Bebtelovimab: considerations for global access to treatments during a rapidly evolving pandemic

Given the activity of bebtelovimab against current global circulating SARS-CoV-2 variants, Hentzien and colleagues[1] raise several questions as to why bebtelovimab is unavailable outside the USA.

Lilly agrees that bebtelovimab should be available outside the USA. We remain open to communication with global health authorities, including presenting the data package upon request;[2] however, due to local regulations, health authorities might not have an emergency use pathway or might decide that the current data package for bebtelovimab is insufficient for authorisation.

The COVID-19 pandemic prompted immediate adaptive innovations by drug developers and regulatory agencies to quickly provide life-saving therapeutics and vaccines. Lilly's COVID-19 monoclonal antibody programme adapted to pandemic requirements during the development of bamlanivimab alone and in combination with etesevimab, positively influencing the development of bebtelovimab and its emergency use authorisation by the US Food and Drug Administration (FDA). As summarized by Dougan and colleagues,[3] the successful development of bebtelovimab was achieved with proactive studies, continuous virus surveillance, and streamlined clinical design. For instance, live virus neutralisation assays that confirmed potent neutralisation against circulating SARS-CoV-2 variants correlated with in vivo efficacy and allowed for efficient transition to in-human phase 1 trials.[4,5] Additionally, US regulatory acceptance of changes in viral load and sustained symptom resolution as surrogate markers of COVID-19 improvement, as opposed to severe and infrequent clinical outcome measures (eg, admission to hospital and death), allowed emergency use authorisation with available phase 2 data.

Emergency use authorisation of bebtelovimab was also achieved through adaptation and proactive communication from the FDA with sponsor companies, to ensure alignment on clinical trial data and packages intended for emergency use authorisation submissions. Thus, when the omicron (B.1.1.529) variant became the predominant variant and authorised antibody treatments were no longer effective, the available data supporting bebtelovimab (non-clinical live virus neutralisation data and phase 1 and 2 results) were deemed sufficient by the FDA for emergency use authorisation of the drug in the USA for the treatment of mild to moderate COVID-19 in certain high-risk patients for whom alternative COVID-19 treatment options approved or authorised by the FDA are not accessible or clinically appropriate. Additionally, Lilly is currently fulfilling conditions of the emergency use authorisation that require a study to further evaluate bebtelovimab,[5] including conducting a trial to evaluate the pharmacokinetics and safety of bebtelovimab in paediatric patients.

This modified regulatory approach which met the US requirements for emergency use during a health emergency, or regulatory mutual recognition, could serve as a global model to accelerate authorisation of next-generation vaccines and therapeutics within the current and future pandemics to help patients worldwide.

RMN, CD, and HU are salaried employees and stockholders of Eli Lilly and Company.

*Russell M Nichols, Carmen Deveau, Himanshu Upadhyaya
rnichols@lilly.com
Eli Lilly and Company, Indianapolis, IN 46285, USA

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Viral replication and infectivity of monkeypox through semen

With great interest, we read the findings presented by Daniele Lapa and colleagues,[1] showing the successful isolation of monkeypox viral DNA from the seminal fluid of an infected patient. The authors suggested that monkeypox might have a genital reservoir because of the persistent viral shedding in seminal samples, even at low viral copies. These findings could indicate that the current monkeypox outbreak predominantly spreads through sexual transmission, especially after the various reports that estimated that most monkeypox cases were reported among individuals who identify as men who have sex with men. Understanding the mode of transmission could allow for the development of proper interventional approaches to reduce the intensity of the current outbreak.

Monkeypox DNA presence in the seminal fluids might be due to local genital replication or passive diffusion

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from urine, blood, or genital lesions.[2] However, the exact mechanism of this event remains controversial in the literature. Although Lapa and colleagues[1] reported that cross-contamination from other sources (blood and urine) is unlikely due to the absence of viral DNA in their specimens, this finding should be interpreted with caution due to some points. First, the finding is based on the results obtained from a single patient. Therefore, an appropriate conclusion is not attainable from this report. Moreover, Noe and colleagues[3] showed no growth when culturing the monkeypox virus seminal samples of two patients with monkeypox using VeroE6 cell lines.

Second, previous investigations have detected monkeypox viral DNA in the blood and urine samples of patients with monkeypox. For example, Thornhill and colleagues[4] reported monkeypox viral DNA-positive PCR results in 7% of blood samples and 3% of urine samples taken from a total of 528 patients with monkeypox. Although these rates are meager, they should be considered, especially because positive blood and urine samples were further reported in other relevant investigations.[3,5] Detecting viral shreds in these samples might suggest potential semen cross-contamination by these particles. Although the authors excluded this possibility in their patient, the sample size is still a major limitation. Third, cross-contamination of viral particles might also occur from genital lesions (eg, exfoliated epithelial cells). However, the authors did not exclude this possibility because their lesion samples were obtained from the head only. According to the evidence from the authors and other studies,[3] skin lesions have the most extended viral shedding intervals and highest viral concentrations. For example, Thornhill and colleagues[4] reported that samples obtained from skin and anogenital regions had the highest positive PCR results (97%) when compared with other samples. Moreover, Tarín-Vicente and colleagues[6] reported that 99% of skin swabs and 78% of anal swabs were positive in their monkeypox population. These findings indicate the potential ability of these lesions to induce cross-contamination with seminal fluids. However, this was not also specified by Lapa and colleagues.

Furthermore, monkeypox viral detection in semen is not sufficient to indicate its sexual transmission since evidence from previous studies on other viruses that caused viremia and could be detected in semen did not indicate their sexual transmission[2,7] Detecting viral particles within the male reproductive system is commonly secondary to viraemia because the blood–testis barrier is liable to viruses, mainly when local or systemic inflammation occurs.[8] Viral persistence through the tract is also likely, irrespective of its ability to replicate because the testes can be an immunologically favored site for the virus. Accordingly, we suggest that the current evidence be carefully interpreted until other investigations confirm the findings.

We declare no competing interests.

*Abdullah Reda, Ranjit Sah, Alfonso J Rodriguez-Morales, *Jaffer Shah*
jaffer.shah@drexel.edu

Faculty of Medicine, Al-Azhar University, Cairo, Egypt (AR); Tribhuvan University Teaching Hospital, Institute of Medicine, Kathmandu, Nepal (RS); Grupo de Investigación Biomedicina, Faculty of Medicine, Fundación Universitaria Autónoma de las Américas, Pereira, Colombia (AJR-M); Master of Clinical Epidemiology and Biostatistics, Universidad Científica del Sur, Lima, Peru (AJR-M); New York State Department of Health, New York, NY 10013, USA (JS)

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Authors' reply

We thank Abdullah Reda and colleagues for their comments on our work.[1] We agree that the possibility that sources for the detection of monkeypox virus genomes in the semen could derive from passive diffusion from other body fluids or specimen contamination from genital lesions deserves careful consideration, based also on previous experience with other human viruses. However, several findings make this possibility unlikely in our case. A possible mechanism favouring diffusion from the blood to the genital tract is increased blood barrier permeability due to inflammatory conditions such as orchitis. Existing evidence shows that orchitis during smallpox was exceedingly rare, and inflammation in the genital tract was excluded in the patient. Moreover, as pointed out in our Comment,[1] we found that monkeypox virus PCR test for urine was negative. Furthermore, this PCR test had a much higher cycle threshold than semen in peripheral blood samples collected within the same timeframe, thus making it unlikely that semen was contaminated by these fluids. Finally, to avoid monkeypox virus contamination from the only genital lesion located on the penis, we required the hands and penis to be

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