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Initial Guidance on Use of Monoclonal Antibody Therapy for Treatment of COVID-19 in Children and Adolescents

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Summary: Although monoclonal antibody therapies for COVID-19 have received emergency use authorization for treatment of adolescents in specified high risk categories, there is currently insufficient evidence for necessity, safety or efficacy to recommend routine use, even in those with specified conditions.

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Abstract

Background. In November 2020, the US Food and Drug Administration (FDA) provided Emergency Use Authorizations (EUA) for two novel virus-neutralizing monoclonal antibody therapies, bamlanivimab, and REGN-COV2 (casirivimab plus imdevimab), for the treatment of mild to moderate COVID-19 in adolescents and adults in specified high-risk groups. This has challenged clinicians to determine the best approach to use of these products.

Methods. A panel of experts in pediatric infectious diseases, pediatric infectious diseases pharmacy, pediatric intensive care medicine, and pediatric hematology from 29 geographically diverse North American institutions was convened. Through a series of teleconferences and web-based surveys, a guidance statement was developed and refined based on review of the best available evidence and expert opinion.

Results. The course of COVID-19 in children and adolescents is typically mild and there is no high-quality evidence supporting any high risk groups. There is no evidence for safety and efficacy of monoclonal antibody therapy for treatment of COVID-19 in children or adolescents, limited evidence of modest benefit in adults, and evidence for potential harm associated with infusion reactions or anaphylaxis.

Conclusions. Based on evidence available as of December 20, 2020, the panel suggests against routine administration of monoclonal antibody therapy (bamlanivimab, or casirivimab and imdevimab), for treatment of COVID-19 in children or adolescents, including those designated by the FDA as at high risk of progression to hospitalization or severe disease. Clinicians and health systems choosing to use these agents on an individualized basis should consider risk factors supported by pediatric-specific evidence, and ensure implementation of a system for safe and timely administration that does not exacerbate existing healthcare disparities.

Keywords: COVID-19; Pediatric; Bamlanivimab; Casirivimab; Imdevimab

1. Introduction

The pandemic of Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has been met with rapid development of novel therapeutics.[1] As new therapies are discovered and become available for use, careful evaluation of evidence is essential to provide guidance for safe and effective use.[2-5] The most recent additions to the COVID-19 armamentarium are virus-neutralizing monoclonal antibodies, which are human or humanized antibodies administered by intravenous infusion that bind to virus or to infected cells to treat SARS-CoV-2 infection.[6] The Food and Drug Administration (FDA) has issued Emergency Use Authorizations (EUA) for two such products, bamlanivimab (LY-CoV555) and REGN-COV2, a combination of casirivimab and imdevimab.[7, 8] Another monoclonal antibody, eteseivimab (LY-CoV016), has not yet received authorization and will not be discussed further here.[9] In this guidance statement, we focus on the use of available SARS-CoV-2 neutralizing monoclonal antibodies in children and adolescents with COVID-19.

Bamlanivimab is a single monoclonal antibody that binds to the receptor binding domain (RBD) of the SARS-CoV-2 spike protein; it was authorized for use in the USA under an EUA on November 9, 2020.[8] Casirivimab and imdevimab (REGN-COV2) are monoclonal antibodies that bind to non-overlapping regions of the SARS-CoV-2 RBD, and were authorized for use in combination under an EUA on November 21, 2020.[7] Because of the rapid advancement of these products from discovery to clinical use, there is little published evidence about their use in humans, and no evidence for use in children or adolescents. We summarize available clinical data for each product below. In both cases, the EUAs allow use in pediatric patients ≥12 years of age and ≥40kg with mild to moderate COVID-19, not requiring hospitalization or new/increased supplemental oxygen for COVID-19, who are deemed to be “at high risk for progressing to severe COVID-19 and/or hospitalization”.[7, 8] Neither agent is authorized for use in patients hospitalized or requiring supplemental oxygen

therapy for COVID-19 because of evidence that these products might cause harm in that setting.[7, 8] The criteria for those at high risk are defined identically in the EUA for each monoclonal antibody treatment and are also discussed below.

