The COVID-19 Treatment Guidelines Panel's Statement on the Emergency Use Authorizations of Anti-SARS-CoV-2 Monoclonal Antibodies for the Treatment of COVID-19

July 8, 2021

Anti-SARS-CoV-2 monoclonal antibodies that target the SARS-CoV-2 spike protein and block virus entry into cells have been evaluated for the treatment of COVID-19. On May 26, 2021, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for the anti-SARS-CoV-2 monoclonal antibody sotrovimab (previously VIR-7831) for the treatment of nonhospitalized patients with mild to moderate COVID-19 who are at high risk of progression to severe COVID-19.[1] In addition, the FDA recently updated the EUA criteria for all authorized anti-SARS-CoV-2 monoclonal antibodies for this indication by broadening the list of medical conditions or other factors that may put a patient at increased risk of progression to severe COVID-19, and thus expanding eligibility for these agents.[2,3] This Panel statement is an update to provide recommendations for the use of sotrovimab and information on the expanded EUA criteria for the use of authorized anti-SARS-CoV-2 monoclonal antibodies.

Please see Therapeutic Management of Nonhospitalized Adults With COVID-19 for information on the Panel's rationale for recommending anti-SARS-CoV-2 monoclonal antibodies for use as authorized under the EUAs.

Sotrovimab

Sotrovimab is an anti-SARS-CoV-2 monoclonal antibody which targets a highly conserved epitope in the receptor binding domain (RBD) of the SARS-CoV-2 spike protein. This epitope does not overlap with sites of mutations identified among SARS-CoV-2 variants of concern and interest, and, in vitro, sotrovimab maintains neutralizing activity against variants B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), B.1.427/429 (Epsilon), and B.1.526 (Iota).[1,4]

Summary Recommendations and Considerations

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends using one of the following anti-SARS-CoV-2 monoclonal antibodies, listed in alphabetical order, to treat nonhospitalized patients with mild to moderate COVID-19 who are at high risk of clinical progression, as defined by the Emergency Use Authorization (EUA) criteria (the Panel's ratings for the recommendations based on EUA eligibility criteria are discussed below).
  - **Casirivimab plus imdevimab**; *or*
  - **Sotrovimab**.
- At this time, the Panel **recommends against** the use of **bamlanivimab plus etesevimab** in these patients due to an increase in the prevalence of potentially resistant variants **(AIII)**.
- Treatment should be started as soon as possible after the patient receives a positive result on a SARS-CoV-2 antigen or nucleic acid amplification test (NAAT) and within 10 days of symptom onset.
- There are no comparative data to determine whether there are differences in clinical efficacy or safety between bamlanivimab plus etesevimab, casirivimab plus imdevimab, or sotrovimab.
  - Some SARS-CoV-2 variants, particularly those that contain the mutation E484K (see Anti-SARS-CoV-2 Monoclonal Antibodies), have reduced susceptibility to bamlanivimab and, to a lesser extent, casirivimab and etesevimab in vitro; however, the clinical impact of these mutations is not known.
  - The availability of bamlanivimab plus etesevimab may be restricted in areas that have an elevated prevalence of variants of concern with markedly reduced in vitro susceptibility to these agents (e.g., P.1 [Gamma], B.1.351 [Beta]). Updates on the distribution of bamlanivimab plus etesevimab are available from the U.S. Department of Health and Human Services Bamlanivimab/Etesevimab website. The Centers for Disease Control and Prevention COVID-19 Data Tracker website provides information on the proportions of SARS-CoV-2 variants by regions in the United States.

