Exploring the Potential Treatment for Mpox

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ABSTRACT

Monkeypox (Mpox) is a virus that originally infected only animals. Caused by the monkeypox virus, this infection presents with symptoms similar to smallpox. Although two years have passed since the 2022 outbreak, new cases continue to emerge monthly. Initially, human cases of mpox were confined to outbreaks in central and western Africa. However, the virus has recently spread globally, possibly due to a decline in vaccination rates. In this context, evidence for effective therapies, such as antivirals, is urgently needed. Three antivirals—tecovirimat, brincidofovir, and cidofovir—are known to have activity against the mpox virus. Their use is currently limited to expanded access for treating non-variola orthopoxvirus infections, with ongoing phase 3 trials. This review will discuss the mechanisms of action, clinical use, and efficacy of these antivirals.

Keywords*: Treatment; Mpox; Orthopoxvirus*

INTRODUCTION

Following its spread across various regions, the World Health Organization (WHO) declared monkeypox (Mpox) a global health emergency. As of March 31, 2024, the WHO recorded 95,226 laboratory-confirmed cases and 185 fatalities. In Indonesia, approximately 88 confirmed cases were reported, with 4 new cases in August 2024.[1]

Mpox is often a self-limiting disease. Historically, mpox treatment has relied solely on supportive therapy, including oral or intravenous fluid replacement, symptomatic treatments such as antipyretics and analgesics, and balanced nutritional intake.[2] Patients with severe skin involvement may experience extensive skin disintegration, leading to protein and fluid loss, requiring treatment similar to that of burn injuries, with a focus on hydration. Minor secondary bacterial infections can be treated with antibiotics such as Cloxacillin or amoxicillin-clavulanate for deeper skin infections.[3] Ocular lesions, which may lead to corneal scarring and permanent vision loss, may require the addition of Trifluridine eye drops.[4] Serious complications, such as encephalitis, should be evaluated through lumbar puncture, with seizure management and antibiotic/antiviral administration if co-infection is present. In cases of sepsis or septic shock, treatment should follow the Surviving Sepsis Campaign guidelines. Presently, there are antivirals believed to be effective against mpox, although their use has been limited to specific populations.[2]

ANTIVIRAL TREATMENT

Three antivirals are administered in severe cases or to high-risk populations. High-risk populations include individuals who are

immunocompromised (e.g., those with HIV, malignancy, solid organ transplants, or prolonged use of high-dose corticosteroids). Those with advanced HIV disease often experience necrotizing lesions more frequently, with higher rates of complications and mortality.[5] IIn pregnancy, monkeypox can result in perinatal losses of up to 77.0%, with direct transmission to the fetus in 62% of cases.[6] A meta-analysis study in Bangladesh indicated that among children under 10 years old with severe mpox, the case fatality rate was 76.47%.[7] The relationship between chronic skin diseases (such as atopic dermatitis) and mpox is unclear, but it is postulated that chronic skin conditions may disrupt skin barriers, occasionally leading to superimposed infections.[8] In cases where the patient develops severe symptoms or complications (e.g., hospitalization, sepsis, acute respiratory distress syndrome [ARDS]), high lesion counts (>100 lesions) have been associated with elevated temperatures, more severe symptoms, and prolonged illness.[9]

ANTIVIRAL AGENTS

Tecovirimat

The Food and Drug Administration (FDA) approved tecovirimat, also known as Tpoxx, for the treatment of smallpox. Tecovirimat targets the cowpox gene V061, which shares similarities with the F13L gene in the vaccinia virus (VACV). This gene plays a crucial role in forming the p37 membrane protein responsible for generating extracellular enveloped viruses. The intracellular mature virus (IMV) requires the p37 protein to encase itself and form an enveloped virus (EV). When tecovirimat targets this protein, the IMV cannot exit the infected cell, thus hindering the spread of the virus within the body. Since this protein is unique to orthopoxviruses, tecovirimat is highly specific and does not inhibit the reproduction of other virus classes.[10]

Brincidofovir

Brincidofovir (BCV) is a phosphonate ester prodrug of Cidofovir (CDV). The FDA approved brincidofovir in 2021 for the treatment of smallpox. Brincidofovir's lipophilic properties allow it to enter host cells more easily than CDV. Once inside human cells, it is hydrolyzed to Cidofovir and activated by two sequential phosphorylations to become Cidofovir diphosphate (CDV-pp). CDV-pp then inhibits the enzyme DNA polymerase, thereby blocking the production of viral DNA and hindering IMV formation by attaching to the viral genetic material strand.[11]

