Dear Colleague
COVID-19 Updates

March 30, 2021

COVID-19 Monoclonal Antibody Treatment in the Outpatient Setting

Updated Guidance

- Next Webinar for Providers (April 16, 1 p.m.): SARS-CoV-2 Variants and Implications for NYC
- COVID-19 Provider FAQ (March 24)
- Letter to Providers: Clinical Considerations for Johnson & Johnson/Janssen COVID-19 Vaccine (March 22)
- Health Advisory #4: Updated Guidance for Use of Respirators by Health Care Personnel Caring for Patients With and Without COVID-19 in Health Care Settings (March 12)
- Dear Colleague: Building Confidence in COVID-19 Vaccines and Vaccination (March 1)
- NYC Health Department COVID-19 web pages
    - Information for Providers
    - Vaccine Information for Providers
    - Resources for Health Care Facilities
    - COVID-19 Data
    - Telehealth Tips

Overview

- Monoclonal antibodies (mAbs) are authorized for emergency use for *non-hospitalized* patients with mild to moderate COVID-19 at high risk of progression to severe disease
- When given early after symptom onset, mAb treatments can decrease the risk of hospitalization and death due to COVID-19
- Certain mAb therapies may be less effective against particular SARS-CoV-2 variants and providers should consider local presence of variants in selecting therapeutic agents
- Treatment sites and referral information can be found at hitesite.org/monoclonalantibody
- Outpatient facilities interested in providing mAb infusions can make requests through the federal Special Projects for Equitable and Efficient Distribution (SPEED) program

Introduction

The COVID-19 public health emergency has claimed the lives of more than 545,000 people in the U.S. (CDC 2021). High-risk patients, including people who are older or who have certain underlying conditions, are at an increased risk of developing severe COVID-19 illness, hospitalization, long-term sequelae and death. Further, many patients who have had mild to moderate COVID-19 infection may experience persisting long-term symptoms, causing health complications and additional burden on the health care system now and in the future.

Multiple treatment options have been investigated to prevent or lessen the severity of COVID-19. One treatment approach includes the use of neutralizing antibodies, such as those in convalescent plasma and mAbs. mAb agents have been developed for the treatment of COVID-19 infections and are the only treatments granted emergency use authorizations (EUA) by the Food and Drug Administration (FDA) for *non-hospitalized* patients with mild to moderate COVID-19 at high risk of progression to severe disease. Despite their potential benefit, mAbs have largely been underutilized for eligible patients.

With the emergence of new variants and ongoing community transmission of COVID-19 in New York City (NYC), COVID-19 continues to pose a threat, particularly to populations disproportionally impacted by COVID-19 in congregate care settings such as nursing homes, adult long-term care facilities, residential substance use, mental health and correctional facilities; in neighborhoods with high poverty; and among Black, Latino and immigrant communities. Early mAb treatment of people at increased risk offers an opportunity to decrease the severity of infection and help reduce the human costs and overall stress on the health care system. To ensure access to these new therapies, the U.S. Department of Health and Human Services (HHS) has established a program to provide mAb therapeutics at no cost to patients and providers, either through the States' distribution networks or through the SPEED program, which supports direct allocation of mAb therapeutics to priority outpatient settings.

This letter presents information on mAbs, including what products are available, current guidelines for patient eligibility and treatment, the evidence behind these recommendations, and how to access and use these therapeutic agents.

Monoclonal Antibodies

mAbs are made in a laboratory and work as substitute antibodies before the body mounts an acquired immune response. They are directed against a specific target on a pathogen and can restore, enhance or mimic the natural immune system's actions against that pathogen. The mechanism by which mAbs function is different from convalescent plasma, which consists of a variety of antibodies against various viral targets that come from a polyclonal response present in the plasma of patients who have recovered from an infection. In contrast, mAbs are developed by identifying the genes from B cells that produce strong neutralizing antibodies against a target pathogen. These genes are then expressed to produce mAbs. For COVID-19, the currently authorized mAbs target the SARS-CoV-2 spike protein, which the virus utilizes to enter host cells.

