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Note

Lack of clinical evidence of antiviral therapy for human monkeypox: A scoping review

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ABSTRACT

Since May 2022, many human monkeypox cases have been reported from non-endemic countries. This systematic review aimed to evaluate and summarize the existing research on the efficacy and safety of tecovirimat, brincidofovir, and cidofovir for patients with monkeypox. We searched studies that reported the efficacy and adverse events of tecovirimat, brincidofovir, or cidofovir for patients with human monkeypox in several databases including preprint servers. Only five studies were included. The efficacy and adverse events were assessed in only five and four patients, respectively. Regarding tecovirimat, all two patients recovered from monkeypox. One had no adverse event and the other has no description of an adverse event. Regarding brincidofovir, all three patients recovered from monkeypox but all of them had increased alanine transaminase, and one had nausea and abdominal discomfort. There was no study on treatment with cidofovir. Based on past studies and our results, tecovirimat might be the best choice due to ease of administration (oral drug), fewer side effects, and past treatment results for human monkeypox administration. However, very few studies were included in this scoping review. Therefore, further studies are needed to assess their efficacy and safety as possible treatments for human monkeypox.

Since May 2022, many human monkeypox cases have been reported from non-endemic countries. According to the World Health Organization, a total of 3413 laboratory-confirmed cases, including one death, have been reported from 50 countries between 1 January and 22 June 2022 (https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON393). Ninety-eight percent of these were reported since May 2022.

In such a global situation, there is an urgent need to accumulate evidence of the efficacy and safety of antivirals for human monkeypox [1,2]. There are three potential bioavailable drugs, tecovirimat, brincidofovir, and cidofovir, that can be used against the monkeypox virus and have been used in the United States of America (USA) and Europe [3,4]. However, no clinical trials have reported on their efficacy and safety in patients with human monkeypox.

To date, one systematic review based on literature up until 2018 has been completed on the potential efficacy of tecovirimat, brincidofovir, and cidofovir against orthopoxvirus infections, including the monkeypox virus [5]. To update and respond to this multi-country monkeypox outbreak in non-endemic countries, our systematic review aimed to evaluate and summarize the existing research on the efficacy and safety of tecovirimat, brincidofovir, and cidofovir for patients with monkeypox.

We report this review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA) extension

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for scoping reviews (PRISMA-ScR) statement [6] (**Supplemental Method 1**). We registered the study protocol on the Open Science Framework (URL: https://osf.io/ehvt7/). According to the pre-defined protocol for this scoping review, we conducted a scoping review based on the 5-stage framework outlined by the Joanna Briggs Institute: identifying the research question; identifying relevant studies; study selection; data charting; and collating, summarizing, and reporting the results (http://joannabriggs-webdev.org/assets/docs/sumari/Reviewers-Manual_Methodology-for-JBI-Scoping-Reviews_2015_v2.pdf).

We used the Population, Concept, and Context framework (https://nursing.lsuhsc.edu/JBI/docs/ReviewersManuals/Scoping-.pdf) to define the inclusion criteria. We included all studies including human patients diagnosed with monkeypox as a positive result of the monkeypox polymerase chain reaction from any anatomical site and who underwent either treatment with tecovirimat, brincidofovir, or cidofovir. We accepted any dose or treatment period. Studies in any setting (including in hospital), phase, country, and length of follow-up were included. On June 2nd, 2022, the following databases were searched from 2018 to the present: MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) and preprint servers. In addition, we searched for ongoing trials in the following trial registers: the World Health Organization International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov (**Supplemental Method 2**). We also searched for references in the studies identified for inclusion. In addition, we searched for references in the study "Efficacy of three key antiviral drugs used to treat orthopoxvirus infections: a systematic review." [5].

