculosis Network European Trials Group (ptbnet), the European Society for Paediatric Infectious Diseases and national pediatric infectious disease societies, we contacted twelve centers in Austria (Graz and Vienna), Germany (Berlin, Bochum, Cologne, Frankfurt, Hamburg and Munich) and Denmark (Aarhus and Copenhagen).

Inclusion Criteria

We included patients below 12 years of age or below 40 kg body weight with SARS-CoV-2 infection [confirmed via real-time polymerase chain reaction (rtPCR) testing of either nasopharyngeal, oropharyngeal or tracheobronchial samples, or viral RNA detection in the blood] receiving mAbs between January 1, 2021, and March 7, 2022, at participating study sites.

Ethical Considerations

The study protocol was approved by the human research ethics committee of the city of Vienna and according to local policies, by institutional review boards of the participating centers. All investigators adhered to the declaration of Helsinki and good clinical practice guidelines. All patients in this cohort were treated with mAbs because of local guidelines at the time or due to clinical judgment of the treating team. The legal caregivers gave written informed consent for the off-label use of the drug. Additionally, informed consent was obtained regarding the use of retrospective data for anonymized analysis if required by local regulations. All data were collated retrospectively, entered into a password protected case report form, and transferred to the principal investigators for subsequent analysis.

Statistical Analysis

Patient parameters were extracted from routine medical charts and included in the case report form. We regarded SARS-CoV-2 infection and mAb treatment as exposure, and investigated the occurrence of adverse events as primary outcome. Adverse events studied included intensive care unit (ICU) treatment, high-flow nasal cannula treatment, neutropenia <0.5 billion/L, lymphopenia <0.2 billion/L, alanine transaminase rise over 3 times upper limit of normal, thrombosis, chills, nausea or vomiting, bronchospasm, hypotonia, allergic reaction, anaphylaxis and death. Descriptive results are presented as proportions (%) for categorical variables, and medians and interquartile range (IQR) for continuous variables. All analyses were performed using the R language for statistical computing version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria) and Exploratory software version 6.9.4 (Exploratory Inc., Mill Valley, CA).

Role of the Funding Source

The study did not receive funding from any third party.

RESULTS

Data Availability

We received patient data from 4 study centers in Austria, 2 in Denmark and 6 in Germany. All 53 reported cases met the inclusion criteria. Of these, 27 cases were reported from centers in Austria (51%), 20 from Germany (38%) and 6 from Denmark (11%).

Patient Characteristics

Median patient age was 5.4 years (range 0–13.8, IQR = 6.2) with 4 patients under 6 months of age (8%), 3 patients between 6 months to under 2 years (6%), 16 patients between 2 and <5 years (30%), 26 patients between 5 and <12 years (49%) and 4 cases 12 years and older (8%). The majority of patients were male (58%). Only 2 patients had received prior COVID-19 vaccination (4%).

In 17 patients, the SARS-CoV-2 variant Omicron was detected (17/53, 32%), followed by Delta (8/53, 15%) and Alpha (2/53, 4%). In 26 patients, the SARS-CoV-2 variant was unknown (49%, Figure, Supplemental Digital Content 1, http://links.lww.com/INF/E872). The most frequently reported pre-existing conditions were immunodeficiency (49%) followed by malignancy (45%), cardiac disease (21%), hematologic disease (19%), chronic lung disease (19%), chronic liver disease (9%), kidney disease (9%) and diabetes (2%, Table 1). All patients had at least 1 pre-existing condition, and all but 4 patients (8%) had multiple pre-existing conditions.

Symptoms and Measurements at Admission

Upper respiratory tract infection was the most frequently reported symptom at admission (58%), followed by fever (57%), gastrointestinal symptoms (23%), lower respiratory tract infection (23%) and neurologic symptoms (13%, Table 1).

Median body weight at admission was 20 kg (3–50.1, IQR = 13), and median height was 111 cm (IQR = 37). Respiratory rate at admission ranged between 15 and 60 per minute (median 24, IQR = 9.5, n = 47) and peripheral oxygen saturation between 60% and 100% (median 98, IQR = 3, n = 49). The median white blood count was 5.35 billion/L (0.31–21, IQR = 4.59, n=50), and median lymphocytes were 0.90 billion/L (0.03–7.07, IQR = 1.42, n = 47).