Available Products

Currently, there are two mAb treatments authorized and available for outpatient use under EUAs for the treatment of newly diagnosed COVID-19 patients at high risk of serious illness and hospitalization because of age or underlying health conditions.

- **Bamlanivimab and etesevimab:** Developed by Eli Lilly, bamlanivimab is a recombinant, neutralizing human IgG1 antibody directed against the spike protein of SARS-CoV-2. Etesevimab is also a recombinant human IgG1 monoclonal neutralizing antibody identified in the plasma of two convalescent patients, which specifically binds to the SARS-CoV-2 surface spike protein receptor binding domain with high affinity and can block the binding of the virus to the ACE2 host cell surface receptor. **The EUA fact sheet for providers can be accessed here.**
- **Casirivimab and imdevimab (also known as Regeneron or REGN-CoV2):** Developed as a mAb treatment cocktail by Regeneron Pharmaceuticals, casirivimab and imdevimab consist of two recombinant human IgG1 mAbs that bind to different regions of the SARS-CoV-2 spike protein receptor binding domain. **The EUA fact sheet for providers can be accessed here.**

While a third mAb treatment, bamlanivimab monotherapy, has been authorized for emergency use by the FDA, it is no longer available for ordering due to concern over increasing prevalence of resistant variants (see section on mAb Efficacy Against SARS-CoV-2 Variants). Sites can order etesevimab alone to pair with current supplies of bamlanivimab.

All agents are given as a one-time intravenous (IV) infusion, though studies on injectable delivery are underway. The combination therapies casirivimab and imdevimab, and bamlanivimab and etesevimab,

are each administered together as a single IV infusion. Both agents should be given as soon as possible after a patient has a positive viral test for SARS-CoV-2 and within 10 days of symptom onset.

Scientific Evidence/Clinical Studies

Therapeutic Benefit for Patients with Confirmed COVID-19

Bamlanivimab and Etesevimab

The EUA for combination therapy with bamlanivimab and another mAb targeting the spike protein, etesevimab, was granted based on data from the BLAZE-1 trial (interim data presented in Gottlieb 2021). Phase 2 results demonstrated a significant reduction in viral load within the first few days and at day 11 along with a faster improvement in symptoms in the treatment group (six days vs. eight days). The initial Phase 3 BLAZE-1 trial cohort included 1,035 high-risk outpatients with mild to moderate symptoms within three days of a positive COVID-19 test. Patients who received the combination therapy, bamlanivimab 2,800 mg and etesevimab 2,800 mg, had a significant reduction in COVID-19-related hospitalizations and deaths, compared to placebo (2% vs. 7%), representing a 70% relative reduction in risk (NIH 2021). Recently released data from a new Phase 3 BLAZE-1 cohort of 769 high-risk outpatients (therapy, n=511; placebo, n=258) showed that the authorized dosage of combination therapy (bamlanivimab 700 mg and etesevimab 1,400 mg) reduced the risk for hospitalizations and death by 87% ($p<0.0001$). Across the two BLAZE-1 Phase 3 cohorts, there were 13 COVID-19-related deaths in patients receiving placebo and no deaths in patients receiving bamlanivimab and etesevimab.

Casirivimab and Imdevimab (Regeneron)

The casirivimab (REGN10933) and imdevimab (REGN10987) EUA was based on Phase 1 and 2 clinical trials, which included 799 non-hospitalized adults with mild to moderate COVID-19 infection who were followed for at least 29 days. An interim analysis of the first 275 patients showed treatment with the mAb cocktail reduced viral load from day one through day seven, with the largest reduction occurring in those who had higher viral loads (Weinreich 2020). The treatment also reduced medical visits and hospitalizations compared to the placebo group (2% vs. 4%), with the highest reductions seen in those at higher risk for complications (3% vs. 9%). In addition, newly announced Phase 3 trial data showed a 70% reduction in hospitalizations and deaths among 4,567 non-hospitalized high-risk COVID-19 patients and the duration of symptoms was also reduced by 4 days (10 vs. 14 days) (Regeneron 2021).

