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ORIGINAL ARTICLE

The Role of Tecovirmat (ST-246) as a Potential Antiviral Agent Against Monkeypox Infection: a systematic review

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Introduction

Since May 2022, the incidence of monkeypox caused by monkeypox virus (MPXV) has increased in several non-endemic countries such as United States, England, Singapore, and Indonesia. Until now, there is no definitive therapy for monkeypox. Tecovirimat is reported to have antiviral effects against MPXV.

Objective

To determine the potensial activity of tecovirimat as an antiviral therapy against monkeypox infection.

Methods

We followed the PRISMA guidelines to search literature through several databases: ProQuest, PubMed, EBSCOhost, SAGE, and Taylor&Francis from inception to May 20th, 2023. Titles and abstracts were reviewed to assess relevance. The inclusion criteria used were original articles, written in English, and assessed the activity of tecovirimat in monkeypox infection.

Results and Discussion

From 558 studies, 15 studies that met the inclusion criteria were taken. There are studies in vitro (n=1), in vivo (n=8), case reports (n=2), case series (n=2), cross-sectional (n=1), and retrospective observational (n=1) published between 2009 and 2022. Tecovirimat was found to have 50% effective concentration of (EC_{50}) <0.04 M against MPXV by reducing viral envelope production and shedding. A significant reduction [>1000-fold decrease ($p<0.05$)] in viral load was found in subjects treated with tecovirimat. Symptoms and skin lesions improved after administration of tecovirimat on days 2 to 3 with a dose of 600 mg, twice a day, for 14 consecutive days. The only reported side effects were mild headache and softer stool consistency.

Conclusion

Tecovirimat is an effective antiviral therapy and has no significant side effects in monkeypox infection.

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Monkeypox is an uncommon zoonotic illness caused by infection with the monkeypox virus (MPXV), a member of the family Poxviridae in the genus Orthopoxvirus. The spread of this DNA virus can occur through contact with infected animals or people, contaminated materials, and vertical transmission through the placenta.[1,2] The incubation period for the MPXV ranges from 5 to 21 days, usually preceded by a prodromal phase lasting 1-5 days. Prodromal symptoms may include fever, muscle aches, back pain, headache, and lymphadenopathy. Subsequently, the eruption phase typically takes place after the fever subsides. This phase is featured by the appearance of single or multiple skin and/or mucosal rashes. The lesions may progress through macules, papules, vesicles, and pustules, eventually crust and desquamate after 2 to 4 weeks.[2,3]

Monkeypox commonly occurs in South and Central African countries. The first identification of monkeypox virus infection in humans was in the Democratic Republic of the Congo in 1970. In Nigeria, since 2017, there have been 500 alleged cases, with more than 200 confirmed cases and a case fatality ratio of around 3%. Since May 2022, the World Health Organization (WHO) has received reports of an increase in monkeypox incidence in regions without a history of travel from endemic countries, including Europe, America, Eastern Mediterranean, and Western Pacific. The global number of reported monkeypox cases continues to rise, totaling 79,231 cases in 110 countries, with 103 countries reporting their first cases and a total of 78,278 cases. Monkeypox was also identified in Indonesia in August 2022.[4–6] To date, there is no specific treatment for monkeypox, and the treatment provided is symptomatic and supportive to alleviate associated complaints. Several antivirals, including brincidofovir, cidofovir, and tecovirimat, have been used to treat this disease.[7,8] Tecovirimat, also known as ST-246, is an antiviral approved by the Food and Drug Administration (FDA) for treating smallpox caused by Variola virus infection. Nevertheless, its application for other orthopoxvirus infections, including monkeypox, lacks approval from the FDA.[9,10]

The effectiveness and efficacy of tecovirimat in treating non-variola orthopoxvirus infections in humans, including MPXV, is still limited. In primate studies, treatment with tecovirimat increased the survival rate by up to 95% compared to 5% in placebo recipients.[6,9] However, until now, there have been no studies describing and evaluating the potential of tecovirimat as an antiviral against monkeypox. This systematic review was conducted to determine the potential activity of tecovirimat as an antiviral agent against monkeypox virus infection.

METHODS

This systematic review followed the Preferred Reporting Items guidelines for Systematic Reviews and Meta-analyses (PRISMA).