Treatment of SARS-CoV-2 Infection

COVID-19-related treatment (other than mAbs) included oxygen (26%), dexamethasone (15%), remdesivir (11%) and other immunomodulatory drugs (6%). Dexamethasone was administered at a median of 5 days after symptom onset (−3 to 15, IQR = 9.25, n = 8) and given for a median of 10 days (2–14, IQR = 5.25, n = 6, Table 2). Remdesivir was administered at a median of 3 days after symptom onset 1–6, IQR = 2, n = 5) and given for a median of 4 days (0–7, IQR = 2.75, n = 6). Immunomodulatory treatment included anakinra (4%) and baricitinib (2%). mAb treatment included sotrovimab, casirivimab/imdevimab and bamlanivimab. Sotrovimab was given to 42 patients (79%) with a median dose of 12.5 mg/kg (7–30.5, IQR = 1, n = 42). Casirivimab/imdevimab was given to 9 patients (17%) with a median total dose of 23.1 mg/kg (17.2–37.5, IQR = 13.3, n = 9). Bamlanivimab was given to 2 patients (4%) with a median dose of 33.1 mg/kg (26.4–39.8, IQR = 6.7, n = 2). The median time between the positivity of rtPCR and the provision of mAbs was 1 day (0–23, IQR = 2.25, n = 52). In 91% of patients, symptoms were present at the time of mAb treatment. Nine percent of patients had no reported symptoms at the time of mAb treatment. All patients had either been tested positive during routine SARS-CoV-2 screening or after exposure to

TABLE 1. Pre-existing Conditions and Symptoms at Admission

Pre-existing conditions*	Yes	(%)	No	(%)	Unknown	(%)	NA	(%)
Immunodeficiency	26	(49%)	6	(11%)	0	(0%)	21	(40%)
Malignancy	24	(45%)	28	(53%)	0	(0%)	1	(2%)
Hematologic disease	10	(19%)	14	(26%)	0	(0%)	29	(55%)
Cardiac disease	11	(21%)	40	(75%)	0	(0%)	2	(4%)
Chronic lung disease	10	(19%)	40	(75%)	0	(0%)	3	(6%)
Chronic liver disease	5	(9%)	39	(74%)	0	(0%)	9	(17%)
Kidney disease	5	(9%)	47	(89%)	0	(0%)	1	(2%)
Diabetes	1	(2%)	52	(98%)	0	(0%)	0	(0%)
Other pre-existing conditions†	37	(70%)	0	(0%)	0	(0%)	16	(30%)
Symptoms at admission								
Upper respiratory tract symptoms	31	(58%)	21	(40%)	1	(2%)	0	(0%)
Fever	30	(57%)	21	(40%)	2	(4%)	0	(0%)
Gastrointestinal symptoms	12	(23%)	41	(77%)	0	(0%)	0	(0%)
Lower respiratory tract symptoms	12	(23%)	41	(77%)	0	(0%)	0	(0%)
Neurologic symptoms	7	(13%)	46	(87%)	0	(0%)	0	(0%)

Unknown, information was unknown to the study center; NA, no information provided by the study center.
*Some patients had >1 pre-existing condition.
†Other pre-existing conditions comprised a variety of medical conditions other than those listed previously, including chromosomal abnormalities and prematurity.

