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REVIEW

Therapeutic strategies to address monkeypox

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ABSTRACT

Introduction: Monkeypox is a viral zoonosis, with symptoms similar to those seen in smallpox patients, although the clinical presentation may be less severe. Until recently, human monkeypox infection was rare, and primarily occurred in Central and West Africa.

Areas covered: An international outbreak began in May 2022, and monkeypox has now been detected on every continent except Antarctica. The first recognized case from the current outbreak was confirmed in the United Kingdom on 6 May 2022, in an adult with travel links to Nigeria, but it has been suggested that cases had been spreading in Europe for months. On 23 July 2022 the Director-General of the World Health Organization declared the monkeypox outbreak a public health emergency of international concern.

Expert opinion: There are no treatments specifically for monkeypox virus infections. However, monkeypox and smallpox viruses are genetically similar, and therapeutics developed to combat smallpox may be used to treat monkeypox. This manuscripts reviews what is known about these potential treatments, including tecovirimat and brincidofovir, based on a literature search of PubMed through 9 August 2022, and explores how these therapeutics may be used in the future to address the expanding monkeypox pandemic.

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1. Introduction

Monkeypox is a viral zoonosis caused by a member of the genus orthopoxvirus and is closely related to variola virus, the causative agent of smallpox [1]. Human monkeypox was first identified in humans in 1970 in the Democratic Republic of the Congo in a 9-month-old boy in an area where smallpox had been eliminated [2]. The first monkeypox outbreak outside of Africa was identified in 2003 in the United States of America and was linked to contact with infected pet prairie dogs (cynomys species) [3]. The first confirmed case during the 2022 global outbreak was identified on 6 May 2022, in an adult with travel links to Nigeria but cases may have been spreading in Europe for several months [4,5]. As of early August 2022, more than thirty thousand cases have been documented around the world [6].

Monkeypox is classically associated with a febrile prodrome followed by a rash that may appear on any part of the human body, with pleiomorphic lesions that evolve simultaneously [2,7,8]. In the current global outbreak of monkeypox, painless anogenital lesions – often without a prodrome – are being observed in persons who have had close contact with an infected person or persons, including men who have sex with men [9].

Monkeypox is usually a self-limited disease with the symptoms lasting from 2 to 4 weeks, but severe cases do occur, with some studies revealing a case fatality rate of 3–10% [10,11]. There are no treatments specifically approved for monkeypox virus infections [12]. However, due to the genetic similarity between monkeypox and smallpox, antiviral drugs developed to treat smallpox, including tecovirimat and brincidofovir, may have clinical applications in the treatment of monkeypox, although clinical experience with these agents is limited [13]. This manuscript reviews what is known about these treatments based on a literature search of PubMed through 9 August 2022.

2. Tecovirimat

Tecovirimat (previously ST-246) is a small-molecule inhibitor of viral egress that has shown efficacy *in vitro* and *in vivo* against orthopoxviruses, including vaccinia, camelpox, cowpox, ectromelia (mousepox), variola viruses, and monkeypox [14]. Tecovirimat was identified after screening a chemically diverse library of more than 350,000 unique compounds, and was subsequently discovered to target a gene that produces p37, a major envelope protein required for the production of extracellular virus [15,16].

Tecovirimat inhibits viral replication *in vitro* by 50% at a concentration (EC_{50}) of ≤0.07 μM, and in mice, the drug was nontoxic and effective against mortality when given orally twice daily at 50 mg/kg of body weight for 14 days beginning before or shortly after infection [17]. In a ground squirrel model of disease, all animals that started treatment with tecovirimat on days 0, 1, 2, and 3 survived lethal challenge with monkeypox virus; in contrast, all (100%) of the placebo group died [18]. These findings indicated that further studies in humans were warranted.