Literature Search

The authors conducted a comprehensive literature search to investigate the potential of tecovirimat as an antiviral therapy against monkeypox and its associated side effects using the search sites ProQuest, PubMed, EBSCOhost, SAGE, and Taylor & Francis. Articles were retrieved from inception to May 20th, 2023. The search terms applied on PubMed were as follows: (((((((“immunology”) OR (“immune response”)) OR (“immunity”)) AND (“antivirus”)) OR (“antiviral”)) AND (“tecovirimat”)) OR (“ST-256”)) AND (“monkeypox”). The literature search was limited to full-text studies published in English.

Study Selection

The inclusion criteria were as follows:[1] Original article;[2] Written in English;[3] Availability of full text (fulltext);[4] Report the effect of tecovirimat on monkeypox infection. The exclusion criteria were as follows:[1] Literature review, letter to the editor;[2] Lack of data availability (the outcome assessment, measurement method, and measuring instrument).

Data Extraction

Five authors independently extracted additional information from the included studies, with the fifth author resolving any differences that arose among the other authors. The extracted data for clinical studies included:[1] Author;[2] Year of publication;[3] Study design;[4] Dosage;[5] Subject;[6] Outcome: clinical signs and adverse effects. Meanwhile, the extracted data for preclinical studies were as follows:[1] Author;[2] Year of publication;[3] Study design;[4] Tecovirimat dosage;[5] Subject;[6] Viral: virus strains and viral dosage;[7] Outcome: viral load and clinical signs.

Outcome Assessment

The outcome assessment in this study was grouped based on the type of study design: clinical study and preclinical study. In the clinical study, the outcome was assessed based on the progress of clinical symptoms, such as changes in the appearance of skin lesions, and side effects occurring in patients after receiving tecovirimat therapy. In the preclinical study, the assessed and observed outcomes included the change in viral load measured using PCR, cytotoxic effects measured using the viral cytopathic assay (CPE), as well as plaque size evaluation and comet tail formation measured using the immunohistochemistry assay (IHC). Additionally, clinical symptoms observed in subjects given tecovirimat after being infected with MPXV were also noted in the preclinical study.

Quality Assessment

The risk of bias assessment was conducted by four authors (FM, MMS, DY, FS). Various quality assessment tools were employed, including the Joanna Briggs Institute (for studies using case reports, case series, and cross-sectional methods)[11], SYRCLE risk of bias[12] (for in vivo studies), Modified New Castle Ottawa[13] (for observational retrospective studies), and adaptations based on previous systematic reviews for in vitro studies.[14] Any disagreements among the four authors were resolved by the fifth author (RR).

Ethical Approval

None of the authors of the articles included in this systematic review conducted any research on people or animals. Each study adhered to the ethical guidelines outlined in the relevant articles. As stated in the individual articles, patient informed consent was obtained for all research.

RESULTS

In total, 558 literature items were identified during the initial search. After filtering based on title, keywords, abstract, and duplication, 32 publications that met the criteria were discovered. Upon reading all 32 articles, 17 were subsequently excluded. The literature assessment followed the PRISMA 2020 flowchart, as depicted in Figure 1.

Risk of Bias

The case report and observational study quality yielded satisfactory results, as indicated by the findings of the critical review (Supplemental Figure 1 and Supplemental Figure 2). However, several components in the collected in vivo studies were not clearly stated (Supplemental Figure 3). In the included in vitro study, no sample size calculations and statistical analysis were found, although other components were deemed satisfactory (Supplemental Figure 4). In a cross-sectional study, the criteria were generally met, but the inclusion criteria and confounding factors were not clearly mentioned (Supplemental Figure 5). The two included case study series also lacked clarity in study inclusion criteria and participant details, and no statistical analysis was conducted (Figure Supplemental 6).

Charasteristic of Included Studies

All studies included in this systematic review were published in English between 2009 and 2022 (Supplemental Table 1 and Supplemental Table 2). The included studies comprised in vitro (n=1), in vivo (n=8), case reports (n=2), case series (n=2), cross-sectional (n=1), and observational retrospective