TABLE 2. Treatment, Clinical Outcome and Potential Side Effects

SARS-CoV-2 Infection-specific Treatment	Yes	(%)	No	(%)	Unknown	(%)	NA	(%)
Oxygen	14	(26%)	39	(74%)	0	(0%)	0	(0%)
Dexamethasone	8	(15%)	45	(85%)	0	(0%)	0	(0%)
Remdesivir	6	(11%)	45	(85%)	0	(0%)	2	(4%)
Immunomodulatory treatment	3	(6%)	50	(94%)	0	(0%)	0	(0%)
SARS-CoV-2 mAb product given								
Sotrovimab	42	(79%)	0	(0%)	0	(0%)	0	(0%)
Casirivimab/Imdevimab	9	(17%)	0	(0%)	0	(0%)	0	(0%)
Bamlanivimab	2	(4%)	0	(0%)	0	(0%)	0	(0%)
Reason for SARS-CoV-2 mAb treatment								
Underlying condition	41	(77%)	0	(0%)	0	(0%)	12	(23%)
Disease severity	13	(25%)	1	(2%)	0	(0%)	39	(74%)
Clinical outcome								
ICU treatment	7	(13%)	46	(87%)	0	(0%)	0	(0%)
HFNC	5	(9%)	34	(64%)	0	(0%)	14	(26%)
Survival	52	(98%)	1	(2%)	0	(0%)	0	(0%)
Potential side effects reported								
Neutropenia (<0.5 billion/L)	6	(11%)	36	(68%)	7	(13%)	4	(8%)
Lymphopenia (<0.2 billion/L)	3	(6%)	39	(74%)	8	(15%)	3	(6%)
ALT rise (>3 times ULN)	1	(2%)	36	(68%)	12	(23%)	4	(8%)
Thrombosis	0	(0%)	52	(98%)	0	(0%)	1	(2%)
Chills	0	(0%)	51	(96%)	0	(0%)	2	(4%)
Nausea or vomiting	2	(4%)	50	(94%)	0	(0%)	1	(2%)
Bronochospasm	0	(0%)	50	(94%)	0	(0%)	3	(6%)
Hypotonia	1	(2%)	51	(96%)	0	(0%)	1	(2%)
Allergic reaction	0	(0%)	51	(96%)	0	(0%)	2	(4%)
Anaphylaxis	0	(0%)	53	(100%)	0	(0%)	0	(0%)

ALT indicates alanine transaminase; HFNC, high-flow nasal cannula; NA, no information provided by the study center; ULN, upper limit of normal; unknown, information was unknown to the study center.

the index case or because of typical symptoms. In 36 patients, the reason for mAb treatment was the underlying condition, and in 8 patients, the reason was the disease severity, and in 5 patients both.

Clinical Outcome and Potential Side Effects of mAbs

All patients in the study survived except one (98%, Table 2). This child received bamlanivimab in an advanced stage of critical COVID-19 with herpes simplex and *Pseudomonas aeruginosa* superinfection and acute respiratory distress syndrome in the ICU.[13] The median duration of hospital stay was 3 days (0–56, IQR = 6, n = 50). Seven patients required treatment in an ICU (13%) with a median duration of ICU stay of 4 days (2–40, IQR = 10.5). Five patients required high-flow nasal cannula treatment (9%) for a median of 3 days (1–38, IQR = 4). The most frequently reported potential side effects were neutropenia (11%), lymphopenia (6%), nausea or vomiting (4%), rise of alanine transaminase over 3 times the upper limit of normal (2%) and hypotonia (2%). None of the participating centers observed thrombosis, chills, bronchospasm, allergic reaction or anaphylaxis. In no case, treatment was discontinued due to side effects.

DISCUSSION

Our study shows preliminary evidence of good tolerability of mAbs in SARS-CoV-2-infected patients younger than 12 years or weighing below 40 kg and having several risk factors for severe COVID-19. In this small cohort of patients, no severe reactions related to mAb treatment were reported. Furthermore, progression to severe disease was not observed with mAb treatment given early in the course of infection.

In adult studies, allergic reactions, anaphylaxis, or infusion-related reactions were the main reported serious side effects occurring in bamlanivimab (2.3% of patients experienced local reactions),[14] casirivimab/imdevimab (1.4% grade ≥2 infusion-related reaction),[15] sotrovimab (1% infusion-related reactions and 1 patient, ie, <1%, with infusion-related dyspnea)[16,17] and regdanvimab (2.9% with hypertriglyceridemia, 1% infusion-related reaction, 2 patients, ie, 8.3%, in the phase 1 study with hepatocellular injury).[18–20] Although studies with head-to-head comparisons are lacking, mAbs are thought to cause fewer side effects such as serum sickness, allergic reactions or life-threatening anaphylaxis than traditional serum therapy or polyclonal preparations (eg, convalescent plasma).[21]

Due to data scarcity in children, despite promising studies in adults, a United States expert consortium in 2021 did not recommend the routine use of imdevimab and bamlanivimab in children, even in cases of high risk for disease progression.[22] Later, the panel revised its recommendation regarding older children and adolescents but stated that especially due to the lack of data on safety and unknown adverse effects, the consortium does not recommend SARS-CoV-2 mAb treatment in younger children.[23] To date, the American Academy of Pediatrics only recommends the use of mAbs in patients above 12 years of age and 40 kg with early (<10 days from symptom onset or first SARS-CoV-2-positive PCR result) mild-to-moderate COVID-19 who do not show signs of severe disease.[7] However, the only mAb product currently available for patients younger than 12 years of age for this indication in the United States is bamlanivimab/etesvimab, which has shown severely reduced in vivo activity against new virus strains.[12,24]