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Article highlights

- An international monkeypox outbreak began in May 2022, and the virus has now been detected on every continent except Antarctica.
- There are no approved treatments for monkeypox virus infections.
- Monkeypox and smallpox viruses are genetically similar, and therapeutics developed to combat smallpox could potentially be used to treat monkeypox.
- The antiviral agents tecovirimat and brincidofovir have activity against monkeypox virus
- Data from randomized clinical trials is urgently needed to address the expanding monkeypox outbreak
- On 25 June 2022, the World Health Organization announced that the global monkeypox outbreak does not constitute a public health emergency of international concern.
- On 23 July 2022 the Director-General of the World Health Organization declared the monkeypox outbreak a public health emergency of international concern.

A phase 1, double-blind, randomized, placebo-controlled ascending dose study was conducted to determine the safety, tolerability, and pharmacokinetics of tecovirimat in healthy human volunteers [19]. Tecovirmat was given in single oral doses of 500 mg, 1 g, and 2 g to fasting healthy volunteers and 1 g to non-fasting healthy volunteers and was well-tolerated and without serious adverse events (the most commonly reported drug-related adverse event was neutropenia, which was later discovered not to be related to treatment). System absorption was noted to be greater in non-fasting volunteers with exposure levels predicted to be sufficient for inhibiting orthopoxvirus replication, including monkeypox.

A phase 2, double-blind, randomized, placebo-controlled, multicenter trial was conducted to assess the safety, tolerability, and pharmacokinetics of tecovirimat when administered as a single daily oral dose (400 mg or 600 mg) for 14 days in non-fasting adult volunteers [20]. The drug was well-tolerated and without serious adverse events. Pharmacokinetic analysis revealed that steady state was achieved by day 5 for the 400-mg treatment group and by day 6 for the 600-mg group and the dose proportionality analysis found that the ratio of dose-normalized peak drug concentration in plasma (C(max)) and relative exposure for each dosing interval (AUC(τ)) ranged from 80% to 85%, suggesting that further testing of tecovirimat was warranted.

Despite these promising findings there have been no randomized, prospective, phase 3 efficacy studies of tecovirimat as a treatment for monkeypox [21]. A retrospective observational chart review of hospitalized patients in the United Kingdom with confirmed monkeypox (defined as a compatible clinical illness with positive monkeypox viral PCR from any anatomical site) between 15 August 2018, and 10 September 2021 [22]. One patient was treated with tecovirimat (600 mg twice daily for 2 weeks orally), experienced no adverse effects, and had a shorter duration of viral shedding and illness (10 days hospitalization) compared with other patients.

Despite limited use in humans, tecovirimat was approved by the United States Food and Drug Administration on 13 July 2018, for treatment of smallpox under Fast Track and Priority Review designations [23]. The drug was approved under the FDA's Animal Rule, in which marketing authorization is based on a medication's efficacy in relevant animal models [24,25]. Limited observational data suggests the drug may also serve as a treatment for monkeypox infection in humans [26]. In January 2022, tecovirimat was registered by the European Medicine Agency for the treatment of monkeypox [21].

3. Brincidofovir

Brincidofovir (formerly CMX001) is an orally bioavailable lipid acyclic nucleoside phosphonate that is absorbed in the small intestine and transported throughout the body as a phospholipid [27]. Brincidofovir is a lipid conjugate of cidofovir, an antiviral approved for the treatment of cytomegalovirus retinitis in AIDS patients and also has activity against poxviruses, but cidofovir must be administered intravenously and is associated with nephrotoxicity [28]. Brincidofovir, by contrast, has good oral bioavailability, no associated nephrotoxicity, and achieves higher intracellular levels of the active drug compared to cidofovir, making it an appealing agent for the treatment of a variety of infectious diseases [16,29,30]. Brincidofovir has shown activity against double-stranded DNA viruses, including poxviruses such as monkeypox [31–34].

In a murine model of lethal monkeypox infection, brincidofovir was protective when administered on the day of infection [29]. The drug has also been evaluated as prophylaxis and as a pre-symptomatic antiviral agent in New Zealand white rabbits infected with rabbitpox virus, a model for orthopoxvirus infections of humans, with potential applications to monkeypox [35].