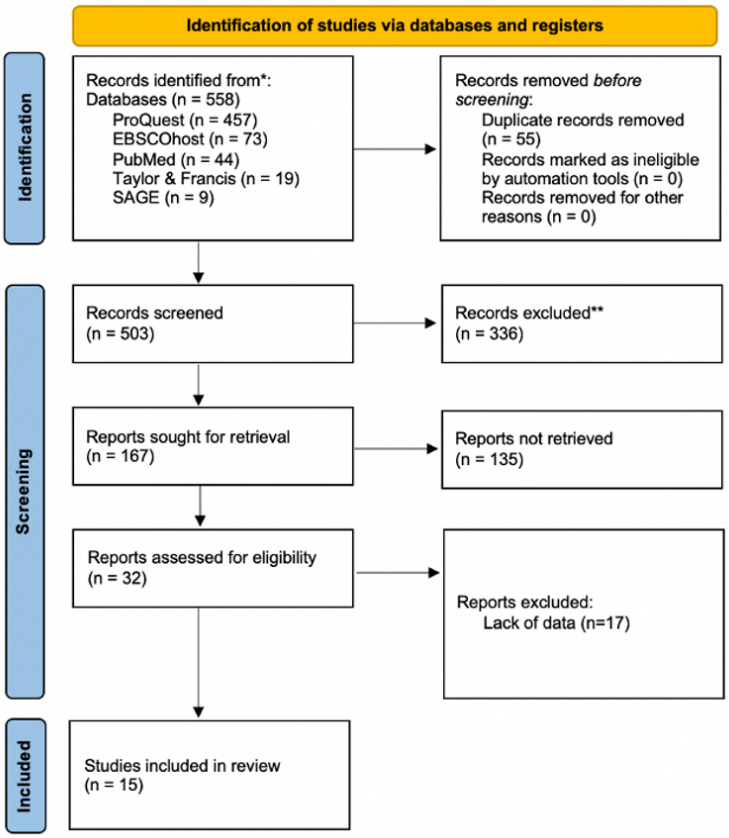

Figure 1 *PRISMA flowchart*

(n=1). A total of 558 articles were retrieved during the initial search. After excluding duplicate articles, 503 potential articles underwent title and abstract screening, followed by a refined selection based on exclusion criteria. Subsequent to the title and abstract screening, 32 articles were included for full-text assessment, resulting in the final inclusion of 15 articles in this systematic review.

Research conducted by Smith et al[15] in in vitro studies demonstrated an effective concentration of 50% for MPXV inhibitory function was <0.05 μM. Reduced plaque size and inhibition of comet tail formation were achieved with a dose of ST-246 between 0.05 - 0.15μM. The in vivo study by Warner et al[16] showed that the effective concentration of 50% for the MPXV inhibitory function was <0.01 μM, and the group of mice that received the therapy experienced a significant decrease in viral titers (>1000x fold) compared to the control group (p<0.05).

Jordan et al[17] reported that Macaca fascicularis treated with tecovirimat at a dose ranging from 3 mg/kg body weight (KgBB) up to 100 mg/kgBW per day exhibited a lower viral load than the control group (p<0.001). In a similar vein, Smith et al[18] conducted an in vivo experiment on prairie dogs administered tecovirimat at a dose of 30 mg/kg/day, observing a decrease in viral load to undetectable levels in the treated group from the day of intervention until the third day after infection. Huggins et al[19] administering tecovirimat to cynomolgus monkeys at a larger dose (300 mg/kg/day), found that the viral load in the subjects was reduced by almost 5 logs and was not influenced by the time of therapy initiation, with no new lesions observed in the intervention group.

Sergeev et al[20] achieved a decrease in viral load to undetectable levels, with an index value of <0.4 lg PFU/ml in the majority of infected mice biomaterials, receiving tecovirimat doses of 30 or 60 μg/gBB (p<0.05). Berhanu et al[21] also reported a significant reduction in viral load (p<0.0001) and lesions (p<0.01) in cynomolgus monkeys receiving tecovirimat at 10 mg/kgBW/day. Russo et al[22] administered tecovirimat at 10 mg/kgBB/day to cynomolgus monkeys infected with a lethal dose of MPXV, and found that 12 out of 13 monkeys survived. The study observed a significant improvement in clinical symptoms compared to controls (p<0.05). In a study by Sergeev et al[23] the in vivo test with ground squirrel subjects showed no deaths in the treatment group (tecovirimat 40 mg/kg/day) after the intranasal MPXV test.