While it is generally accepted that morbidity and mortality from acute COVID-19 are low for CYP, children with one or especially multiple comorbidities are more prone to severe disease. Nevertheless, even more than two years into the pandemic, risk factors for developing severe disease in children are ill-defined compared to older age groups. Real-life data show that infants and children with comorbidities, especially severe respiratory, cardiovascular, neuromuscular, and malignant diseases are prone to unfavorable outcomes (Table, Supplemental Digital Content 2, http://links.lww.com/INF/E873, which summarizes pediatric patients prone to severe COVID-19). Other children at risk for severe disease progression might be those with poor or absent ability to mount a humoral immune response and thus representing another group potentially benefiting from mAb treatment.[25] These include children with malignancies and, although data are still conflicting, patients with inborn errors of immunity such as combined immunodeficiencies, immune dysregulation disorders and innate immune defects impairing type I interferon.[26] Many national decision-making bodies suggest the use of mAbs in vulnerable individuals.[7,27] The table, Supplemental Digital Content 3, http://links.lww.com/INF/E874, summarizes present international recommendations on using mAbs against SARS-CoV-2 in pediatric patients. These recommendations are based on expert opinions, and physicians are encouraged to make case-by-case decisions.

To date, high-quality data on the safety of SARS-CoV-2 mAb use in CYP under 12 years of age and below 40 kg body weight is lacking. As a result, pediatric societies worldwide are forced to base their recommendations on the scarce evidence about these potentially beneficial therapeutics.[22,28] One retrospective cohort study focused on adolescents receiving SARS-CoV-2 mAbs in the emergency department.[29] It reviewed 17 patients (13–21 years old, weighing >40 kg) with mild-to-moderate disease and risk for disease progression through pre-existing conditions such as diabetes, obesity, or trisomy 21. Like our results, the study showed no significant adverse events, no sign of anaphylaxis or severe allergic reaction. Progression to severe COVID-19 was only observed in one 17-year-old patient.[29] Another observational study investigated the provision of mAbs against SARS-CoV-2 in 73 children 24 days to 18 years of age—including 37 children below 12 years of age—with secondary immunodeficiency, congenital heart disease, primary immunodeficiency, neurodevelopmental disorder, obesity, chronic bronchopneumopathy, heart transplant, acquired heart disease or chronic kidney failure.[11] Again, the study found no significant adverse effects or reactions such as anaphylaxis, hypotension or dyspnea.

While it is evident that during the COVID-19 pandemic, randomized controlled trials may not always be feasible because of practical issues with recruitment, enrollment time and informed consent, infants and children are often neglected in clinical trials, and researchers or sponsors choose not to include them in safety and effectiveness trials. In our study, most patients were unvaccinated against SARS-CoV-2, and 43% of participants (23/53) were not eligible for vaccination at that time because they were under 5 years of age.[30]

Recent in vitro and in vivo data suggest that the activity of available monoclonal antispike protein antibodies against the B.1.1.529 (Omicron) variant may be reduced.[31–34] However, there is evidence that sotrovimab, adintrevimab, cilgavimab and tixagevimab retained neutralizing activity.[12,34] Furthermore, the concentrations of sotrovimab obtained in the plasma of adult patients (the maximum concentration at the end of infusion of 118 μg/mL and concentration at day 29 of 25 μg/mL) easily exceed the increased IC_{50} neutralization levels of approximately 1 μg/mL reported for BA.1, BA.2, BA.4 and BA.5[32] It has to be noted that conflicting in vitro data exist, with IC_{50} neutralization levels against most variants above >50 μg/mL in other studies.[32,35] No data for plasma levels of pediatric patients are available. However, based on the average dose of 12.5 mg/kg of body weight used in the present study, rather higher concentrations might be expected than in adults after the standard dose of 500 mg (corresponding to 6.7 mg/kg in a 75-kg adult). Given the high speed of drug development during the pandemic, new antibodies may soon become available, and it would be desirable that clinical trials on the safety and efficacy of these products also include children.[36,37]