Cidofovir

Cidofovir (CDV) is FDA-approved solely for the treatment of cytomegalovirus retinitis. CDV exhibits broad activity against various viral DNAs, including orthopoxviruses. Its mechanism is similar to that of brincidofovir (BCV), where DNA synthesis is slowed during the replication phase once CDV-pp is incorporated into the growing DNA strand.[12] Cidofovir diphosphate may also inhibit DNA polymerase 3′–5′ exonuclease activity. However, oral absorption of CDV is low, necessitating administration via intravenous infusion. Renal dialysis rapidly filters and excretes plasma CDV.[13]

TIMING OF ADMINISTRATION

Several studies are exploring whether early administration of antivirals can improve patient outcomes. In an in vivo study involving Cynomolgus macaques, those treated with tecovirimat within the first five days of the experiment had a 100% survival rate, compared to a lower survival rate when treatment began on the fifth day. However, subjects receiving therapy on the seventh day also had a 100% survival rate.[14] Another study on macaques demonstrated higher survival rates with tecovirimat administration on days four and five compared to day six (83% vs. 50%, respectively).[15] In a cohort study involving human mpox cases, the group that received tecovirimat within seven days of symptom onset saw Mpox lesion progression in three individuals (5.4%), whereas in the group that received antivirals on day seven or later, more than 15 individuals (26.8%) experienced lesion progression.[16] Additional cross-sectional studies have compared the effects of tecovirimat administered within the first five days to later administration. Early administration led to faster

symptom improvement (-5.5 days), but this was observed only in subjects with severe illness, not in those with milder symptoms (0.9 days).[17] Some studies involving human subjects treated with tecovirimat did not show significant effects on reducing recovery time or viral load.[18] Due to the varied results, further research is needed, particularly from larger studies like randomized controlled trials (RCTs).

The early initiation of BCV and CDV in mpox has not been extensively studied. However, a study on BCV in a rabbitpox virus model showed improved survival when administered as early as possible, compared to administration after 24 or 48 hours (100% vs. 93%).[19]

DURATION OF TREATMENT

The recommended duration for tecovirimat treatment is 14 days to ensure adequate suppression of viral replication and provide sufficient time for the host's immune system to combat the infection. This recommendation is based on animal studies and human safety data. Humoral immunity in monkeys was assessed by day 10 post-infection, with any residual virus being eliminated once treatment was completed. However, in certain cases, the duration of treatment may be extended until the infection is fully under control.[15]

Similar to other acyclic nucleoside phosphonates, brincidofovir and cidofovir, which are subsequently converted to CDV-pp, have a prolonged intracellular half-life, allowing for less frequent dosing than would be expected based on their plasma half-lives. CDV-pp is gradually eliminated from cells, with a half-life of nearly seven days, making the recommended dosing schedule once a week for two weeks.[20]

ADVERSE EVENTS AND TOLERABILITY

Several studies have evaluated the safety of tecovirimat in human subjects across four trials, including two phase I trials, one phase II trial, and one phase III trial. In the phase I and II studies, side effects were mild, mostly including headache, nausea, dry mouth, and bloating.[15] There were no fatal side effects reported. The largest trial was a placebo-controlled pharmacokinetic and safety study conducted with 449 volunteers. Over 14 days, 359 individuals received tecovirimat at a dose of 600 mg twice daily, while 90 received a placebo. Tecovirimat showed no meaningful adverse effects, and no deaths were reported. The most commonly reported side effects were headaches and gastrointestinal complaints, such as nausea. A serious adverse event, pulmonary embolism, occurred in one patient, but it was later determined not to be related to the treatment.[15]

Three phase I trials have been conducted on brincidofovir (BCV), with the most commonly reported adverse events (AEs) related to gastrointestinal issues, including nausea and vomiting. Other frequently reported AEs included elevated serum transaminase levels, which were mostly mild and asymptomatic. A randomized controlled trial (RCT) of BCV also showed similar results to the phase I trial, where BCV was administered once a week for 3 weeks in cytomegalovirus (CMV) infection among allogeneic hematopoietic cell transplantation (HCT) recipients. In another placebo-controlled trial of BCV in adenovirus infection among allogeneic HCT recipients, both BCV and placebo groups reported at least one AE, primarily gastrointestinal events (nausea, vomiting, abdominal pain, decreased appetite). There were also fatal AEs, such as acute graft-versus-host disease (aGVHD), a complication of HCT recipients, which was unrelated to BCV.[21]

