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Monoclonal antibodies for treating COVID-19

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■ ABSTRACT

Bamlanivimab and casirivimab-imdevimab are novel virus-neutralizing monoclonal antibodies authorized to treat mild to moderate COVID-19 in outpatients at risk for progression to severe disease. Treatment early in the disease may show efficacy in reducing progression to severe disease, although safety and efficacy data are limited. They are not authorized for hospitalized patients with more advanced disease.

■ INTRODUCTION

Neutralizing monoclonal antibodies (MAB) have been used to prevent and treat several disease states ranging from autoimmune conditions such as multiple sclerosis to specific types of cancers such as leukemia. Along these lines, the use of MABs to treat patients with COVID-19 has recently come into the spotlight. They offer passive immunity through antibody-dependent cellular cytotoxicity and phagocytosis and antibody-mediated neutralization or prevention of viral entry into host cells.¹ The spike protein (S) of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for multiple steps in replication, including host cell attachment via the S1 subunit binding.² The S1 receptor-binding domain is the primary MAB target, which blocks interaction with the host cell angiotensin-converting enzyme 2 receptor.

Eligible MABs are derived from B cells in plasma of recovering COVID-19 patients. MAB candidates are screened to find the highest potency for decreasing viral replication.³ Manufacturing processes provide standardized doses of MABs through recombinant technology. This compares with convalescent plasma

collected from recovered COVID-19 patients with polyclonal antibodies IgG, IgM, and IgA and varying degrees of neutralizing antibody titers.³ High-titer convalescent plasma products (IgG titer > 1:1,000 against SARS-CoV-2 S protein) have been studied against placebo, showing patients had less progression to severe illness when administered during early COVID-19 disease.⁴

In November 2020, the Food and Drug Administration (FDA) issued emergency use authorization to 2 MAB products: bamlanivimab and the combination of casirivimab and imdevimab. The therapies are authorization to treat COVID-19–positive outpatients with symptom onset within 10 days prior to infusion and who have comorbid disease states with high risks for adverse outcomes (Table 1).^{5,6} The therapies are not authorized for hospitalized patients requiring oxygen therapy or who have an increase in baseline oxygen therapy due to COVID-19.

■ BAMLANIVIMAB

Bamlanivimab, also known as LY-CoV555, is a recombinant MAB that targets the SARS-CoV-2 spike protein. It has been studied for the treatment of COVID-19 in both outpatient and hospitalized patients.

Outpatients

The interim analysis of the BLAZE-1 randomized, placebo-controlled phase 2 trial reported on bamlanivimab (LY-CoV555) at 3 doses (700 mg, 2,800 mg, 7,000 mg) in 452 outpatients with mild to moderate COVID-19 and a positive SARS-CoV-2 test result within 3 days of infusion.⁷ Most patients were White (88%) with a median age of 46 years, female (55%), and had a median body mass (BMI) index of 29 kg/m². Approximately 69% of patients had a least 1 risk factor for severe COVID-19 including age 65 years and older, BMI of 35 kg/m² or higher, or at least 1 coexisting illness.

The statements and opinions expressed in COVID-19 Curbside Consults are based on experience and the available literature as of the date posted. While we try to regularly update this content, any offered recommendations cannot be substituted for the clinical judgment of clinicians caring for individual patients.

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TABLE 1**FDA emergency use authorization criteria for bamlanivimab and casirivimab-imdevimab**

Patients must meet all 3 of the following:

1. Positive SARS-CoV-2 viral test and symptoms for ≤ 10 days
2. Do not require hospitalization or supplemental oxygen or do not require change in baseline oxygen
3. Meet the patient criteria listed below
 - 65 years and older
 - 55 years and older AND at least 1 of the following risk factors for severe disease:
 - A. Cardiovascular disease
 - B. Hypertension
 - C. Chronic obstructive pulmonary disease or other chronic respiratory disease
 - Patients 18 years and older AND at least 1 of the following:
 - A. Body mass index of ≥ 35 kg/m²
 - B. Chronic kidney disease
 - C. Diabetes mellitus
 - D. Currently receiving immunosuppressive therapy
 - E. Immunosuppressive disease
 - Patients 12 to 17 years old AND weighing at least 40 kg AND at least 1 of the following:
 - A. BMI 85th percentile or higher for their age and gender based on growth charts from the Centers for Disease Control
 - B. Sickle cell disease
 - C. Congenital or acquired heart disease
 - D. Neurodevelopmental disorders including cerebral palsy
 - E. Medical-related technological dependence such as tracheostomy, gastrostomy, or positive-pressure ventilation (not related to COVID-19)
 - F. Asthma, reactive airway, or other chronic respiratory disease that requires daily medication control

Adapted from references 5 and 6.

Pooling all 3 bamlanivimab doses showed patients had a decrease in viral load (mean -3.81) by day 11, similar to placebo. Time to symptom resolution in the pooled bamlanivimab groups was 5 days compared with 8 days with placebo. Rate of hospitalization or emergency department visit was 1.6% versus 6.3% for placebo. For patients with at least 1 risk factor for severe COVID-19, the rate was 4% versus 15% for placebo. However, the study was not powered to assess a difference in clinical outcomes, and these results should be interpreted with limited generalizability.

