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COVID-19 Monoclonal Antibodies: Key Issues After Emergency Use Authorization

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This Duke-Margolis resource on COVID-19 response policies is intended to inform and help guide policy makers addressing the evolving COVID-19 pandemic in the United States and around the globe, and will be updated as the pandemic and response capabilities change over time.

It contains recommendations for a U.S. Federal response as well as steps and resources for stakeholders across the health care ecosystem. We will add further resources to address a range of related, critical policy challenges.

We thank our many collaborators, co-authors, and reviewers who have contributed significant expertise and guidance on these rapidly evolving issues. Please reach out to us with additional suggestions for resources and effective policies at dukemargolis@duke.edu - we welcome your input.

Introduction

Many monoclonal antibody (mAb) candidates are currently being developed and studied in clinical trials – with the goal of reducing or preventing the progression of COVID-19 by neutralizing the virus in infected or exposed persons. At this time, Eli Lilly's bamlanivimab (LY-CoV555) has received emergency use authorization (EUA) from the U.S. Food and Drug Administration (FDA) for use in symptomatic, non-hospitalized patients at high risk of progressing to severe disease. Regeneron's REGN-COV2, a combination of two neutralizing mAbs (REGN10933 and REGN10987), has also submitted an EUA request to FDA and is awaiting an agency decision that could occur at any time.

Emerging evidence on these mAb candidates indicates that they significantly reduce hospitalizations when administered early to patients with mild or moderate symptoms. Subgroup analysis indicated that patients who are older, obese, or have chronic diseases that place them at higher risk for COVID-19 complications have a larger treatment effect. In short, well-designed clinical trials have demonstrated a significant benefit in terms of reduced symptoms and hospitalizations for each product, as well as reduced viral loads. But while some evidence shows larger absolute benefits in patients at higher risk of symptom progression to hospitalization, evidence defining optimal dosing and differential benefits (or risks) as a function of underlying

characteristics of COVID-19 patient groups is limited. Additional studies are underway to address effectiveness at lower doses and benefits and risks in additional groups.

Based on the available evidence, these antibodies could significantly impact the course of illness, hospitalizations, and other serious health outcomes for COVID-19 patients at risk of progression to more severe disease. However, several immediate and short-term issues must be addressed to enable these treatments to be used effectively. **Immediate actions by health care providers, payers, states, and clinical researchers are needed to address a set of practical implementation issues for COVID-19 monoclonal antibodies, so that the available supply of antibodies will have maximum impact on reducing hospitalizations and other COVID-19 complications, and to avoid inequities in access and outcomes.**

The remainder of this issue brief describes key issues impacting access to and appropriate use of antibodies, as well as potential strategies to address them. These issues include:

- Timely testing and specialized infusion capacity
- Payment for administration
- State-guided allocation to specialized infusion sites
- Monoclonal antibody supply and guidance for use

Timely Testing and Specialized Infusion Capacity

Effective use of antibodies will require significant new health care capabilities. Hospitals and other health care providers, working with test providers and state and local public health authorities, will need to provide timely diagnostic testing, notification of test results, education and referral for mAb treatment, and infusion at a dedicated site with appropriate medical oversight (potentially including "pop-up" or home infusion); protective equipment for health personnel; and timely supply and storage of the antibodies. Approaches to referral and treatment include:

- **Testing provider referral to available infusion site**: Test providers, including primary care groups, pharmacies, COVID-19 testing sites, or public health sites, should inform patients who test positive about the potential benefits of treatments and how they can take steps to receive treatment. Ideally, there would be a "smooth handoff" of the patient to a local infusion site.
- **Integrated approach**: Some integrated health care organizations have the capacity to order testing, share test results, and provide infusion treatment within a single health system.

In either approach, infusions could be conducted at dedicated hospital sites (e.g., specialized space near an emergency department or other available acute care space); at special ambulatory

sites or repurposed infusion clinics; at "pop-up" sites that could be located in areas of significant outbreaks; or via mobile vans or potentially home administration. No such acute outpatient treatment capacity has been needed so far for the timely, acute treatment of non-hospitalized COVID-19 patients. All will require dedicated infusion nurse staffing, technician and administrative support, and sufficient medical oversight to manage possible allergic reactions. The Federal government intends to provide a "playbook" for infusion providers on all capabilities needed for successful implementation.

Payment for Administration

The Federal government has acquired current supplies and secured advance purchase contracts with both Lilly and Regeneron, with some expect increased production. Similar contracts can be implemented for other manufacturers with antibodies in development that will reach the market in 2021. Consequently, no patients should have to pay for an antibody treatment in the coming months of the public health emergency.