Summary Recommendations and Considerations, continued
• In regions where SARS-CoV-2 variants of concern or interest with modestly reduced in vitro susceptibility to bamlanivimab plus etesevimab (e.g., B.1.427/429 [Epsilon], B.1.526 [Iota]) are common, some Panel members would preferentially use casirivimab plus imdevimab or sotrovimab while acknowledging that it is not known whether in vitro susceptibility data correlate with clinical outcomes. • The Panel **recommends against** the use of **anti-SARS-CoV-2 monoclonal antibodies** for patients who are hospitalized because of COVID-19, except in a clinical trial **(AIIa)**. However, their use should be considered for persons with mild to moderate COVID-19 who are hospitalized for a reason other than COVID-19 and who otherwise meet the EUA criteria.
Rating of Recommendations: A = Strong; B = Moderate; C = Optional **Rating of Evidence:** I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

Rationale for Recommending Sotrovimab

Sotrovimab was originally identified from a survivor of SARS-CoV infection in 2003 and targets an epitope in the RBD of the spike glycoprotein that is conserved between SARS-CoV and SARS-CoV-2. The data supporting the EUA for sotrovimab are from the Phase 3 COMET-ICE trial (*ClinicalTrials.gov* Identifier NCT04545060). COMET-ICE included outpatients with mild to moderate COVID-19 who were at high risk for progression to severe disease and/or hospitalization. A total of 583 participants were randomized to receive intravenous sotrovimab 500 mg (n = 291) or placebo (n = 292).

The median participant age at baseline was 53 years; 22% of the participants were aged ≥65 years. Across the arms, 63% of the participants were Hispanic/Latinx and 7% were Black or African American.

The primary endpoint was the proportion of participants who were hospitalized (for ≥24 hours) or who died from any cause within 29 days of randomization. Endpoint events occurred in three of 291 participants (1%) in the sotrovimab arm and 21 of 292 participants (7%) in the placebo arm ($P = 0.002$), resulting in a 6% absolute reduction and an 85% relative reduction in hospitalizations or death among the sotrovimab recipients compared to the placebo recipients.

The angiotensin-converting enzyme 2 (ACE2) binding site of the SARS-CoV-2 RBD is commonly targeted by monoclonal antibodies and is where key mutations are located in current variants of concern and interest. The target binding site of sotrovimab is in a region of the RBD that does not overlap with the ACE2 binding site, and sotrovimab appears to retain activity against current variants of concern and interest, including B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), B.1.427/429 (Epsilon), and B.1.526 (Iota).[1,4]

Updated Criteria for Use of All Anti-SARS-CoV-2 Monoclonal Antibodies with Active Emergency Use Authorizations

To date, the FDA has active EUAs for bamlanivimab plus etesevimab, casirivimab plus imdevimab, and sotrovimab. The issuance of an EUA does not constitute FDA approval of a product.

On May 14, 2021, the FDA broadened the criteria in the EUAs for bamlanivimab plus etesevimab and casirivimab plus imdevimab that specify the medical conditions and factors that may put patients at higher risk of progression to severe COVID-19 and, therefore, eligible to use the products.[2,3] The same criteria were also included in the EUA for sotrovimab.[1] Changes to broaden the criteria included lowering the body mass index (BMI) cutoff to 25 and adding other conditions and factors (e.g., pregnancy and race or ethnicity). There are no longer any age criteria (other than being aged ≥12 years) for use of the agents in those with the following conditions: sickle cell disease, neurodevelopmental

disorders, medical-related technological dependence, asthma, cardiovascular disease, hypertension, and chronic lung disease. The updated EUA criteria are listed below.

Panel Recommendations

- The quality of the data that supports the recommendations for the use of anti-SARS-CoV-2 monoclonal antibodies differs based on the criteria for high risk of progression to severe COVID-19 used. Consequently, the Panel weighed the strength of the recommendations based on the evidence for the risk of progression. Treatment is recommended based on the FDA EUA criteria for:
  - Patients with high-risk conditions that were represented in clinical trials **(AIIa)**, *and*
  - Patients with other medical conditions and factors that had limited representation in clinical trials **(BIII)**; however, in cases where the patient has an immunocompromising condition or is receiving immunosuppressive therapy, the rating is **AIII** (see the Panel's rationale for this exception below).

