VIEWPOINT

The Challenges Ahead With Monoclonal Antibodies
From Authorization to Access

Robert H. Goldstein, MD, PhD
Division of Infectious Diseases and Division of General Internal Medicine, Department of Medicine, Massachusetts General Hospital, Boston; and Harvard Medical School, Boston, Massachusetts.

Rochelle P. Walensky, MD, MPH
Division of Infectious Diseases, Massachusetts General Hospital, Boston; and Harvard Medical School, Boston, Massachusetts.

Video

When President Trump received an infusion of a monoclonal antibody cocktail (REGN-COV2 from Regeneron) on October 2, 2020, his physicians were presumably reacting to promising data reported in the company's news release from 3 days earlier. The company had announced the results of a trial involving 275 individuals randomized 1:1:1 to placebo, low-dose monoclonal antibody treatment, or high-dose treatment.[1] Per the news release, those patients with high viral loads and those who had not already mounted their own antibody response showed a greater decrease in viral load and time to resolution of symptoms. Additional data on more important outcomes, including rates of hospitalization, development of serious illness, and mortality were not available. It was not clear, although unlikely, if the study was powered to detect these outcomes.

The news release, announced in anticipation of an investor discussion, noted that the company "plan[s] rapidly to discuss results with regulatory authorities." Specifically, Regeneron is pursuing an Emergency Use Authorization from the US Food and Drug Administration (FDA). Federal law allows the FDA commissioner to grant the use of unapproved diagnostics and therapeutics during a declared public emergency, which the US government declared on March 27, 2020, through an Emergency Use Authorization.

> Monoclonal antibodies have the potential to be even more effective than remdesivir, by treating patients in early stages of infection and, possibly, averting hospitalization.

Rapid development and distribution of novel therapeutics is critical during a public health crisis. As of October 31, 2020, the number of COVID-19 infections exceeded 9 million in the US and the number of deaths surpassed 220 000. It is estimated that excess deaths in the US related to the COVID-19 pandemic will exceed 400 000 by year's end.[2] Emergency Use Authorizations have been an important part of the US response to this pandemic and have resulted in a rapid expansion in diagnostic testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), improvements in personal protective equipment supply chains, and development of medical devices that address the shortage of ventilators. The process has allowed for the use of remdesivir, one of the few, albeit limited therapies in the current treatment arsenal.[3,4] Monoclonal antibodies have the potential to be even more effective than remdesivir, by treating patients in early stages of infection and, possibly, averting hospitalization. Allowing for widespread distribution as quickly as possible could potentially prevent substantial morbidity and mortality. With this hope, it is essential to remain mindful of the challenges experienced previously and how they might manifest multifold.

Prepublication news releases have become common for pharmaceutical companies. Although these communications provide investors with reassurance, they also leave clinicians uncertain about how best to leverage new interventions for treatment, often with limited availability of the drug. Remdesivir was granted Emergency Use Authorization on May 1, 2020, two days after a brief news release from Gilead Sciences Inc (the drug's manufacturer) announced efficacy of the drug in decreasing the duration of symptoms for patients with moderate to severe COVID-19 infection.[5] The news release and distribution of remdesivir, which started on May 5, occurred 3 weeks before any primary clinical data were published or made publicly available.[6] What followed was predictable—hospitals were tasked with providing a limited supply of medication without knowing which patients might benefit most and if the drug actually decreased mortality or other important outcomes.

The early days of remdesivir distribution were marked by confusion and a lack of transparency.[7] In the absence of government-led equitable distribution, grassroots efforts by individual hospitals attempted to fill the void, working to ensure that the drug was available to patients most likely to benefit, that redistribution between hospitals could occur in response to the shifting epicenters of the pandemic, and that hospitals were not overly taxed by patients transferred specifically for remdesivir. Once remdesivir was administered, patient outcomes were not systematically cataloged. Many called for the creation of a patient registry that would monitor distribution demographics, safety events, and clinical outcomes.[8] Perhaps such a registry might have demonstrated before now that treatment with remdesivir did not confer a mortality benefit.[3]

An Emergency Use Authorization for a monoclonal antibody in the absence of public release of efficacy data is likely to magnify the problems that occurred with remdesivir. Production of the drug appears to be extremely limited. When remdesivir was authorized, Gilead announced production of 607 000 vials of the drug or enough to treat 78 000 hospitalized patients. Regeneron has suggested that

Corresponding Author: Robert H. Goldstein, MD, PhD, Division of Infectious Diseases, Massachusetts General Hospital, 55 Fruit St, Cox 5, Boston, MA 02114 (rgoldstein3@partners.org).

only 50 000 doses of REGN-COV2 will be made available in the initial weeks after a potential authorization (since October 13, the 7-day average of daily cases in the US has, once again, remained greater than 50 000).[9] The company hopes to increase production and provide 300 000 doses to US clinicians, leaving it to individual clinicians and hospitals (possibly in the absence of primary data) to determine which patients might best benefit from this limited resource.

Unlike remdesivir, which is administered to inpatients, monoclonal antibodies are most effective when used very early in the disease course with outpatient administration to individuals not requiring hospitalization. The objective measures of local disease burden, such as hospital case counts that provide some clarity for remdesivir distribution, will not be effective markers in the outpatient setting. Nearly all of the cases diagnosed in outpatient clinics and drive-through testing sites may qualify for monoclonal antibody administration; only 5% of total US COVID-19 cases have required hospitalization. Distribution will need to be widespread and should anticipate shifts in virus transmission. At current daily case counts and available doses, the supply of monoclonal antibody product could feasibly be exhausted in less than 2 weeks.