To review the existing literature on the efficacy and safety of tecovirimat, brincidofovir, and cidofovir on human patients with monkeypox, we included studies based on the following criteria: (1) reports of human patients diagnosed with monkeypox; (2) reports such as case reports, case-control studies, or cohort studies; (3) reports including the patients treated with at least one of the following three medications; tecovirimat, brincidofovir, or cidofovir. Studies written in languages other than English were excluded. Two of three researchers (NK, DH, and TS) conducted the study selection independently. The two authors compared their lists, and any differences in opinion were resolved by discussion and, where this failed, through arbitration by the third researcher. Data extraction was carried out by one researcher (NK) using standard data extraction forms, including study type, the number of participants, treatment, outcomes, efficacy, and adverse events as in the pre-defined protocol (https://osf.io/ehvt7/). One of two researchers (DH and TS) confirmed the data extraction. If necessary, we contacted the authors of these studies. We organized the extracted data described above as qualitative synthesis.

Of the 433 studies identified, five (n = 5) were included in this scoping review [7–11] (Table 1). Two were case report/series [7,8], and three were trial registrations [9–11]. The study selection process is shown as a PRISMA flow chart in Fig. 1. Three studies were from the USA [8,9,11], and the rest were from the United Kingdom [7,10]. This review included one case report, one case series, one interventional study, and two expanded access. Three of them are ongoing studies or have not yet reported the results. Therefore, the efficacy and adverse events of antiviral treatment were assessed in only five and four patients, respectively. Among them, two were given tecovirimat, and three were given brincidofovir. There was no study on treatment with cidofovir.

Regarding the patients with tecovirimat, one patient was given a dose of 600 mg twice daily for two weeks with no adverse events, and the other patient had no detailed description of the dose or adverse events in the study. Both patients recovered. Regarding the patients on brincidofovir, one patient was given a single dose of 200 mg, and the other two were given 200 mg once weekly for two doses. All of them recovered. However, all of them had increased alanine transaminase (ALT), and one had nausea and abdominal discomfort.

Only five studies were included in this scoping review. We found that too few studies reported on antiviral treatment usage and subsequent clinical courses. As shown in Figs. 1 and 49 (57.6%) of the 85 studies in the full-text screening were excluded because either they did not mention treatments or did not use antiviral treatment.

The reported mortality rates of human monkeypox ranged from 1 to 10% [12,13], and early antiviral intervention may help prevent fatal outcomes and the spread of infection. Currently, tecovirimat, brincidofovir, and cidofovir are possible candidates for treating human monkeypox. The safety of tecovirimat, brincidofovir, and cidofovir has previously been confirmed in healthy human participants [5,14]. Their efficacy has been established in animal experiments [5]. Based on past studies and our results [15], tecovirimat would be the best choice due to ease of administration (oral drug), fewer side effects, and past treatment results for human monkeypox administration. Specifically, we suggest the administration of tecovirimat for severe cases or high risk for severe cases rather than routine use for all human monkeypox cases, as most monkeypox patients resolve spontaneously and there are limited

Table 1
Summary of included studies.

Author, country	Study type	Number of participants	Treatment medication, dose, and period	Efficacy	Adverse events
Adler et al. UK, 2022 [7]	Case series	7 (4 adults were treated with antiviral drugs)	1: Brincidofovir 200 mg, once weekly, for one dose; 2&3: Brincidofovir 200 mg, once weekly, for two doses; 4: Tecovirimat 600 mg twice daily for 2 weeks	All of 7 were full recovery	Transaminitis (n = 3); Nausea, and abdominal discomfort (n = 1)
Rao et al. US, 2022 [8]	Care report	1	Tecovirimat, dose and period were not described	Recovered	Not described
U.S. Army Medical Research and Development Command, US, 2014 [9]	Expanded access (Finished, not reported)	Not defined	Tecovirimat, 600 mg, not defined	Not defined	Not defined
Olliaro et al. UK, 2019 [10]	Expanded access (Ongoing)	Not defined	Tecovirimat, the dosage is based on age and weight, daily for 14 days	- Total number, type, and location of lesions - Temperature - Degree of incapacity - Whether the subject has survived with or without sequelae or succumbed to the disease - Viral load and serology	- Complications
Tippin et al. US, 2010 [11]	Interventional (Ongoing)	210 (including other viruses)	Brincidofovir, 200 mg, once or twice weekly for up to 3 months.	1. Number of Subjects Who Had a Sustained and Significant Reduction in Plasma Viral Load of Primary dsDNA Virus	Not defined