Limitations

This study has several limitations. First, the small sample size and retrospective design allow only limited conclusions about the safety of the mAbs used. Second, the type of product, the timing of administration and the dosage were not standardized and varied among subjects and participating study sites. Third, no standardized criteria for patient selection were available at the time of recruitment. In addition, some participants received mAbs as "rescue therapy," that is, in cases of life-threatening severe COVID-19, which is not part of the authorization of mAbs in adults. Finally, although we included patients with a wide range of pre-existing conditions at high risk for severe COVID-19, children with hematologic and oncologic conditions accounted for the majority of patients. Our study was not designed to prove effectiveness in preventing hospitalization and death, but to look at risk factors and

clinical situations triggering pediatricians to treat CYP with mAbs as well as tolerability in this small group of patients.

CONCLUSION

This study is among the first to investigate the application of mAbs in children younger than 12 years of age or less than 40 kg of body weight who are at high risk for severe COVID-19. Although more data are needed, mAbs were well tolerated as off-label treatment by patients in this cohort.

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REFERENCES

1. World Health Organization. WHO coronavirus (COVID-19) dashboard. [Overview]. January 1, 2022. Available from: https://covid19.who.int. Accessed August 31, 2022.
2. Bundle N, Dave N, Pharris A, et al. COVID-19 trends and severity among symptomatic children aged 0-17 years in 10 European Union countries, 3 August 2020 to 3 October 2021. *Euro Surveill*. 2021;26:1–8.
3. Qi K, Zeng W, Ye M, et al. Clinical, laboratory, and imaging features of pediatric COVID-19. *Medicine (Baltim)*. 2021;100:e25230.
4. Zimmermann P, Curtis N. Why is COVID-19 less severe in children? A review of the proposed mechanisms underlying the age-related difference in severity of SARS-CoV-2 infections. *Arch Dis Child*. 2021;106:429–439.
5. Wang L, Berger NA, Kaelber DC, et al. Comparison of outcomes from COVID infection in pediatric and adult patients before and after the emergence of Omicron. *medRxiv [preprint]*. 2022;2:2021.12.30.21268495.
6. Cloete J, Kruger A, Maureen M, et al. Rapid rise in paediatric COVID-19 hospitalisations during the early stages of the Omicron wave, Tshwane District, South Africa. *medRxiv*. 2021;12:21.21268108.
7. Martin B, DeWitt PE, Russell S, et al. Characteristics, outcomes, and severity risk factors associated with SARS-CoV-2 infection among children in the US National COVID Cohort Collaborative. *JAMA Netw Open*. 2022;5:e2143151.
8. Zimmermann P, Curtis N. COVID-19 in children, pregnancy and neonates: a review of epidemiologic and clinical features. *Pediatr Infect Dis J*. 2020;39:469–477.
9. Agency EM. COVID 19 treatments. [Human regulatory]. 2021. Available from: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/covid-19-treatments. Accessed May 1, 2022.
10. An EUA for casirivimab and imdevimab for COVID-19. *Med Lett Drugs Ther*. 2020;62:201–202.
11. Romani L, Calò Carducci FI, Chiurchiù S, et al. Safety of monoclonal antibodies in children affected by SARS-CoV-2 infection. *Child (Basel, Switzerland)*. 2022;9:10–15.
12. O'Horo JC, Challener DW, Speicher L, et al. Effectiveness of monoclonal antibodies in preventing severe COVID-19 with emergence of the delta variant. *Mayo Clin Proc*. 2022;97:327–332.
13. Menger J, Apostolidou S, Edler C, et al. Fatal outcome of SARS-CoV-2 infection (B1.1.7) in a 4-year-old child. *Int J Legal Med*. 2022;136:189–192.
14. 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.
15. 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.
16. An EUA for sotrovimab for treatment of COVID-19. *Med Lett Drugs Ther*. 2021;63:97–98.
