EDITORIAL COMMENTARY

Bebtelovimab in the Real World: Promise and Fulfillment

Robin K. Avery[1] and M. Veronica Dioverti Prono[1]

[1]Department of Medicine, Division of Infectious Diseases, Johns Hopkins University, Baltimore, Maryland, USA

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) monoclonal antibodies have revolutionized the treatment of coronavirus disease 2019 (COVID-19) and have mitigated the risk of severe disease in high-risk individuals [1]. In contrast to the early phase of the pandemic, we now have an intervention that effectively prevents hospitalizations and severe illness. However, it has been known for months that a looming disaster is approaching, that is, the United States (US) federal government funding for COVID-19 monoclonal antibodies will run out, with reference to the current monoclonal antibody, bebtelovimab. This is particularly ominous for immunocompromised people, including many organ transplant and some hematopoietic stem cell transplant recipients who are taking the immunosuppressive drug tacrolimus or similar agents, who are at risk for severe drug–drug interactions with nirmatrelvir-ritonavir.

Previous monoclonal antibodies have been found to have markedly reduced activity against Omicron subvariants (except sotrovimab for BA.1). Bebtelovimab is the only monoclonal antibody authorized for treatment that retains activity against all subvariants to date, including BA.4 and BA.5 [2]. Tixagevimab-cilgavimab is authorized for preexposure prophylaxis but not for treatment. In February 2022, the US Food and Drug Administration issued an Emergency Use Authorization (EUA) for bebtelovimab on the basis of its in vitro neutralization activity and clinical data from before the rise of the Omicron variant [3, 4]. At that time, the US Health and Human Services Secretary announced the purchase of 600 000 doses [5], followed by 150 000 more doses in June 2022 [6], projected to meet treatment needs through the end of August 2022. But what then? Patients, clinicians, and others are now asking: What happens when the current supply of bebtelovimab runs out?

To understand the gravity of this situation, it is necessary to examine the evidence for the benefits of bebtelovimab in patients at risk for progressing to severe infection during the Omicron era. This evidence has been lacking until now. Thanks to the wisdom of investigators from the Mayo Clinic, who devised a health system–wide program for monoclonal antibody administration that facilitated data collection on real-world outcomes, we now have the evidence that is needed. We now have a better understanding of who gets treatment with bebtelovimab, what their underlying diseases and comorbidities are, and what their risk is for progression to severe illness and death, in comparison to patients who receive nirmatrelvir-ritonavir. As it is unlikely that a randomized trial comparing these therapies would be feasible, this is the best evidence we are likely to have in a time frame relevant for policy decisions.

In this issue of *The Journal of Infectious Diseases* [7], Razonable and colleagues present a retrospective cohort study of >3600 patients treated with either bebtelovimab (n = 2833) or nirmatrelvir/ritonavir (n = 774) under EUA criteria from 20 March 2022 onward, when BA.2 became the dominant subvariant. They describe a shared decision-making process incorporating patient factors, drug factors, and patient preferences. The primary outcome was progression to severe disease (World Health Organization score of ≥4). Secondary outcomes were requirement for intensive care unit care, and all-cause mortality by day 30. The bebtelovimab cohort included older people with more comorbidities (heart, lung, and/or kidney disease; rheumatologic disease, malignancy, and immunocompromised status), whereas the nirmatrelvir/ritonavir cohort had higher median body mass index and more diabetes. Despite having a higher degree of comorbidities, the bebtelovimab group had outcomes that were comparable to those in the nirmatrelvir-ritonavir group (1.4% vs 1.2% progressed to severe disease and 0.2% vs 0% died, respectively).

In patients at risk for severe drug–drug interactions with nirmatrelvir-ritonavir, including organ transplant recipients, bebtelovimab has been a mainstay of treatment. In addition, there are concerns about rebound symptoms after nirmatrelvir-ritonavir [8] and the possibility of antiviral resistance developing in the future. While other outpatient therapies are available, molnupiravir is likely less effective, and a 3-day outpatient course of remdesivir can be logistically challenging. Having all of these

therapies in our armamentarium is crucial to ensuring the best outcome for our most vulnerable patients.

The study by Razonable et al is important and timely, given the worrisome prospect of a loss of funding for bebtelovimab in the near future. This study confirms what front-line clinicians have already observed about excellent outcomes with bebtelovimab. It is to be hoped that these data will inform policy and funding decisions, potentially to the great benefit of high-risk patients who might otherwise not have the opportunity to receive this treatment.

References

1. Razonable RR, Ganesh R, Bierle DM. Clinical prioritization of anti-spike monoclonal antibody treatment of mild to moderate COVID-19. Mayo Clin Proc **2022**; 97:26–30.
2. Takashita E, Yamayoshi S, Simon V, et al. Efficacy of antibodies and antiviral drugs against Omicron BA.2.12.1, BA.4, and BA.5 subvariants. N Engl J Med **2022**; 387:468–70.
3. United States Food and Drug Administration. Emergency use authorization for bebtelovimab. **2022**. https://www.fda.gov/media/156152/download. Accessed 5 August 2022.
4. Dougan M, Azizad M, Chen P, et al. Bebtelovimab, alone or together with bamlanivimab and etesevimab, as a broadly neutralizing monoclonal antibody treatment for mild to moderate, ambulatory COVID-19. medRxiv [Preprint]. Posted online 12 March **2022**.
5. US Department of Health and Human Services. Secretary Becerra announces HHS purchase of 600,000 treatment courses of new monoclonal antibody that works against Omicron. **2022**. https://www.hhs.gov/about/news/2022/02/10/secretary-becerra-announces-hhs-purchase-600000-treatment-courses-new-monoclonal-antibody-that-works-against-omicron.html. Accessed 5 August 2022.
6. US Department of Health and Human Services, Administration for Strategic Preparedness and Response. Biden-Harris administration purchases additional doses of bebtelovimab to treat high-risk COVID-19 patients. **2022**. https://aspr.hhs.gov/newsroom/Pages/bebtelovimab-30June22.aspx. Accessed 5 August 2022.
7. Razonable R, O'Horo J, Hanson S, et al. Comparable outcomes for bebtelovimab and ritonavir-boosted nirmatrelvir treatment in high-risk patients with coronavirus disease-2019 during severe acute respiratory syndrome coronavirus 2 BA.2 Omicron epoch. J Infect Dis **2022**. In press.
8. Boucau J, Uddin R, Marino C, et al. Virologic characterization of symptom rebound following nirmatrelvir-ritonavir treatment for COVID-19. Clin Infect Dis **2022** Jun 23;ciac512. doi:10.1093/cid/ciac512. Online ahead of print.