However, infusion and related costs may be substantial, especially for patients who may need assistance with timely referral and treatment. Administration costs are expected to be covered by private insurers and state Medicaid plans. A recent CMS regulation related to COVID-19 therapeutics affirms Medicare coverage, and a more recent CMS program instruction from November 10 states that Medicare payment will be equal to the payment for hospital outpatient infusion of more complex chemotherapy drugs. CMS also stated that by using the same payment authority that applies to COVID-19 vaccines, this payment will apply regardless of the setting where the antibody is infused and no copayment will apply to Medicare beneficiaries. CMS also created specific billing codes for the infusion of the Lilly antibody, facilitating tracking of this particular product. Continuing to assign antibody-specific codes to future authorized antibodies will help ensure appropriate tracking. CMS also noted that Medicaid plans are required to cover monoclonal treatments with no copays. Coverage mechanisms for administration to uninsured patients have not been established.

Payment rates must be adequate to support sufficient development of referral and specialized infusion capacity. Medicare will pay $309.60 for the antibody infusion. Some providers regard this payment as inadequate, especially given the special steps required to set up this infusion capacity. Because of the potential impact on complications and related hospitalization costs, private payers have generally affirmed support for setting payments on the higher end of existing infusion rates to encourage appropriate use. If private payers also base payment on rates for complex outpatient chemotherapy infusion, the commercial infusion payment would likely be around or above $700. Additional payments to test providers for timely referral may also help; Medicare has an "evaluation and management" payment for counseling in conjunction with testing that could be expanded to support timely referral. Integrated-care systems would likely prefer a single bundled payment that encompasses referral and treatment to provide flexibility

in developing a more comprehensive model of care. Finally, an incremental payment for key data collection – to contribute to a registry or to participate in a practical trial, for example – would support needed additional evidence collection.

State-Guided Allocation to Specialized Infusion Sites

The Federal government has set up a distribution system for available COVID-19 supplies with weekly allotments linked to a state's share of new cases and hospitalizations, building on the direct manufacturer-to-provider distribution system implemented for remdesivir. In particular, the Federal government is overseeing a distribution system in which manufacturers shift available products directly to sites identified by states and territories. The Federal government has set up an online dashboard to notify states weekly about their new allocations of available antibody supply, with allocations based on reported data from each state on 7-day new hospitalizations (a lagging indicator, but related to health system stress) and confirmed cases. States then can direct portions of their allocations to be directly shipped to hospitals and potentially other local infusion providers; shipments are generally expected to occur within 1-2 days.

The first HHS allotment for distribution of the Lilly antibody included over 79,000 doses intended for hospitals. In addition to responding to requests from particular infusion providers, states should set up a mechanism, building on their existing COVID-19 emergency response systems, for providers to notify state authorities about their capacity and need for antibodies. States should track regional distribution and, if possible, data on the characteristics of patients receiving antibody treatment to identify geographic and other gaps in antibody availability.

States should also take steps to avoid and address any emerging gaps in access for patient groups most likely to benefit, building on best practices for access that emerge in early use patterns. These include encouraging alternatives to traditional infusion sites as noted above. States may partner with providers to establish special ambulatory sites, repurposed infusion clinics, or at "pop-up" sites or mobile vans that could be deployed to areas of significant outbreaks. Infusions designed for residents of long-term care facilities and home infusion for patients unable to travel easily could reach additional high-risk groups. The goal of such state activities should be to promote equitable access for groups that would otherwise face substantial barriers to treatment, and to maximize avoidance of serious complications, hospitalizations, and health care system stress.

To implement more effective distribution models, states and providers will benefit from predictability regarding the amount of product they should expect to receive in the future. In conjunction with clarity around the weekly allocation formula, the Federal government should set expectations about future overall supplies and a baseline level and range of supplies that states might expect, given possible future developments in the pandemic. Recognizing that

demand by region or state can change dramatically as outbreaks peak and subside, the Federal government can then inform states of the percent of baseline that they will actually receive in upcoming shipments (e.g. 50% of baseline, 150% of baseline, etc.). Smaller, more frequent shipments to states will enable more timely adjustments to regional infection rate changes and will discourage hoarding. In addition, Federal funding to support a minimum infusion capacity in each region, or Federally-supported infusion units that could be deployed to augment states experiencing greater outbreaks (as has been done with testing), would also help states provide timely antibody treatments when needed.

Monoclonal Antibody Supply and Guidance on Use

Lilly has signed a contract with the U.S. Department of Defense (DOD) and HHS for 300,000 initial doses over the next two months, and the federal government can purchase up to an additional 650,000 through the end of June 2021. Regeneron's contract with DOD and HHS is for an estimated 70,000-300,000 doses over the next several months. Additional antibodies may reach the market by early 2021 to augment these supplies.