Cidofovir (CDV) can accumulate in the proximal renal tubules via organic anion transporter 1 (OAT1), leading to dose-dependent nephrotoxicity. Therefore, CDV should not be administered to patients with serum creatinine levels above 1.5 mg/dL. Clinical trials have also revealed that CDV may cause neutropenia, decreased intraocular pressure, uveitis/iritis, and metabolic acidosis.[22]

EFFICACY

The effectiveness of tecovirimat has been demonstrated in animal trials. In four studies involving non-human primates (NHPs), crab-eating macaques were injected intravenously with a lethal dose of monkeypox virus at 5×10^7 plaque-forming units (PFUs) per subject.[15] In studies with rabbits, New Zealand white rabbits were given lethal doses of the rabbitpox virus

Utrecht intradermally at 1000 PFUs per subject.[23] Tecovirimat was administered on the fourth day of the trials, after symptoms and lesions appeared in NHP studies, and after pyrexia and viremia were observed in the rabbit studies.

In the first two experiments with NHPs, the minimal effective dose was found to be 3 to 10 mg/kg, resulting in decreased viral loads and lesion counts, as well as nearly complete protection against mortality (approximately 95% survival rate, compared to 5% in the placebo group).[15] In another NHP study with delayed treatment, 83% of subjects who received a dosage of 10 mg/kg four to five days after exposure survived, compared to a 50% survival rate for those treated six days post-exposure. In the treatment-duration study, 50% of subjects survived after receiving 3 doses daily at 10 mg/kg starting on the fourth day post-exposure, while 100% survived after receiving treatment on the fifth and seventh days. An 80% survival rate was achieved with ten doses per day. [24]

In rabbits, administering tecovirimat orally at a dose of ≥20 mg/kg/day for 14 days reduced the death rate, viral load, and clinical symptoms. All dosage levels (20-120 mg/kg/day) resulted in over 90% survival, while all untreated rabbits succumbed to the disease. Tecovirimat effectively protects against lethal challenges from all orthopoxviruses studied in animal models. Unfortunately, no clinical trials have been conducted in humans for smallpox due to ethical concerns about deliberately infecting human subjects with the virus.[15]

In vitro studies have shown that BCV can inhibit the variola virus, which causes smallpox, as well as the replication of mousepox and rabbitpox viruses.[25] Initial studies of BCV efficacy were demonstrated in randomized, blinded, placebo-controlled studies in the rabbitpox model. Rabbits infected with rabbitpox virus and treated immediately with BCV upon showing signs of fever had a 100% survival rate. Rabbits treated 24 or 48 hours after the onset of fever had a survival rate of 93%. The survival advantage was statistically significant for all three treatment groups compared to the placebo group, which had a 48% survival rate.[19]

The effectiveness of CDV has been extensively demonstrated in animal models, including those with vaccinia virus (VACV), cowpox virus, and ectromelia virus.[12] Three trials were conducted in monkeys with monkeypox, using different routes of administration (aerosol, intravenous, and intratracheal), with CDV treatment at 5 mg/kg. All trials showed decreased mortality, clinical improvement, reduced lesion severity, and controlled virus replication.[26]

The use of tecovirimat, brincidofovir, and cidofovir in humans has primarily been in response to outbreaks, with existing case studies based on emergency use to control severe infections rather than intentional research purposes (summarized in **Table 1**).

FACTOR DETERMINING EFFICACY

The bioavailability of a drug plays a significant role in determining its efficacy. Administering tecovirimat with a meal containing moderate fat and calories (600 calories and 25 grams of fat), as compared to taking it in a fasted state, increased the drug exposure (AUC) by 39%. In contrast, for brincidofovir, a moderate to high-fat diet reduces the AUCinf by 31% and decreases Cmax by 49%. Therefore, it is recommended to take brincidofovir before meals or with a low-fat diet.[27]

In animal studies, the efficacy of tecovirimat could be reduced in immunocompromised subjects. Significant differences were observed in the pharmacokinetics of tecovirimat between subjects with HIV on antiretroviral therapy (ART) and those without HIV. Subjects with HIV had significantly lower Cmin (42%), Cmax (39%), and AUC0–12 (40%). This reduction may be due to non-metabolic drug interactions with the subjects' antiretroviral therapy.[28]

Using brincidofovir together with OATP1B1 and 1B3 inhibitors (such as clarithromycin, cyclosporine, erythromycin, gemfibrozil, HIV and hepatitis C virus protease inhibitors, and rifampin) increases brincidofovir's Area Under the Curve (AUC) and Cmax, which may heighten the risk of adverse reactions associated with brincidofovir.[29]