Food and Drug Administration Emergency Use Authorization Criteria for Use of Anti-SARS-CoV-2 Monoclonal Antibodies

Updated May 14, 2021

Medical conditions or other factors that were represented in clinical trials evaluating anti-SARS-CoV-2 monoclonal antibodies:

- Older age (aged ≥65 years) **(AIIa)**
- Obesity (BMI >30) **(AIIa)**
- Diabetes **(AIIa)**
- Cardiovascular disease (including congenital heart disease) or hypertension **(AIIa)**
- Chronic lung diseases (e.g., chronic obstructive pulmonary disease, moderate-to-severe asthma, interstitial lung disease, cystic fibrosis, pulmonary hypertension) **(AIIa)**

Other conditions or factors that had limited representation in clinical trials, but are considered risk factors for progression to severe COVID-19 by the CDC:

- An immunocompromising condition or immunosuppressive treatment **(AIII)** (based on theoretic considerations, many experts strongly recommend therapy for patients who are immunosuppressed despite their limited representation in clinical trials).
- Overweight (BMI 25–30) as the sole risk factor **(BIII)**
- Chronic kidney disease **(BIII)**
- Pregnancy **(BIII)**
- Sickle cell disease **(BIII)**
- Neurodevelopmental disorders (e.g., cerebral palsy) or other conditions that confer medical complexity (e.g., genetic or metabolic syndromes and severe congenital anomalies) **(BIII)**
- Medical-related technological dependence (e.g., tracheostomy, gastrostomy, or positive pressure ventilation [not related to COVID-19]) **(BIII)**

It is important to note that the likelihood of developing severe COVID-19 is increased when a person has multiple high-risk conditions or comorbidities.[5-7] Other factors (e.g., race or ethnicity) or medical

conditions may also place individual patients at high risk for progression to severe COVID-19. The current EUAs state that anti-SARS-CoV-2 monoclonal antibodies may be considered for many of these other patients **(BIII)**. For additional information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the CDC webpage Extra Precautions: People With Certain Medical Conditions. Health care providers should consider the benefits and risks of using anti-SARS-CoV-2 monoclonal antibodies for each individual patient.[1]

See the Considerations in Children section below for additional discussion on use of these products in nonhospitalized children with COVID-19.

Rationale for the Panel's Recommendation

Recommendations for the use of these monoclonal antibodies according to the updated EUA criteria should be considered in the context of the following limitations:

- The Panel's recommendations are based on preliminary results from the clinical trials evaluating the products. The details on the study design, methods, and follow-up period of these trials are currently limited. When peer-reviewed data for the Phase 3 trials become publicly available, the Panel will review the results and update the recommendations if necessary.
- The clinical trials evaluating the different anti-SARS-CoV-2 monoclonal antibodies used a variety of inclusion criteria to define what constituted a high risk of clinical progression to severe COVID-19. It should be noted that some of the conditions considered to confer high risk had limited or no representation in the trials.

Considerations in Children

There are insufficient data for the Panel to recommend either for or against the use of anti-SARS-CoV-2 monoclonal antibody products for nonhospitalized children with COVID-19 who have risk factors for severe disease. Based on data on efficacy in adults, anti-SARS-CoV-2 monoclonal antibody products may be considered for children who meet EUA criteria, especially those who have more than one risk factor, on a case-by-case basis in consultation with a pediatric infectious disease specialist. For children aged ≥16 years, risk factors predictive of disease progression in adults can be used. Choice of anti-SARS-CoV-2 monoclonal antibody may be based upon availability and data on the circulation of SARS-CoV-2 variants of concern in the local population and in vitro susceptibility data. Additional guidance on the use of anti-SARS-CoV-2 monoclonal antibodies for the treatment of COVID-19 in children is provided in a publication endorsed by the Pediatric Infectious Diseases Society.[8]

References

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