It is likely that, initially, supplies will exceed infusion capacity. However, the Lilly emergency use authorization applies to COVID-19 patients soon after diagnosis with mild to moderate symptoms and a range of characteristics – age, obesity, and/or significant chronic conditions – that place them at higher risk of progression to hospitalization. The impact estimated in the emergency authorization is a reduction from 10% to 3% risk of hospitalization. With U.S. caseloads in the current surge exceeding 150,000 patients per day, it is likely that at least 30% of these cases or at least 45,000 patients per day meet the criteria for the emergency authorization, including a disproportionate share of patients from underserved and at-risk populations. **If efforts to expand referral and infusion succeed and all such patients were treated, the expected near-term supply of antibodies would be exhausted within four days (based on an estimated supply of 150,000 doses per month).**

Consequently, steps to increase the effective supply of antibodies are critical. The Federal government should explore recruitment of additional manufacturing capacity to help meet this potential treatment need, as well as additional advance purchase commitments – not only for the Lilly and Regeneron products, but also to increase supply of other promising antibodies in advanced clinical testing.

With the potential mismatch between supply and demand, clinicians and patients would benefit from further guidance on how to use limited supply. Rates of development of moderate or even mild symptoms differ substantially based on risk factors including age, obesity, and comorbid conditions, and are important considerations in prioritizing use. However, more evidence is needed on whether these risk factors plus the nature or extent of symptoms or other potentially readily measurable indicators (e.g., viral concentration in a COVID-19 diagnostic test) are

associated with significant differences in likelihood of benefit or risk. In addition, timing and dosage may affect response. For all of these reasons, better evidence on differential benefits across patient groups would enable more informed clinical decision making. In addition to support for the timely development of such evidence, further ethical guidance – like the work undertaken by the National Academy of Medicine for vaccine distribution and access – could also be helpful for guiding use if supplies are limited.

Feasible Mechanisms for Needed Evidence Development

Several short-term steps could augment the limited evidence available on monoclonal antibodies with supporting payments for data collection. These include:

- Incorporating key data on dosing, patient characteristics, and (as available) subsequent course in COVID-19 registries already maintained by some health systems, such as Providence Health, HCA, or OptumHealth.
- Implementing a multicenter registry that consistently captures key information from multiple participating health care organizations, for example like that supported by Mayo Clinic and collaborators for convalescent plasma patients, or by PCORnet for certain COVID-19 patients and health care providers. Such registries would need to be linked to key information on the patient's subsequent course if not available to the infusion provider, for example by collaborating with payers and CMS to link insurance claims.
- Implementing single- or multi-payer based registries consisting of key clinical data submitted by participating health care organizations linked to insurance claims information. Such data collection at the time of treatment would need to be supported by sufficient payment and limited to key objective data, and preferably automated to avoid significant additional burden on stressed health care providers.

Building on or in addition to these efforts, simple randomized studies should also be considered. For example, available evidence indicates the 2800mg dose used in the clinical studies for Lilly's bamlanivimab is likely higher than needed to achieve benefit. In the EUA for this antibody, FDA authorized dosing at a much lower 700mg, and an additional clinical trial on dosing is underway. A relatively simple "real world" clinical study could randomize patients to the authorized or somewhat lower doses – especially if supplies are limited and the alternative may be greater rationing. Another simple trial might compare dosing very early versus a little later in the course of illness – still well before any serious complications have occurred, but allowing some additional time to determine whether a patient is very likely to recover without complications, as most patients do even in high-risk categories. Studies should also address the relative performance of alternative approaches to referral and infusion, in terms of patient completion rates, costs, and complications. These parallel, simple trial mechanisms should capture the same key baseline characteristics and major outcomes as currently ongoing, more traditional trials (e.g., NIH's ACTIV) so that results can be adequately compared.

Steps should be taken now to develop this evidence generation capacity, including identifying potential participating health care providers and payers, identifying a minimal common data set to facilitate learning, and providing support for setting up the registry or network and covering the costs of data collection. Short of formal studies, support for a "learning network" to share early experience with referral and infusion could help address implementation challenges and identify critical areas of further need (e.g., state implementation support). Priority issues for further evidence development should include:

- Optimal dosing for COVID-19 mAbs, stratified by sub-population or patient risk factors
- Timing of mAb treatment post identification of symptoms, positive COVID-19 test, or other initiating event
- Treatment effects by patient risk category (low, medium, high)
- Variability in application of mAb treatment across different referral protocols and/or types of infusion site
- Variability in approaches to post-treatment monitoring
- Comparative effectiveness questions when multiple products are authorized/approved
- Utility of post-exposure prophylaxis