Table 1. Clinical Studies of human monkeypox

Author	Study	Sample	Treatment	Days of hospitalization;	Outcomes	Adverse drug events	Mortality
Hermanussen et al., 2023[31]	Case Report	12	Tecovirimat 600 mg bid Duration based on clinical response: one patient was treated for 6 days, seven patients for 7 days, one patient for 14 days, and two patients for 28 days	7 days (3-28)	10 patients have quick recovery time, 1 patient need to prolong treatment, 1 patient with HIV relaps and need reinitiate treatment	1 patient show elevated transaminase levels. 1 patient have psychosis symtomps	None
Inada et al., 2023[32]	Case Report	2	Tecoviramat 600 mg bid for 14 days	14, 15 days	Fully recovered (viral DNA become undetectable in day 4 and the other one undetected in day 8)	elevated AST, ALT and CK in day 8	None
Adler et al., 2022[33]	Retrospective Observational Study	7	one patient use brincidofovir 200mg orally (one dose), two patients use Brincidofovir 200 mg orally (two doses), one patient receive Tecovirimat 600 mg bid for 2 weeks orally and three others only symptomatic treatment	with tecovirimat : 10 days with brincidofovir : 29 days (26-35) without antiviral : 27 days (22-39)	All patients fully recovery	those who receive BCV reported Transaminitis and for Tecoviramat no adverse events was found	None
Mailhe M et al., 2023[34]	Observational Cohort Study	17	only 1 patient receive two injection of IV Cidofovir 5mg/kg	3 (3-4 days)	Mostly fully recovered but follow up the patient with severe ophthalmic lesion still evolving	Not specified	None
Scandale et al., 2022[35]	Case report	1	IV Cidofovir 5 mg/kg single dose	Not Specified	Fully recovered (Ocular papule resolve in 3 days)	Not specified	None
Raccagni et al., 2022[36]	Case Report	4	IV Cidofovir 5 mg/kg single dose	6 days (3-8)	Fully recovered	Not specified	None
Desai et al., 2022[37]	Uncontrolled cohort study	25	Tecovirimat for 14 days Dose : weight based	Not specified	10 patients fully recovered in day 7, 13 patients fully recovered in day 21, 1 patient not fully recovered and no new lesions, 1 have grow new lesions.	Fatigue, headache, nausea, diarrhea	None
Mbrenga et al., 2022[38]	Uncontrolled cohort	14	Tecovirimat 600 mg bid for 14 days in adult and weight based in children	Not specified	13 fully recovered and 1 died	one develop anemia on day 9 treatment, and the other develop unknown serious adverse events after discharged	1
McLean et al., 2023[39]	Retrospective cohort study	196	Tecovirimat, dose and duration unspecified	Not specified	All recovery	49 (25%) have mild headache and GI events, 4 subject have severe AEs : morbilliform rash, GI bleeding, elevated transaminase, anorectal ulcer , all severe AEs are unrelated to treatment	None

POTENTIAL FOR RESISTANCE

Tecovirimat resistance mutations arise in the F13L gene, which is involved in the formation of enveloped orthopoxvirus virions. Tecovirimat has a relatively low resistance barrier. A cowpox virus strain resistant to tecovirimat has been identified through in vitro research due to a mutation in the V061 gene, similar to the variola F13L gene. For these resistant variants, the in vitro dose (>40 μM) required to inhibit viral reproduction by 50% (EC50) was more than 800 times higher than that of the wild-type cowpox virus (0.050 μM).[30] A case of mpox resistant to tecovirimat has been reported, where anorectal lesions were found to have an F13L gene mutation (N267D variant of VP37). This mutation resulted in a 350-fold increase in the half-maximum effective concentration of tecovirimat compared to the wild-type virus (2103 nM for N267D vs. 5.9 nM for WT MPXV).[31]

Multiple investigations using orthopoxviruses have utilized cidofovir (CDV) to study the development of resistance related to brincidofovir (BCV), as CDV-PP is the same active metabolite. The viral DNA polymerase gene is the site of mutations leading to BCV/CDV resistance. The amino acid sites A314 and A684 of DNA polymerase are most commonly associated with these mutations. Because several mutations are required for high-level resistance to BCV/CDV, achievable medication doses may still be effective against the resistant virus in vivo, contributing to a high barrier to resistance.[32]

POTENTIAL FOR CHEMOPROPHYLAXIS

Early initiation of therapy is associated with improved survival benefits and reduced disease symptoms in animal models. In experiments where medication was started one day after exposure, animals showed no signs of sickness, indicating that tecovirimat holds promise for post-exposure prophylaxis.[33] Tecovirimat administered quickly after lethal orthopoxvirus exposures, even before apparent signs of illness, is highly protective against death and significantly reduces morbidity.[30]

Exposure to the vaccinia virus (VACV) in vivo suggests that administering tecovirimat (Tpoxx) before symptom onset is a viable option, as the effectiveness of post-exposure vaccination rapidly decreases as infection progresses, whereas Tpoxx remains effective even after disease symptoms have appeared.[43] However, in prophylactic pre-exposure studies, it is not recommended to administer Tpoxx alongside the smallpox vaccine when there is almost no risk of exposure.