17. Gupta A, Gonzalez-Rojas Y, Juarez E, et al; COMET-ICE Investigators. Early treatment for Covid-19 with SARS-CoV-2 neutralizing antibody sotrovimab. *N Engl J Med*. 2021;385:1941–1950.
18. Ryu D-K, Song R, Kim M, et al. Therapeutic effect of CT-P59 against SARS-CoV-2 South African variant. *Biochem Biophys Res Commun*. 2021;566:135–140.
19. Syed YY. Regdanvimab: first approval. *Drugs*. 2021;81:2133–2137.
20. Kim JY, Jang YR, Hong JH, et al. Safety, virologic efficacy, and pharmacokinetics of CT-P59, a neutralizing monoclonal antibody against SARS-CoV-2 spike receptor-binding protein: two randomized, placebo-controlled, phase I studies in healthy individuals and patients with mild SARS-CoV-2. *Clin Ther*. 2021;43:1706–1727.
21. Kreuzberger N, Hirsch C, Chai KL, et al. SARS-CoV-2-neutralising monoclonal antibodies for treatment of COVID-19. *Cochrane Database Syst Rev*. 2021;9:CD013825.
22. 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.
23. Wolf J, Abzug MJ, Anosike BI, et al. Updated guidance on use and prioritization of monoclonal antibody therapy for treatment of COVID-19 in adolescents. *J Pediatric Infect Dis Soc*. 2022;11:177–185.
24. Food and Drug Administration. Fact sheet for health care providers Emergency Use Authorization (EUA) of bamlanivimab and etesevimab. [Fact sheet]. 2022. Available from: https://www.fda.gov/media/145802/download. Accessed May 1, 2022.
25. Sananez I, Raiden SC, Algieri SC, et al. A poor and delayed anti-SARS-CoV2 IgG response is associated to severe COVID-19 in children. *EBioMedicine*. 2021;72:1036151–1036110.
26. Bucciol G, Tangye SG, Meyts I. Coronavirus disease 2019 in patients with inborn errors of immunity: lessons learned. *Curr Opin Pediatr*. 2021;33:648–656.
27. Tenenbaum T, Hufnagel M, Knuf M, et al. Stellungnahme der DGPI, API, DGKJ, DGPK, GPOH, GKJR, GPP und STAKOB zur Klinik, Diagnostik und Therapie von Kindern mit COVID-19 [DGPI]. 2022. Available from: https://dgpi.de/klinik-diagnostik-therapie-kinder-mit-covid-feb-2022. Accessed May 1, 2022.
28. Lanari M, Venturini E, Pierantoni L, et al; Other Collaborators. Eligibility criteria for pediatric patients who may benefit from anti SARS-CoV-2 monoclonal antibody therapy administration: an Italian inter-society consensus statement. *Ital J Pediatr*. 2022;48:7.
29. Mak G, Dassner AM, Hammer BM, et al. Safety and tolerability of monoclonal antibody therapies for treatment of COVID-19 in pediatric patients. *Pediatr Infect Dis J*. 2021;40:e507–e509.
30. deSante-Bertkau JE, Knilans TK, Persad G, et al. Off-label prescription of COVID-19 vaccines in children: clinical, ethical, and legal issues. *Pediatrics*. 2022;149:e2021054578.
31. Bruel T, Hadjadj J, Maes P, et al. Serum neutralization of SARS-CoV-2 Omicron sublineages BA.1 and BA.2 in patients receiving monoclonal antibodies. *Nat Med*. 2022;28:1297–1302. doi:10.1038/s41591-022-01792-5.
32. Takashita E, Kinoshita N, Yamayoshi S, et al. Efficacy of antibodies and antiviral drugs against Covid-19 omicron variant. *N Engl J Med*. 2022;386:995–998.
33. Iketani S, Liu L, Guo Y, et al. Antibody evasion properties of SARS-CoV-2 Omicron sublineages. *Nature*. 2022;604:553–556.
34. Planas D, Saunders N, Maes P, et al. Considerable escape of SARS-CoV-2 Omicron to antibody neutralization. *Nature*. 2022;602:671–675.
35. Tuekprakhon A, Nutalai R, Dijokaite-Guraliuc A, et al; OPTIC Consortium. Antibody escape of SARS-CoV-2 Omicron BA.4 and BA.5 from vaccine and BA.1 serum. *Cell*. 2022;185:2422–2433.e13.
36. Clinicaltrials.org. Evaluation of ADG20 for the prevention of COVID-19 (EVADE). [US National Library Of Medicine]. 2021. Available from: https://clinicaltrials.gov/ct2/show/NCT04859517. Accessed May 1, 2022.
37. Clinicaltrials.org. Evaluation of ADG20 for the treatment of mild or moderate COVID-19 (STAMP). [US National Library Of Medicine]. 2021. Available from: https://www.clinicaltrials.gov/ct2/show/NCT04805671. Accessed May 1, 2022.