The final analysis for the BLAZE-1 study included a fourth treatment arm that used the combination of bamlanivimab and etesevimab 2800 mg/2800 mg.⁸ Results were similar to the interim analysis with no significant differences compared with placebo. The bamlanivimab-etesevimab group hospitalization or emergency department rate was 0.9% (1 of

109 patients) compared to placebo at 5.8% (9 of 152 patients, $P = .049$). The manufacturer of bamlanivimab and etesevimab submitted a request to the FDA in November 2020 for emergency use authorization of this combination therapy, which is currently under review.

Commonly reported adverse effects with bamlanivimab included nausea, diarrhea, dizziness, headache, and vomiting. Infusion-related reactions including pruritus, flushing, rash, and facial swelling were more common in the bamlanivimab groups than in the placebo group (2.3% vs 1.4%). All patients completed the infusions. Antihistamines were administered in some cases to address infusion-related reactions.⁷

Hospitalized patients

In contrast, ACTIV-3, a randomized, blinded,

placebo-controlled phase 3 trial evaluating bamlanivimab in hospitalized patients with COVID-19 infection and without end-organ failure, was halted early with bamlanivimab failing to demonstrate improved outcomes in oxygen requirements and organ function compared with placebo.³ This suggests the limited utility of MABs in treatment of hospitalized patients with moderate to severe COVID-19.

Bottom line

Based on these data, the FDA authorized bamlanivimab 700 mg in 200 mL of normal saline infused intravenously in a single dose to treat patients with mild to moderate COVID-19. No dosage adjustments are recommended for special patient populations.

■ CASIRIVIMAB AND IMDEVIMAB

Casirivimab (REGN10933) and imdevimab (REGN10987) are recombinant MABs with non-overlapping binding to the SARS-CoV-2 S1 protein receptor-binding domain. The use of 2 monoclonal antibodies administered together is theorized to limit the development of viral mutations. In vitro, the combination of casirivimab and imdevimab retains activity to mutated SARS-CoV-2 pathogens.^{9,10}

A phase 1/2 randomized, placebo-controlled trial assigned outpatients with mild to moderate COVID-19 to 1 of 2 doses of casirivimab and imdevimab (2,400 mg or 8,000 mg; total n = 533) or placebo (n = 266).^{6,11} Casirivimab and imdevimab were administered in equal doses. Most patients were White (81%) with a median age of 44 years, female (51%), and had a median BMI of 30 kg/m²; 34% were deemed high risk for severe COVID-19 infection, as defined in **Table 1**.

The time-weighted average change from baseline in SARS-CoV-2 viral load from day 1 to 7 between the pooled casirivimab-imdevimab dose groups and placebo was significantly different at -0.36 log₁₀ copies/mL ($P < .0001$). Median time to symptom resolution was 5 days versus 6 days, respectively. Medically attended visits, including hospitalization, emergency department visit, urgent care visit, or physician office or telemedicine appointments, were lower in the pooled casirivimab-imdevimab groups at 2.8% compared with placebo recipients at 6.5%. Hospitalizations and emergency department visits were lower in the casirivimab-imdevimab groups for both the full population and the high-risk group (2% vs 4%; high risk 3% vs 9%). In the initial analysis of 275 patients, 113 were serum SARS-CoV-2 antibody-negative at enrollment, and rates of medically attended visits

were 15% in the placebo group compared with 6% in the pooled casirivimab-imdevimab groups.¹¹

The most common treatment-emergent, grade 3 and 4 adverse effects in the casirivimab-imdevimab recipients were pneumonia, hyperglycemia, nausea and vomiting (2,400 mg dose), intestinal obstruction and dyspnea (8,000 mg dose). One patient in the 8,000 mg dose group experienced an anaphylactic reaction within 1 hour after infusion that resolved with epinephrine treatment. One infusion-related reaction was reported in the placebo group. There were 2 reactions in the 8,000 mg group resulting in therapy discontinuation and no reactions in the 2,400 mg group.

Bottom line

Based on similar efficacy among the various experimental doses but improved safety with the 2,400 mg dose, casirivimab 1,200 mg plus imdevimab 1,200 mg (total 2,400 mg) was FDA authorized for administration together in 250 mL of normal saline intravenously for single dose. No dosage adjustments are recommended for special patient populations.

■ RECOMMENDATIONS FROM EXPERT PANELS

The Infectious Diseases Society of America (IDSA) suggests against the routine use of bamlanivimab among ambulatory patients with COVID-19; however, their guidelines state that for patients at increased risk for severe disease, bamlanivimab is a reasonable option after informed clinical decision making with the patient of the benefits and risks.¹² As for pediatric patients with COVID-19, the Pediatric Infectious Diseases Society (PIDS) suggests against the routine use of MAB therapy given the typically mild disease course in this patient population.¹³ To support this statement, the authors cite a low number of clinical outcomes observed in studies and low level of certainty of hospitalization and emergency department avoidance as surrogate markers of avoidance of more severe outcomes such as intensive care unit admission, mechanical ventilation, or death.^{7,11} A statement from IDSA regarding use of casirivimab-imdevimab is forthcoming.