Brincidofovir has been used as prophylaxis against the cytomegalovirus (CMV) in a study, but comparing the effects of 100 mg of brincidofovir twice weekly against a placebo did not show a clinically significant reduction in CMV infection through week 24 post-hematopoietic cell transplantation (HCT).[44]

THERAPEUTIC POTENTIAL IN THE FUTURE

A tricyclodicarboxylic acid derivative named NIOCH-14, a precursor of tecovirimat, has demonstrated antiviral activity equivalent to tecovirimat in cell culture studies with variola virus and in mouse lung trials aimed at reducing monkeypox virus multiplication. NIOCH-14 has successfully suppressed clinical manifestations of the monkeypox virus in guinea pigs.[45]

Two inosine monophosphate (IMP) dehydrogenase inhibitors, ribavirin and tiazofurin, can also inhibit the replication of the mpox virus. In mice inoculated with 3 × 10^5 PFUs of cowpox virus, subcutaneous injection of ribavirin at 100 mg/kg once daily for 5 days resulted in a 100% survival rate compared to the placebo group, where no animals survived.[46]

Tyrosine kinase inhibitors, such as dasatinib and imatinib mesylate, may be useful against infections caused by poxviruses. Dasatinib has shown excellent efficacy against poxviruses in vitro; however, it exhibited poor efficacy in mouse models infected with VACV, likely due to its immunotoxic effects. Imatinib also shows antiviral activity in a vaccinia virus-infected mouse model. Treatment with 100 mg/kg/day of imatinib reduced the amount of viral genomes and improved survival rates in vaccinia-infected mice.[47]

Adamantine compounds, monoterpenoid derivatives, PAV-866 and its derivatives, resveratrol, and interferon gamma have potential as therapeutic agents against other

orthopoxviruses in vitro. However, their efficacy against mpox is limited.[48]

ILLUSTRATION CASE IN INDONESIA

A 24-year-old male patient presented to the emergency room of Cipto Mangunkusumo National Referral Hospital in November 2023. He reported a high fever followed by blisters on his lower legs, which subsequently spread to his face and throughout his body. Polymerase Chain Reaction (PCR) testing confirmed the presence of the monkeypox virus.

The patient was initially treated at an infectious disease hospital in Jakarta, Indonesia, for a week before being transferred to Cipto Mangunkusumo National Referral Hospital due to obstructive ileus, suspected to be caused by anal stricture. He had been diagnosed with pulmonary tuberculosis (TB) and HIV four months prior and had been receiving anti-tuberculosis medication for three months. On physical examination, he presented with multiple ulcers covered with black crusts on the face, scalp, neck, chest, abdomen, back, buttocks, pubis, both legs, scrotum, penis, digit 4 of the left hand, digit 2 of the left palm, upper left palm, back of the right hand, and the lateral right knee.

During hospitalization, he started antiretroviral therapy with tenofovir, lamivudine, and efavirenz. Two days later, he developed a high fever of 39°C, and a new blister appeared on the right hand, which subsequently spread to his extremities. Throughout his treatment, he received antibiotic therapy, including meropenem, vancomycin, levofloxacin, cotrimoxazole (for PCP), fluconazole, steroids, and intravenous heparin. Despite the clear need for antiviral therapy for monkeypox, especially given his immunocompromised status and secondary infections, tecovirimat was unfortunately not available in Indonesia.

CONCLUSION

To date, antiviral treatments for monkeypox have not received FDA approval. Several phase 3 clinical trials are ongoing, including the Study of Tecovirimat for Human Monkeypox Virus (STOMP) and the Placebo-Controlled Randomized Trial of Tecovirimat in Non-Hospitalised Monkeypox Patients (PLATINUM). This study concludes that these three antivirals have been tested in healthy humans with no severe adverse events, are well tolerated, and have shown efficacy against other orthopoxviruses. The study underscores the need for further manufacturing, development, and research to ensure these treatments can be effectively used in patients.

AUTHOR'S CONTRIBUTION

Study design (K, LKC), manuscript writing (K), critical revision (K, LKC, RS, NL, AP, SS)

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CONFLICT OF INTEREST

The authors declare no conflict of interest

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