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Review Article

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Effectiveness and safety of three Antivirals in the Treatment of Severe Manifestations of Monkeypox in Humans. An Approach

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Abstract

Monkeypox or "Mpox", is a zoonosis caused by the monkeypox virus, a double-stranded DNA virus, belonging to the genus *Orthopoxvirus*, of the family *Poxviridae*. There are two main clades of the virus, both endemic in Africa: clade I, associated with the Congo Basin, and clade IIa, related to West Africa. In 2022, a global clade IIb outbreak led the WHO to declare a health emergency, lifted in May 2023. However, in August 2024, the emergency was reactivated due to a resurgence of the disease in Africa, linked to a new strain of clade Ib, which is predominantly transmitted sexually.

The incubation period of the virus varies between 7 and 21 days, and symptoms can last two to five weeks. Initially, patients present with fever, myalgia, headache, and lymphadenopathy, followed by a skin rash that goes through five phases: macular, papular, vesicular, pustular, and crusted. Most cases are self-limiting, although serious complications can arise, especially in immunosuppressed individuals.

For the treatment of severe cases of Mpox, there are three drugs approved by the Food and Drug Administration (FDA) for smallpox: tecovirimat, cidofovir and brincidofovir, although the latter have limitations due to their toxicity.

This document aims to present the efficacy and safety of FDA-approved antiviral treatments for the management of severe manifestations of Mpox by collecting, selecting and synthesizing up-to-date and relevant scientific literature.

Background

The *Monkeypox virus*, corresponding to a double-stranded DNA virus of the genus *Orthopoxvirus*, family Poxviridae, has two main clades: clade I in the Congo basin and clade IIa in West Africa [1]. The 2022 global outbreak corresponded to clade IIb, leading the WHO to declare Mpox an international public health emergency (IPHE) on July 23, 2022. However, on May 11, 2023, after a significant reduction in the spread, the WHO lifted the IPHE. On August 14, 2024, the WHO again declared a IPHE due to a resurgence in the Democratic Republic of the Congo (DRC) and other African countries, associated with a new clade Ib strain, which appears to be transmitted predominantly sexually. No cases have been reported outside Africa [2]. The incubation period for the virus ranges from 7 to 21 days, with symptoms lasting two to five weeks. Initial symptoms include fever, myalgia, headache, back pain, sore throat, and swollen lymph nodes, followed by a skin rash that goes through five stages: macular, papular, vesicular, pustular, and crusted. Patients are infectious until all lesions scab [3].

Most cases are self-limited, but severe manifestations can occur, especially in immunosuppressed people. Although case fatality was less than 1% in the 2022 outbreak, some patients presented

with severe symptoms requiring hospitalization, such as persistent rashes, coalescent lesions, edema, secondary infections, and multi-organ complications [4].

Approval and use of tecovirimat, brincidofovir and cidofovir.

The U.S. The Food and Drug Administration (FDA) approved TPOXX (tecovirimat) as the first drug specifically indicated to treat human smallpox. This approval was carried out under the Animal Rule, a regulation that allows the efficacy of medications to be validated based on rigorous and controlled preclinical studies in animals, especially in cases where it is not feasible or ethical to conduct clinical trials in humans [5]. In contexts such as epidemic outbreaks or resistance to other treatments, the Centers for Disease Control and Prevention (CDC) has an Expanded Access Investigational New Drug (EA-IND) protocol, which facilitates its use in emergency situations or outside the therapeutic standard. Randomized trials are evaluating its effectiveness in humans [5].

In 2021, the FDA approved Tembexa (brincidofovir) for the treatment of smallpox in adults, children, and neonates under the Animal Rule. This approval was based on studies in animal models, such as rabbits infected with the rabbitpox virus and mice exposed to the ectromelia virus, both related to orthopoxviruses. Safety data came from patients treated with the drug for other conditions, such as bone marrow transplants. However, its safety and effectiveness in the treatment of Monkeypox (Mpox) have not been confirmed [6]. In the context of Monkeypox, the use of brincidofovir requires authorization from the CDC through the EA-IND protocol, designed for emergency situations. This medication is considered in patients who do not respond to treatment with tecovirimat or who have contraindications to its use. Randomized controlled trials are also being conducted to evaluate its effectiveness in Mpox [7].