To develop guidance on the potential use of these agents for treatment of mild to moderate COVID-19 in high risk adolescents and young adults, as authorized by the current EUAs, we assembled a panel of experts in pediatric infectious diseases, pediatric infectious diseases pharmacy, pediatric intensive care medicine, and pediatric hematology from 29 geographically diverse North American institutions to evaluate the evidence for safety and efficacy of these agents in pediatric patients. This consensus statement has been reviewed and approved by all members, and endorsed by the Pediatric Infectious Diseases Society.

2. Guidance statement

Statement: Based on evidence available as of December 20, 2020, the panel suggests against routine administration of monoclonal antibody therapy (bamlanivimab, or casirivimab and imdevimab) for treatment of COVID-19 in children or adolescents, including those designated by the FDA as at high risk of progression to hospitalization or severe disease.

Remark: Clinicians and health systems choosing to use these agents on an individualized basis should consider risk factors supported by pediatric-specific evidence, and ensure implementation of a system for safe and timely administration that does not exacerbate existing healthcare disparities.

3. Rationale

This guidance statement is based primarily on the current lack of efficacy or safety data in pediatric patients, the generally lower risk of progression to severe disease in children and adolescents, and the apparently modest efficacy of these treatments in adults. Neither agent is authorized for use in patients hospitalized or requiring supplemental oxygen therapy for COVID-19 because of evidence that these products might cause harm in that setting.[7, 8] In this context, along with documented adverse events in adult studies, and plausibility for differential efficacy or safety in younger patients, the potential costs and risks of administration of these products might outweigh the benefits even in children or adolescents designated as being at higher risk of hospitalization or progression to severe disease. Moreover, while the FDA authorized use for adolescents only with specific comorbidities, there are neither sufficient data to support a high risk of severe illness in any pediatric population, nor comparative data to inform risk stratification across the identified groups. Similar reasoning may also apply to young adults, who are also at lower risk of severe disease than older adults, and for whom there are insufficient data to identify potentially high-risk groups and limited evidence for efficacy and safety of monoclonal antibody therapy.

The intent of this guidance is not to preclude the use of these agents in any pediatric patients, but to clarify that routine or standard use in patients meeting EUA criteria is not justified by currently available evidence. The term “suggest” is used to indicate that the panel concluded that the risks of routine use might outweigh the benefits, but that evidence is limited and guidance could change as more data become available. Individual clinicians or institutions may choose to administer these agents to children and adolescents who meet EUA criteria on a case-by-case basis, and should ensure appropriate infrastructure exists to support use of these agents, including a mechanism to rapidly test and treat eligible patients, ability to maintain strict infection control precautions in the

ambulatory setting, and an allocation system that is equitable and does not exacerbate healthcare disparities, particularly while resources are scarce.

4. Evidence Summary

Bamlanivimab

Available clinical evidence for bamlanivimab comprises published interim results from the Blocking Viral Attachment and Cell Entry with SARS-CoV-2 Neutralizing Antibodies (BLAZE-1) trial, a randomized, double-blind, placebo-controlled phase II study conducted at 41 US centers.[8, 10, 11] Participants were required to have positive SARS-CoV-2 viral testing and symptoms of mild or moderate COVID-19. This interim analysis compared 3 treatment groups receiving a single infusion of bamlanivimab at a dose of 700 mg, 2800 mg, or 7000 mg (101, 107, and 101 participants allocated, respectively) against a placebo group (143 participants). Participants evaluated in the interim analysis were all ≥18 years of age, with a median age of approximately 45. Almost 70% of subjects had some risk factor for severe disease, defined as age ≥65 years, body-mass index (BMI) ≥35 kg/m^2, or a comorbid condition.[10]