The administration of monoclonal antibodies will further tax outpatient clinics and challenge the ability of clinicians and health care centers to provide adequate and equitable access. The currently studied monoclonal antibody preparations require a 1-hour intravenous infusion. Those hospitals and clinics that can currently provide infusions of therapeutics generally do so in dedicated facilities previously reserved for delivery of immune-suppressing biologic agents and chemotherapy. As outpatient medical care returns to prepandemic capacity, the risk increases for a new round of disturbances to necessary medical treatments, health care–associated transmission of the virus to immunosuppressed patients, and insufficient distribution to rural and safety net hospital systems that lack the capacity for large-scale infusion operations.

Regeneron has not announced the cost of its monoclonal antibody product, although analysts suggest it will likely be priced at $3000 per dose with the potential for $1 billion in global sales.[10] Unlike remdesivir, which is provided to hospitalized patients as part of a bundled hospital payment and which allows delivery to any medically eligible inpatient, the cost of the monoclonal antibody and its infusion will most often be billed through outpatient clinicians and centers. For patients with insurance, the federal government has guaranteed coverage of all COVID-19 treatments without any cost sharing. But for those without insurance, the Department of Health and Human Services has provided relatively limited reimbursement for COVID-19 care and many clinicians and medical centers are not eligible for federal programs, leaving the exorbitant outpatient cost burden on the patient. Nearly 8 million US residents have lost their employee-sponsored health insurance due to the COVID-19 pandemic, worsening disparities in insurance coverage for Black and Latinx people, and leaving those with the highest rates of infection unable to afford the best possible treatment. It is quite possible that inequities in access to monoclonal antibodies and other novel therapies will increase already well-documented health care disparities.

More treatments for SARS-CoV-2 are urgently needed. Emergency Use Authorization is a necessary tool that can be used to make promising interventions available to those infected, treat patients earlier in the disease, and avert hospitalizations. Shifting the attention from inpatient to outpatient management of COVID-19 requires transparency in clinical efficacy, widespread equitable distribution of novel therapeutics, and controls on cost. Failure to address these issues will intensify the numerous challenges that the health care system has faced throughout this pandemic, will result in a repeat of shortcomings and failures with achieving an effective and equitable therapeutic response, and importantly, will only exacerbate the disparities in care and outcomes related to this disease.

ARTICLE INFORMATION

Published Online: November 11, 2020. doi:10.1001/jama.2020.21872

Conflict of Interest Disclosures: None reported.

REFERENCES

1. Regeneron's REGN-COV2 antibody cocktail reduced viral levels and improved symptoms in non-hospitalized COVID-19 patients. News release. Regeneron; September 29, 2020. Accessed October 17, 2020. https://investor.regeneron.com/news-releases/news-release-details/regenerons-regn-cov2-antibody-cocktail-reduced-viral-levels-and

2. Woolf SH, Chapman DA, Sabo RT, Weinberger DM, Hill L, Taylor DDH. Excess deaths from COVID-19 and other causes, March-July 2020. JAMA. Published online October 12, 2020.

3. WHO Solidarity Trial Consortium. Repurposed antiviral drugs for COVID-19—interim WHO SOLIDARITY trial results. *medRXiv*. Preprint posted October 15, 2020. doi:10.1101/2020.10.15.20209817

4. Spinner CD, Gottlieb RL, Criner GJ, et al. GS-US-540-5774 Investigators. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. *JAMA*. 2020;324(11):1048-1057. doi:10.1001/jama.2020.16349

5. Gilead announces results from phase 3 trial of investigational antiviral remdesivir in patients with severe COVID-19. News release. Gilead Sciences Inc; April 29, 2020. Accessed October 17, 2020. https://www.gilead.com/news-and-press/press-room/press-releases/2020/4/gilead-announces-results-from-phase-3-trial-of-investigational-antiviral-remdesivir-in-patients-with-severe-covid-19

6. Biegel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of COVID-19—final report. *N Engl J Med*. First published online May 22, 2020. Updated online October 8, 2020. doi:10.1056/NEJMoa2007764

7. Ison MG, Wolfe C, Boucher HW. Emergency Use Authorization of remdesivir: the need for a transparent distribution process. *JAMA*. 2020;323(23):2365-2366. doi:10.1001/jama.2020.8863

8. Sarpatwari A, Kaltenboeck A, Kesselheim AS. Missed opportunities on emergency remdesivir use. *JAMA*. 2020;324(4):331-332. doi:10.1001/jama.2020.11932

9. Walker J, Loftus P. Antibody drugs touted by Trump could be next to get authorized for COVID-19. *Wall Street Journal*. October 9, 2020. Accessed October 17, 2020. https://www.wsj.com/articles/antibody-drugs-touted-by-trump-could-be-next-to-get-authorized-for-covid-19-11602235803

10. Lee J. SVP Leerink analysts predict $1 billion in peak sales of Regeneron's experimental COVID-19 treatment. MarketWatch. Published October 6, 2020. Accessed October 17, 2020. https://www.marketwatch.com/story/svb-leerink-analysts-predict-1-billion-in-peak-sales-of-regenerons-experimental-covid-19-treatment-2020-10-06