Regarding cidofovir, the FDA has not approved its use to treat orthopoxvirus infections, such as Smallpox or Monkeypox, although it is approved for the treatment of cytomegalovirus retinitis in patients with acquired immunodeficiency syndrome (AIDS) and its effectiveness it has been tested in animal models infected with other poxviruses. Its use for severe cases of monkeypox should be carried out under the CDC EA-IND protocol [5].

Mechanism of action of antivirals

Tecovirimat is a broad-spectrum antiviral used in adults and pediatrics. Inhibits the viral protein p37. This protein interacts with host cell molecules Rab9 (GTPase) and TIP47 (Rab9-specific effector protein) favoring the formation of an extracellular complex for mpox virions. When p37 is inhibited by Tecovirimat, it is prevented from forming extracellular envelopes, preventing the release of virions into the extracellular space [8]. Cidofovir is a "nucleotide monophosphate analogue" that, after phosphorylation, competitively inhibits the incorporation of deoxycytidine triphosphate into viral DNA, disrupting chain elongation. Although its effectiveness in Mpox has not been tested in humans, it has shown positive results in vitro and in animals [8].

Brincidofovir is a prodrug of cidofovir, conjugated to an alkoxyalkyl lipid moiety similar to lysophosphatidylcholine (LPC), allowing its absorption in the small intestine. Once inside host cells, brincidofovir is cleaved to release cidofovir, which is phosphorylated to form cidofovir diphosphate, its active form. This active metabolite selectively inhibits viral DNA synthesis mediated by Orthopoxvirus DNA polymerase, thus reducing viral DNA replication [8].

Effectiveness and safety of antivirals.

A1) Effectiveness of tecovirimat. Tecovirimat has shown high efficacy in the treatment of Mpox in preclinical and clinical studies. In infected Cynomolgus monkeys, all those treated with tecovirimat survived, with a significant reduction in viral load and lesions compared to the placebo group. The effective dose in monkeys was 3 to 10 mg/kg/day, while 400 mg/day is recommended in humans [9]. In studies with infected ground squirrels, tecovirimat administered at 100 mg/kg/day from days 0 to 4 post-infection was effective, with a high survival rate, especially when administered early after infection [10].

Tecovirimat has demonstrated efficacy in reducing Mpox severity and mortality in animal models, and clinical trials support its efficacy in humans, including patients resistant to other antivirals [11]. In patients with advanced HIV, Mpox can be complicated due to immunodeficiency. Reduced food intake may affect the absorption of tecovirimat, which should be taken with fatty foods for optimal effectiveness. It is crucial to treat secondary bacterial and fungal infections that may mask symptoms of Mpox [12].

A2) Safety of tecovirimat. Tecovirimat is administered orally or intravenously, with better absorption after eating. However, the intravenous formulation is not approved by the European Medicines Agency (EMA) and should be avoided in patients with severe renal impairment due to the toxicity of the excipient hydroxypropyl-β-cyclodextrin. Capsules are contraindicated only in patients with hypersensitivity to the drug. Tecovirimat may interact with medications such as repaglinide, used in type 2 diabetes, which may

cause hypoglycemia; therefore, careful glucose monitoring is recommended [13]. The safety of tecovirimat was evaluated in three non-randomized studies with 358 patients (355 treated with tecovirimat and 3 with brincidofovir). Adverse effects were minimal: 16 patients reported unwanted effects, including 11 mild events, two mental health problems, and an increase in liver enzymes. One death and one case of anemia were recorded, but were not considered related to the medication [1]. The safety profile is favorable, but caution should be exercised with rapid intravenous administration due to possible side effects such as ataxia and lethargy. The lack of cross-resistance with other antivirals reinforces its usefulness in resistant strains [11].