The primary outcome was change in log viral load from baseline to day 11 after the positive SARS-CoV-2 test. The study population, including the placebo group, had an overall mean decrease of -3.81 (6.36 at baseline, 2.56 at day 11). Compared with the placebo group, the 2800-mg dose group showed a statistically significant difference of -0.53 (95%CI -0.98 to -0.08; p=0.02). A smaller, non-significant difference was observed for participants who received the 700-mg dose specified in the EUA (-0.20, 95%CI -0.66 to 0.25, p=0.38), whereas the decrease experienced by the 7000-mg dose group was less than that of the placebo group and not statistically significant (0.09, 95% CI -0.37 to 0.55; p=0.70). The major clinical outcome was COVID-19 related hospitalization, emergency

department (ED) visit, or death. The rate of this outcome was 1.6% (5 of 309) among treated subjects versus 6.3% (9 of 143) among placebo recipients, with a number needed to treat (NNT) of 21. In a *post hoc* analysis of subjects who were ≥65 years of age and/or had a BMI ≥35 kg/m^2, the rates of hospitalization or ED visit were 4% (4 of 95) for those who received bamlanivimab and 15% (7 of 48) for those who received placebo, with an NNT of 10. No other results stratified by risk factors were reported.[10] There was no reported evaluation of effect on risk of severe or life-threatening illness. None of the bamlanivimab recipients experienced serious adverse events, and the most common adverse event in the bamlanivimab was nausea (3.9%). Infusion reactions were reported in 2.3% of bamlanivimab recipients and 1.4% of placebo recipients; most reactions were described as mild, but at least one case of anaphylaxis has been reported.[10, 11] To date, there are no reports of the safety, efficacy or use of bamlanivimab in children or adolescents.

Casirivimab and imdevimab (REGN-COV2)

Current clinical evidence for casirivimab and imdevimab is described in published interim results from a continual enrollment, multicenter, randomized, double-blind, placebo-controlled, phase 1-2 clinical trial.[7, 12-18] Data were presented for 275 participants, among whom 93 received placebo, 92 low-dose, and 90 high-dose casirivimab and imdevimab.[18] A larger number of participants (799) are reported in a press release, however, these data are not yet published.[13, 16]

Compared to placebo, there was a greater time weighted average reduction in viral load by day 7 for those treated with casirivimab and imdevimab (difference 0.56 $\log_{10}$ copies/mL). *Post hoc* analysis demonstrated that participants who had a higher viral load and seronegative status at baseline appeared to have a larger reduction in viral load.[16, 18] Treatment with casirivimab and imdevimab reduced the absolute risk of need for a medically attended visit by 3% (3% vs 6%) overall with an NNT of 33, and by 9% (6% vs. 15%) in seronegative participants with an NNT of 11.[18] In data

presented in the FDA EUA, treatment with casirivimab and imdevimab reduced the absolute risk of COVID-19-related ER visits or hospitalization by 2% (2% vs. 4%; p=0.078) overall with an NNT of 50, and by 6% (3% vs. 9%; p=0.049) in participants considered to be at high risk with an NNT of 17.[13, 16]

Administration of combination casirivimab and imdevimab was reported to be safe, with few serious adverse events. However, adverse events in those who received the combination treatment included infusion reactions and anaphylaxis. .[7, 12-18] To date, there are no reports of the efficacy, safety, or use of casirivimab or imdevimab in children or adolescents.

COVID-19 Pediatric High-Risk Groups

Under the EUAs, both monoclonal antibody products are authorized for use only in patients with mild to moderate COVID-19 who are "at high risk for progressing to severe COVID-19 and/or hospitalization".[7, 8] The specified risk categories relevant to pediatric patients include: obesity (BMI ≥35, or ≥85th centile for age in adolescents); chronic kidney disease; diabetes; immunosuppressive disease or immunosuppressive treatment; sickle cell disease; congenital or acquired heart disease; neurodevelopmental disorder; medical-related technology dependence; and asthma, reactive airway disease, or other chronic respiratory disease that requires daily medication for control.[11, 16]

In general, children and adolescents are at relatively low risk for hospitalization or severe disease with COVID-19, with around 7% requiring hospitalization and 2% requiring admission to intensive care.[19] Because the overall rate of adverse infection outcomes is low, even those with a higher relative risk of severe disease may remain at low absolute risk. Therefore, data suggesting that a child or adolescent is at a relatively higher risk would not necessarily be sufficient to indicate use of

an untested intervention designed to prevent progression of disease, if the number needed to treat remains high.