The National Institutes of Health (NIH) states that bamlanivimab and casirivimab-imdevimab should not be considered the standard of care and that there are insufficient data to recommend either for or against their use in ambulatory patients with COVID-19.^{14,15} The NIH cites the small patient populations and low number of hospitalizations or emergency room visits in clinical trials as factors con-

tributing to the inability to draw meaningful conclusions on the efficacy of these therapies.

■ ADDRESSING CLINICAL PRACTICE CHALLENGES

The outpatient administration of MAB infusions poses logistical challenges. Prescribers offering MAB therapy to patients must obtain verbal consent and provide the FDA-approved fact sheet. Given the requirement that patients have COVID-19 symptoms for 10 days or fewer, a quick throughput from screening, consent, scheduling, and infusion is imperative. The emergency use authorization specifies administration at healthcare facilities equipped to treat severe infusion reactions and activate an emergency response. As many infusion sites treat immunocompromised patients requiring chemotherapy or other high-risk infusions, additional infection prevention measures are needed to minimize those patients' exposure to SARS-CoV-2 infection. Examples of these measures include separate entrances and infusion locations within the clinic, adequate personal protective equipment and disinfecting procedures, and negative pressure rooms. The broad range of patients eligible for MAB infusions may lead to overwhelming demand of infusion chairs and appointment spots. Some institutions use a phased approach (eg, limiting restriction criteria to a small patient subset of the FDA-authorized definition) with expansion when processes are streamlined.

Both bamlanivimab and casirivimab-imdevimab require dilution and preparation using aseptic technique by qualified healthcare professionals. Both products are infused over 60 minutes and require a 60-minute postinfusion observation period. On arrival to the clinic, patients must be assessed for clinical stability, as some patient's symptoms may have worsened, requiring a higher level of medical attention and possible emergency department transfer. The clinic protocol should outline the vital sign thresholds for safe infusion initiation. Finally, patients must be monitored for serious adverse effects for at least 7 days after the infusion. Healthcare providers are required to report these events to the FDA and manufacturers as instructed on the authorization documents.^{5,6}

In October 2020, the US government announced its agreement to purchase 300,000 doses of both bamlanivimab and casirivimab-imdevimab and provide the medications to patients at no cost, with additional doses purchased throughout 2021.^{16,17} Medicare will reimburse an average of \$310 for administering the infusion.¹⁸

■ FUTURE DIRECTIONS

Several studies involving further evaluation of MABs as treatment and prevention are ongoing. A study evaluating both bamlanivimab and LY-CoV016 for prevention of COVID-19 in long-term care facility residents is in progress¹⁹ along with a study assessing casirivimab-imdevimab for COVID-19 prevention in asymptomatic people who have a household contact with COVID-19.²⁰ These studies highlight nontraditional infusion locations and open the arena for retail, home infusion, and community spaces to deliver these products in the future. Logistical challenges, such as management of hypersensitivity reactions and gathering of COVID-19-positive patients while upholding infection prevention protocols, are potential hurdles that may limit use.

As the pandemic progresses and SARS-CoV-2 variants emerge, therapeutic agents such as MABs may have decreased susceptibility, although the implications of these variants are not known.

The Advisory Committee on Immunization Practices issued a statement recommending that the COVID-19 vaccination be deferred for at least 90 days in people who have received passive antibody therapy, such as MABs, to avoid potential interference with the immune response to the vaccine.²¹ MABs offer rapid protection against infection and provide protection for weeks to months. Vaccines take longer to provide protection because they must challenge the immune system. However, the advantage of a vaccine is that they usually provide long-term protection.

■ KEY POINTS

- Monoclonal antibodies primarily target the spike protein receptor-binding domain of SARS-CoV-2, blocking its interaction with host cells.
- Combining casirivimab and imdevimab is theorized to limit the development of viral mutations.
- The US government plans to buy large quantities of both MAB therapies and provide them to patients at no cost.

■ SUMMARY

Bamlanivimab and casirivimab-imdevimab are novel MABs available under FDA emergency use authorization for the treatment of mild to moderate COVID-19 in outpatients with risk factors for progression to severe disease. Early recognition, diagnosis, and MAB treatment may yield the best results in avoiding a higher level of medical care. Efficacy and safety data

are limited owing to small sample sizes and low rates of clinical outcomes (eg, hospitalizations, death) and should be interpreted with caution. The exact patient population who will derive the most benefit from this therapy is not yet known. The applicability of targeting MAB therapy to COVID-19 antibody-negative patients is difficult to scale given the limited availability of testing and concerns for excluding treatment in patients with false-positive results. Widespread use of effective vaccines and practicing other preventative strategies remain the key solutions to ending the COVID-19 global pandemic.

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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