COVID-19 Prevention Trials

mAbs are being studied as a prevention therapy in uninfected subjects exposed to COVID-19. The Phase 3 BLAZE-2 prevention trial enrolled 965 nursing home residents and staff to assess prevention of infection. Of the 299 nursing home residents, those receiving bamlanivimab had 80% lower risk of symptomatic COVID-19, compared to those receiving the placebo (Cohen 2021). Similarly, Regeneron is being investigated in a Phase 3 study for the prevention of COVID-19 in people at high-risk of infection

due to household exposure. The interim analysis of the first 400 enrolled participants showed 100% prevention of symptomatic infection and approximately 50% lower overall rates of infection (symptomatic and asymptomatic) (Regeneron 2021). Of note, in this trial, the treatment was given subcutaneously rather than via IV infusion, which would simplify treatment delivery. Full data is expected early in the second quarter of 2021.

mAb Efficacy Against SARS-CoV-2 Variants

Efforts are underway to assess the implications of emerging variants of concern on the efficacy of currently available mAbs, and new mAb products specifically targeting some of these variants (e.g., B.1.351, which emerged in South Africa) are under development. The FDA will continue to update the EUA Provider Fact Sheets as new information on product efficacy against variants becomes available. Providers should consider the local prevalence of mAb-resistant variants when considering treatment options. NYC variant data can be found on the NYC Health Department's main COVID-19 web page. National variant surveillance reports are available from the CDC.

In general, combination treatments have shown better overall activity against known variants of concern and seem less likely to promote emergence of variants post-treatment. A recent study found that all currently authorized mAb products have retained activity against the B.1.1.7 (U.K.) variant (Wang 2021). New data from the FDA on the emerging B.1.526 variant (New York) with the E484K mutation has shown bamlanivimab alone has no activity, bamlanivimab plus etesevimab has a 17-fold reduction in activity, and casirivimab and imdevimab retains full activity (see above links to EUA fact sheets). There was also reduced activity reported against the B.1.351 (South Africa) and P.1 (Brazil) variants with bamlanivimab and etesevimab combined, and bamlanivimab monotherapy had no functional activity. **For these reasons, bamlanivimab monotherapy is no longer recommended for use.**

Current Recommendations for Therapeutic Use

Guidelines

The National Institutes of Health (NIH) and the Infectious Diseases Society of America's (IDSA) COVID-19 Treatment Guidelines recommend the use of bamlanivimab 700 mg plus etesevimab 1,400 mg for outpatients with mild to moderate COVID-19 who are at high risk of clinical progression. IDSA notes that while the data are strongest for bamlanivimab plus etesevimab, casirivimab and imdevimab may have similar clinical benefit, but data are more limited.

Eligibility Criteria

The FDA has issued EUAs to permit the emergency use of these unapproved products for the treatment of symptomatic mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing (nucleic acid amplification test [NAAT] or antigen test), and who are at high risk for progressing to severe COVID-19 illness, hospitalization or both.

Per the EUAs, high risk is defined as patients who meet at least one of the following criteria:

Adults age 18 and older who meet one or more of the following:	**Children ages 12 to 17 with one or more of the following:**