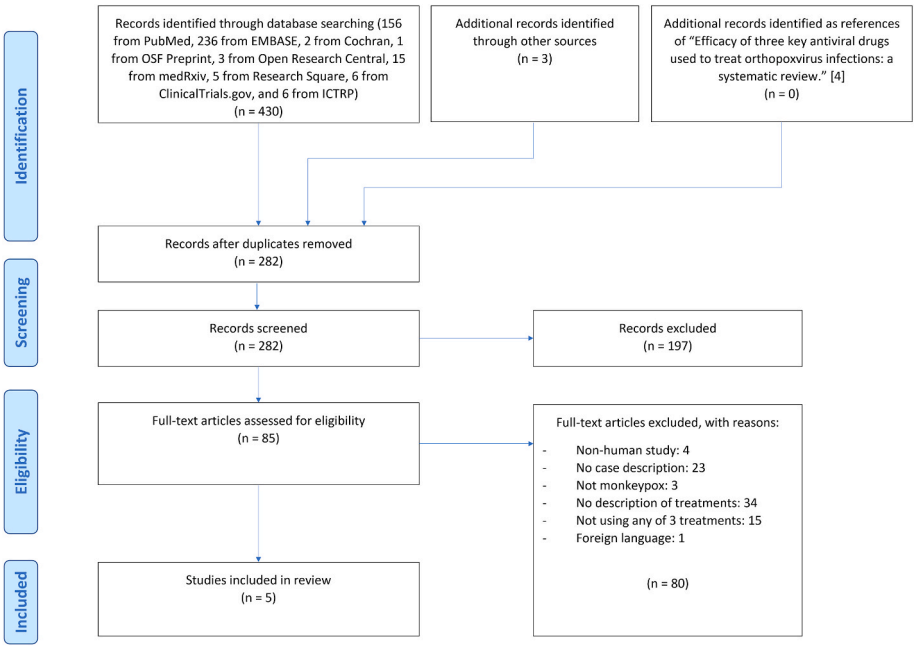

Fig. 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram of this scoping review.

tecovirimats [16,17].

Cidofovir is essentially an intravenous treatment for cytomegalovirus retinal microvilli in patients with acquired immune deficiency syndrome and is prone to side effects such as renal dysfunction. Brincidofovir is an oral prodrug form of cidofovir. It was previously discontinued as a treatment for human monkeypox due to hepatic dysfunction [7]. Tecovirimat is also an oral drug, which has been approved as the first drug for smallpox treatment [5] and is available for clinical use for monkeypox under an expanded-aces protocol [18]. No serious adverse events were reported, the most common adverse effect was a headache, and no hematological or biochemical abnormalities were noted [5,19].

Further studies are needed to assess the efficacy and safety of each antiviral drug as a treatment for patients with human monkeypox. Therefore, we encourage more observational studies of human monkeypox, including evaluation of the use of each antiviral drug (especially tecovirimat), treatment-related mortality, side effects, and the duration of infectivity of the virus in both endemic and non-endemic areas. These observational studies based on the antiviral treatment, and eventually randomized controlled trials with large enough sample sizes and a systematic review will help establish which antivirals are appropriate for treating human monkeypox, which would be an essential countermeasure to the human monkeypox outbreak.

Authors' contributions

NK conceived the study. NK, YK, and MI contributed to the protocol design and plan. NK and YK developed the literature search strategy and charting data. NK, DH, and TS conducted a literature review for study selection. NK, YK, and MI drafted and revised the manuscript. NK, DH, TS, YK, and MI approved the final manuscript.

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The funders played no role in the design of the study and collection, analysis, and interpretation of data or in writing the manuscript.

Ethical statement

Ethical approval was not required as this is a review of the available literature.

Data availability

Not applicable to this manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jiac.2022.10.009.

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