In a serial case study by Matias et al[24] involving three adult patients, resolution of the lesions occurred between the 7th and 14th days after consuming tecovirimat twice daily at a dose of 600 mg, for 14 days. There is a case report by Hernandez et al[25] and Ajmera et al[26] who administered tecovirimat at the same dose. Hernandez et alreported that patients had skin lesions that healed quickly, and no side effects were found. Ajmera et alstated that the improvement of the lesions in patients began on the third day of therapy.

In a case series involving two patients with monkeypox-associated encephalitis by Pastula et al[27], patients recovered after three weeks of oral tecovirimat therapy (patient 1) and after five weeks of intravenous therapy (patient 2). A retrospective observational study by Adler et al in six monkeypox patients stated that a patient who received tecovirimat experienced a shorter duration of illness (10 days) compared to those who did not receive therapy or received brincidofovir, and found no side effects. According to this retrospective observational study by Adler et al[7] in six patients with monkeypox, those who received tecovirimat had shorter hospitalization lengths (10 days) than those who did not receive treatment or those who received brincidofovir, and there were no side effects. The patients' hematological, renal, and liver profiles also remained within normal limits during the first week of therapy. According to a cross-sectional research by O'Laughlin et al[28], patients with monkeypox saw a median three-day improvement in symptoms after taking tecovirimat, with 3.5% of patients also reporting moderate adverse effects such as headaches and softer stool consistency.

DISCUSSION

Tecovirimat is considered as an antiviral option for preventing and treating monkeypox infections, although it has not yet received approval from the FDA. The use of antivirals becomes a significant consideration for preventing monkeypox infection, particularly for individuals with contraindications to vaccines. This includes individuals with weakened

immune systems, such as those with HIV, transplant recipients, and individuals undergoing cancer therapy. Tecovirimat is one such antiviral being explored for these populations.[15,18]

As of now, there are no systematic reviews analyzing the effectiveness of tecovirimat. It's important to note that the search for relevant studies may be limited by language barriers, potentially missing publications in other languages that meet the criteria. While preclinical studies have been conducted in various animal models, conducting similar studies in humans is challenging due to the rare occurrence of monkeypox cases and ethical concerns surrounding such research.

Based on comparable drug levels in blood plasma observed in cynomolgus monkeys and humans following the administration of tecovirimat, with a dose of 10 mg/kg/day (monkeys) and 400 mg (phase I clinical trials), Jourdan et al concluded that 400 mg was the appropriate dose for humans. Three case reports from the United States suggested that using tecovirimat at a dose of 600 mg twice daily for 14 days led to clinical improvement without negative side effects.[17] The research conducted involved the oral administration of more drugs than intravenous administration. Additionally, the use of tecovirimat in conjunction with the ACAM2000 vaccine was found to be effective in preventing and reducing the severity of clinical lesions, especially when administered after exposure.[21]

According to the CDC's recommendations, tecovirimat is administered to patients with severe clinical symptoms, such as hemorrhagic disease, numerous confluent lesions, ocular or periorbital infections, encephalitis, sepsis, or other conditions requiring hospitalization, as outlined in serial case reports in the United States. Tecovirimat is also prescribed in cases of severe infections, including secondary infections, particularly those necessitating surgical management, affecting anatomic sites prone to scarring or strictures, such as the penis, vulva, vagina, urethra, and rectum. Consideration of tecovirimat is crucial for patients at high risk of severe disease, such as those who are severely immunocompromised, in the pediatric population, pregnant or lactating, or have conditions leading to impaired skin integrity. Unfortunately, there is a lack of available data regarding the potential fetotoxic effects and tecovirimat content in the breast milk of nursing mothers. Tecovirimat has been used in pediatric patients aged 28 months without side effects.[29]

The limitations of this systematic review include heterogeneity in terms of research types, research subjects, efficacy parameters, initiation time of therapy, therapy duration, and drug dosage, accompanied by different types of virus strains. This diversity makes it challenging to determine the optimal time to initiate therapy and the appropriate therapeutic dose.

Through this study, it is hoped that the use of antivirals, especially for individuals with severe clinical symptoms who cannot receive vaccines, can be considered in medical practice.

CONCLUSION

According to the findings of this systematic review, tecovirimat (ST-246) emerges as a potent antiviral treatment for monkeypox, demonstrating efficacy in reducing viral load and treating skin lesions. The recorded negative effects associated with tecovirimat use are limited to mild headaches and softer stools. However, further investigation, particularly in the human population, is deemed urgent to enhance our understanding and better predict potential future monkeypox epidemics.

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