We evaluated available evidence on criteria that might confer increased risk of severe disease in children and adolescents. Severe disease was not defined in the EUAs; in our analysis we considered 'severe COVID-19' as disease requiring supplemental oxygen or ICU admission.[3] We reviewed data from published literature where available, and registry data if sufficient published data were lacking. With respect to chronic respiratory conditions, we considered asthma separately from other conditions (e.g. cystic fibrosis or bronchiectasis). And, we interpreted "medical device dependence" to be a surrogate for 'medical complexity' as discussed in our earlier guidance, although this may not hold true for some patients, such as those with only gastrostomy tubes.[3]

There is limited observational evidence suggesting that some of the specified conditions, including obesity[19-30], profound immunocompromise or hypogammaglobulinemia[31-39], chronic cardiac disease[19, 21, 22, 34, 40-46], neurodevelopmental disorders or 'medical complexity'[19, 22, 34, 43, 45, 47, 48], and sickle cell disease[47, 49-58] increase the risk of hospitalization or severe COVID-19 in children and adolescents. Even for these conditions, it is difficult to determine the absolute risk, and it is unknown whether hospitalization or severe disease could be prevented by monoclonal antibody therapy. For some of the conditions, such as sickle cell disease or immunocompromise, the driving force for the apparent increased risk of hospitalization might be explained by protocolized treatment for fever or other symptoms rather than tendency to severe disease, and further investigation is needed.[59, 60] There is insufficient evidence to determine whether non-asthma lung disease[19, 21, 22, 34, 40-46] and diabetes mellitus[61-64] significantly increase risk of hospitalization or severe COVID-19. In contrast, available data suggest that some of the listed conditions do not independently affect the risk of hospitalization or progression to severe COVID-19. Although asthma was noted to be prevalent in hospitalized children with COVID-19 in two US multi-

state cohorts, studies that have specifically analyzed asthma as a risk factor for severe pediatric COVID-19, as distinct from other chronic respiratory conditions, have not shown an association with worse outcomes.[22, 41, 43, 65-69] Similarly, although prospective analysis of immunocompromised condition as a risk factor is sparse, studies to date suggest that children who are mild-moderately immunocompromised[3] are not at increased risk for severe COVID-19.[19, 32-36, 38, 39, 60] Lastly, a number of observational studies of children with chronic kidney disease who develop SARS-CoV-2 infection have not found it to be a risk factor for severe COVID-19.[34, 40, 44, 70-74]

COVID-19 and healthcare disparities

The current pandemic has highlighted longstanding disparities in healthcare, with a disproportionate negative effect on communities of color. Recent data have found that adults and children of racial and/or ethnic minority groups have, on average, a rate of SARS-CoV-2 infections that is more than four times higher than non-Hispanic whites.[75-77] Disparities in disease severity have also been well documented. Several studies have noted that, on average, three out of every four children hospitalized with COVID-19 and/or MIS-C come from racial or ethnic minority groups.[78, 79] Though consensus has not been established, it is likely these inequalities are driven by a combination of societal- and individual-level factors. Access to care and equitable distribution of therapeutic interventions is also likely to be an important driver of these disparities. Thus, to avoid further exacerbating this divide, attention should be given to the equitable distribution of these novel therapeutics when individualized decisions are being made on their use.

5. Conclusions and Research Priorities

Currently, there is insufficient evidence for utility, safety or efficacy to recommend routine use of monoclonal antibody therapy for children and adolescents with COVID-19, even those considered to be at higher risk of hospitalization or severe disease. At this time, neither bamlanivimab nor casirivimab plus imdevimab should be considered standard of care in any pediatric population, even in patients who meet high-risk criteria. There are no data supporting safety and efficacy in children or adolescents, and the evidence supporting use in the adult population (including young adults) is modest and/or unpublished, and has limited applicability to pediatrics or to many specified risk groups. More research is needed to identify pediatric patients at high absolute risk of severe COVID-19 and to determine the impact of monoclonal antibody therapies in this population. This guidance will be re-evaluated as more evidence becomes available.

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