The prairie dog MPXV model has been characterized and used to study the efficacy of antipoxvirus therapeutics, including tecovirimat [36,37]. To determine the exposure of BCV following oral administration to prairie dogs, A pharmacokinetics (PK) study of brincidofovir in prairie dogs indicated that plasma exposure (maximum concentration [C_{max}]) was lower than in other animal models administered the same doses, indicating that suboptimal BCV exposure may explain the lower protective effect on survival [38]. In light of these findings, further studies are warranted in humans as brincidofovir is an oral antiviral possessing a unique mechanism of action from tecovirimat and may be the preferred agent if rapid and widespread administration were necessary [12,39].

4. Expert opinion

We are in the midst of a monkeypox pandemic [40,41]. Prior to 2022, only a handful of cases were detected outside of Africa [42]. The disease has now been detected in dozens of countries around the world [43,44]. Early clinical suspicion, prompt reporting to public health authorities, and awareness of high-risk exposures are essential for identifying and containing the expanding outbreak [43]. Medical management is heterogenous; drug approvals for the treatment of monkeypox are based upon *in vitro* and animal data as well as safety and tolerability in healthy volunteers [21]. Clinical trial data is urgently needed,

both to define the optimal treatment of monkeypox infection and to clarify the role of post-exposure prophylaxis.

As the virus spreads, it continues to evolve. Shotgun metagenomics allowed the rapid reconstruction and phylogenomic characterization of the first monkeypox virus outbreak genome sequences and researchers have found continuous accelerated evolution [45]. This suggests that the trajectory of the current outbreak may change as the virus mutates, and that novel containment and treatment strategies may be necessary [5,6,41]. Our understanding of high-risk populations may change, too.

Drawing on lessons from the severe acute respiratory syndrome 2 (SARS-CoV-2) pandemic, it is essential to have data from robust, prospective, randomized trials to inform clinical management [46,47]. These studies are labor-intensive, however, and may be difficult to conduct for a condition such as monkeypox that is relatively uncommon. More efficient trial designs are urgently needed to accelerate development, minimize costs, and make research participation more appealing to patients [48].

One potential pathway, which has been utilized throughout the SARS-CoV-2 pandemic, involves adaptive platform trials in which multiple experimental treatment groups are concurrently compared with a single control group [46,47]. This approach allows experimental groups to enter and exit the trial at different times and may be modified as the standard of care evolves, which can be expected for a virus that is experiencing accelerated evolution [49].

The sluggish embrace of randomized trials during the SARS-CoV-2 pandemic allowed unproven treatments to proliferate, with millions of people exposed to therapeutic agents that provide no meaningful benefit. It is incumbent upon the medical community and policy makers to design studies that will produce reliable, reproducible knowledge about monkeypox. Multicenter collaborations will be essential to ensure that trials are adequately powered and sufficiently diverse [50]. In the absence of such data, misinformation may proliferate [51–53].

Treatment is just one component of the multi-pronged approach to address the ongoing monkeypox outbreak. Robust testing, public awareness, vaccination of high-risk groups, and containment measures all have important roles to play in curbing the spread of this potentially-lethal virus [54,55]. However, substantial challenges remain.

Although vaccines are considered safe and effective for use in people with smallpox infection, there is limited experience with monkeypox and people in high-risk groups must agree to be inoculated with vaccines that can trigger rare, but serious, side effects [56]. This increasingly includes healthcare workers and people who engage in certain forms of sexual activity [55,57,58].

On 25 June 2022, the World Health Organization announced that the global monkeypox outbreak does not constitute a public health emergency of international concern. However, the same body did not recognize SARS-CoV-2 a public health emergency of international concern until 30 January 2020 [59]. By that time, the epidemic in Wuhan, China was already in decline and the virus had spread to the United States and Europe.

As our understanding of monkeypox evolves, so too must our approach to prevention, containment, and treatment. Public health messaging must keep pace with science and management must be based on robust, randomized data to ensure that patients receive optimal care. Missteps from the SARS-CoV-2 pandemic must not be repeated.

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