• Obesity with a body mass index (BMI) of 35 or greater
• Chronic kidney disease
• Type 1 or 2 diabetes mellitus
• An immunosuppressive disease
• Are currently receiving immunosuppressive treatment
• Age 65 or older
• Ages 55 to 64 and have any of the following:
  ○ Cardiovascular disease
  ○ Hypertension
  ○ Chronic obstructive pulmonary disease/other chronic respiratory disease
	• Obesity with a BMI greater than or equal to 85% of patients of the same age and gender, based on the Centers for Disease Control and Prevention (CDC) growth charts
	• Sickle cell disease
	• Congenital or acquired heart disease
	• Neurodevelopmental disorders (for example, cerebral palsy)
	• Dependence on a medical-related technology such as a tracheostomy, gastrostomy or positive pressure ventilation (not related to COVID-19)
	• Asthma, reactive airway or other chronic respiratory disease that requires daily medication

Exclusion Criteria

mAbs may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high-flow oxygen or mechanical ventilation. They are not authorized for use in patients who:

- Are hospitalized due to COVID-19;
- Require oxygen therapy due to COVID-19; or
- Require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19-related comorbidity.

Safety and Side Effects

As mAbs are investigational therapies authorized for emergency use, data on adverse effects are limited. The most common adverse event is nausea. Some IV-related reactions have been reported such as fever, chills, nausea, headache, hypotension, bronchospasm, angioedema, throat irritation and rash. Some anaphylaxis and serious IV-related reactions have been observed, but all reactions resolved after stopping the treatment infusion. Patients receiving mAb treatment should be observed for at least one hour after completing infusion. Providers should be prepared to respond to anaphylaxis or any serious IV-related reaction.

COVID-19 Vaccination

Patients are advised to defer COVID-19 vaccination for 90 days after receiving mAb treatment. Any eligible patient who develops COVID-19 after vaccination can receive mAb treatment (CDC 2021).

Access to mAb Treatment and Patient Referrals

Treatment with mAbs is most beneficial to patients if given early in symptom progression. Treatment should be given as soon as possible after a patient has a documented confirmed positive COVID-19 test result and within 10 days of symptom onset. For this reason, it is important to have a quick turnaround between when a patient is tested for COVID-19, identified as positive, and provided mAb treatment. Strategies such as rapid point-of-care testing and pre-screening for eligibility can help decrease referral time so that patients can receive treatment earlier. Symptomatic patients who fit the eligibility criteria should be informed of the therapy as an option when they present for testing to lay the groundwork for treatment if they test positive for COVID-19. The NYC Department of Health's Monoclonal Antibody Treatment for COVID-19 patient handout can be given to patients at the time of testing so that they can learn about mAb treatment and promptly seek care if they test positive.

Referral Sites

There are several hospitals and health care networks that have established mAb treatment programs. For a list of treatment sites in the NYC metropolitan region with information on how to refer eligible patients, visit hitesite.org/monoclonalantibody. This website also includes a resource library for providers and patients. Additional treatment sites may be found on the HHS mAb treatment locator with the caveat that not all sites may be actively providing mAb therapy, so check ahead.

NYC Health + Hospitals provides treatment and care regardless of immigration status or ability to pay. Patients with a positive COVID-19 test can contact NYC Health + Hospitals by connecting to ExpressCare.nyc and clicking "Talk to a Doctor Now" or they can call 212-COVID19 (212-268-4319) and

press 9 for monoclonal antibody treatments. Patients can call to check their treatment eligibility and schedule their appointment between 9 a.m. and 9 p.m., seven days a week.

Treatment Costs

While the medications are provided to treatment sites for free through a federal program, there may be charges for administration of the infusion based on coverage type. Patients with Medicare, and Medicaid and Child Health Plus, should not be charged. For other insurance types, patients should contact their health plan about copay, deductible or other cost-sharing. For uninsured patients, facilities may request reimbursement for the treatment costs through the COVID-19 Uninsured Program.