B1) Effectiveness of brincidofovir. This antiviral has shown remarkable efficacy in animal models against *Orthopoxvirus* infections, significantly reducing mortality when administered early in infections such as rabbitpox and mousepox [11]. In clinical studies, brincidofovir was evaluated in more than 1,400 patients, including immunocompromised children, with treatments of up to 12 weeks. A dose of 200 mg weekly for 3 weeks showed that adverse effects, mainly gastrointestinal and mild transaminase elevations, were transient and well tolerated. Although resistance can develop due to mutations in the viral DNA polymerase, these viruses tend to be less virulent, which is favorable [14]. The combination of brincidofovir with tecovirimat has been shown to be more effective than its individual use, improving viral suppression and reducing the risk of resistance, showing synergy even in cases resistant to other antivirals [14].

B2) Safety of brincidofovir. The safety profile of brincidofovir requires attention, especially in relation to liver function. Preclinical studies have shown that brincidofovir can cause significant elevations in hepatic transaminases, particularly alanine aminotransferase (ALT), indicating a potential risk of hepatotoxicity [1, 15]. This information highlights the need for close monitoring of liver function during treatment to manage potential serious adverse effects.

Despite its advantages over cidofovir, such as reduced nephrotoxicity, the safety of brincidofovir remains a considerable concern. Continuous monitoring is required to balance antiviral efficacy with the risk of hepatic adverse effects, ensuring safe drug administration [15].

C1) Effectiveness of cidofovir. Cidofovir has been shown in laboratory tests to be effective in stopping the growth of the virus that causes smallpox and in treating animals with similar diseases. It has demonstrated effectiveness against double-stranded DNA viruses, such as poxviruses. Preclinical studies show that it significantly reduces mortality in animal models infected with poxviruses, such as rabbitpox and mousepox [16]. The 1% topical presentation has been evaluated for mild skin infections, but its effectiveness may be limited in the presence of severe bacterial complications [11]. Although cidofovir may be an alternative when tecovirimat is not suitable, it is crucial to determine the optimal dosage to maximize benefits and minimize adverse effects [17].

C2) Safety of cidofovir. The significant nephrotoxicity of cidofovir limits its clinical use, requiring preventive measures such as the administration of probenecid and adequate hydration to mitigate renal risk. Despite its efficacy in preclinical studies, the use of cidofovir in patients with renal involvement or who do not respond to other treatments should be carefully monitored. In the treatment of Mpox, cidofovir is considered in severe cases where other options have not been effective, but it is crucial to evaluate renal function to avoid adverse effects [17].

A comprehensive review evaluated the safety and efficacy of brincidofovir and tecovirimat from in vitro and animal studies, clinical trials, and cases of Orthopoxvirus infection. Nine clinical trials were reviewed in healthy individuals, patients with other viral infections, and hematopoietic cell transplant recipients. Tecovirimat and brincidofovir have been shown to be generally safe and well tolerated, although specific evidence in patients with Mpox is limited. No randomized clinical trials designed specifically for Mpox were found [1].

Discussion

There are some antivirals in use in animals such as those mentioned, with authorization from the FDA and others still under study. *Viruses are viruses* is a phrase from André Lwoff, a notable French scientist awarded the Nobel Prize in 1965, so any attempt to design antivirals must be considered a contribution to confront these small adversaries that could concomitantly be exerting their action in opportunistic diseases.

Conclusion

The three antivirals studied present both benefits and collateral effects, however, there is a conviction of their use in cases of monkeypox in humans. Although smallpox is said to have been eradicated in humans years ago, the possibility of a current outbreak would

not be unheard of, we must be prepared, especially for its possible use as a biological weapon in the future, no one knows.

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