Becoming an Outpatient mAb Treatment Site

To date, mAb therapy has largely been distributed to hospitals by each state and treatment has been delivered primarily in infusion clinics and emergency departments. The SPEED program was established to expand direct access to select outpatient settings that are able to provide the infusions on-site, including federally qualified health centers, long-term care facilities (including nursing homes and adult care facilities), hemodialysis providers and correctional facilities. If your health care facility is interested in establishing a treatment site to administer mAb therapy to patients under the EUA, the SPEED program details in its outpatient administration playbook six activities that should be carried out:

1. Allocating dedicated facility space and developing a logistical plan to manage patient flow
2. Ensuring sufficient infusion supplies are available, especially those that may be difficult to procure
3. Developing a plan for staffing and personnel
4. Preparing for the drug administration process
5. Preparing for drug ordering and making sure a process for reimbursement is in place
6. Preparing for reporting adverse events and record keeping

A high-level checklist and treatment administration resources can also be found in the American College of Emergency Physicians' Monoclonal Antibody Toolkit.

Equitable Access to mAbs

Many of NYC's lower income neighborhoods and communities of color have suffered from the highest rates of COVID-19 infections, hospitalizations and deaths over the course of the COVID-19 public health emergency due to long-standing structural inequities. A recent study on the impact of COVID-19 on U.S. life expectancies in 2020 showed a stark difference in estimated declines for Black (2.10 years) and Latino (3.05 years) communities, compared to Whites (0.68 years) (Andrasfay 2021). These disproportionate impacts are now also being compounded by lower vaccination rates among these

populations due to disparities in access, vaccine hesitancy and medical mistrust. Mass vaccination of the general population will likely take many months to achieve, which further underscores the need for effective bridging interventions that can mitigate severity of disease in the most at-risk patients.

Considering these challenges, mAbs are a potentially life-saving therapy, especially for Black, Latino, Indigenous, and immigrant patients and other medically marginalized populations with poorer health outcomes. Linguistically and culturally appropriate educational materials and counseling should be made available to all patients to ease concerns and ensure fully informed consent. For more information on ensuring all eligible patients have equitable access to mAb therapies, refer to this allocation framework and these key considerations for decision-making.

Conclusion

The advent of mAbs as outpatient therapeutics for the treatment of mild to moderate COVID-19 adds an additional tool for combating the COVID-19 public health emergency, which is especially needed as we contend with highly transmissible COVID-19 variants. The currently authorized mAbs are investigational products, and clinical studies continue under their respective EUAs. Ongoing and future trials will shed further light on the definitive clinical benefit of these drugs. The data collected so far support the safety and benefits of mAb therapy in reducing hospitalizations and severe disease in patients at high risk for complications from COVID-19. Its use should be strongly considered in support of populations at highest risk.

Resources

Patients

- NYC Health Department patient handout: Monoclonal Antibody Treatment for COVID-19
    - Translations will be available on the COVID-19 provider page under Clinical Management
- HHS: Available COVID-19 Treatment Options
- FDA EUA Fact Sheets for patients, parents and caregivers (English and Spanish)
    - Bamlanivimab and etesevimab
    - Casirivimab and imdevimab

Providers

- HHS: Provider's Guide to COVID-19 Treatment Options
- Assistant Secretary for Preparedness and Response (ASPR): COVID-19 Monoclonal Antibody Therapeutics Information for Providers

- National Infusion Center Association: mAb Playbooks and Other Related Resources
- HHS: Overview of Direct Order Process for COVID-19 Therapeutics
- NIH COVID-19 Treatment Guidelines: Anti-SARS-CoV-2 Monoclonal Antibodies
- IDSA Guidelines on the Treatment and Management of Patients with COVID-19
- Project ECHO HHS ASPR Outpatient Therapeutics Miniseries: Monoclonal Antibodies
- Centers for Medicare and Medicaid Services: Monoclonal Antibody COVID-19 Infusion Reimbursement Toolkit
- Health Resources Services Administration (HRSA): COVID-19 Uninsured Program

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- Sign up to receive NYC Health Alerts.
- Join the City Health Information network to receive this newsletter by email.
- Register for the monthly NYC Health Department's COVID-19 Provider Webinar.