TECOVIRIMAT: A COMPREHENSIVE REVIEW OF NOVEL DRUG FOR MONKEYPOX DISEASE

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ABSTRACT

Orthopoxvirus infections caused by pathogenic agents require therapeutic intervention. Animal models of orthopoxvirus disease are crucial for assessing the effectiveness of antiviral medications and determining the right dose and duration of treatment in the absence of disease-affected individuals. Antiviral drugs for the treatment of severe orthopoxvirus infections have been developed as a result of research on smallpox

INTRODUCTION

Monkeypox virus (MPXV), a member of the Orthopoxvirus genus, Chordopoxvirinae subfamily, and Poxviridae family, is a zoonotic disease that causes monkeypox. Monkeypox and smallpox both are caused by the orthopox virus, resemble each other. These viruses contain a linear double-stranded DNA, which are found in the cytoplasm of infected cells. Viral hosts include non-human primates and several rodent species [1-3]. In 1980, the World Health organization (WHO) declared smallpox to be eradicated worldwide. Scientists Preben Von-Magnus discovered monkeypox virus in laboratory cynomolgus monkeys in Denmark in 1958 as a result of two outbreaks of a disease resembling smallpox in colonies of monkeys seized in Malaysia and trafficked through Singapore. The virus was initially identified in monkeys in a Danish laboratory, thus the name monkeypox was given. The first human case was a 9-month-old boy from the Democratic Republic of the Congo (DRC) was diagnosed in the 1970 [4-7]. Since then, monkeypox has spread to other African nations, primarily in Central and West Africa, and has become endemic in the DRC. The first cases of monkeypox outside of Africa were noted in Europe in 2003. In the resource-limited endemic regions where monkeypox is found, clinical detection, diagnosis, and prevention still pose difficulties [1, 3, 8]. Since the beginning of May 2022, more than 3000 instances of the MPXV have been reported in more than 50 nations across five continents. In contrast to West or Central Africa, where the MPXV is widespread, the majority of verified cases with a travel history reported journeys to Europe and North America.

On July 23, the WHO designated the MPXV epidemic a worldwide health emergency [8, 9]. For the first time, MPXV cases and clusters have been recorded concurrently in both endemic and non-endemic nations across a wide variety of geographic locations. The effectiveness of tecovirimat to treat monkeypox has not been completely assessed in humans since there have been few opportunities to conduct clinical studies in nations where monkeypox virus infection is thought to be endemic. Instead, trials on nonhuman primates like monkey, rabbit, prairie dogs and macaque monkey served as the basis for the efficacy results that helped the FDA approved tecovirimat for treating infection due to the monkeypox virus [4-6]. The monkeypox virus is not on the US Centers for Disease Control and Prevention’s (CDC) list of biological agents that warrant concern for biosecurity, but it is on the matrix developed by the EU task group on bioterrorism [1, 7]. The current drug review on tecovirimat is planned to find the evidences of the efficacy and safety of the drug against MPXV.

DISCOVERY

A high-throughput screening for substances having inhibitory in vitro activity against the vaccinia virus and the cowpox virus led to the discovery of tecovirimat. At a dosage of 5 μM, 759 compounds were shown to reduce the vaccinia virus (VACV) or cowpox virus (CPXV)-induced cytopathic effect (CPE) by more than 50% using a high-throughput screening test on 356,240 compounds from a structurally diverse chemical library [10, 11]. On follow up of these early hits, researchers discovered a chemically similar set of substances that, at concentrations ranging from 0.013 to 5pM, suppressed virus-induced CPE by 50% (EC50) [11]. Based on further exploring structure-activity relationships, structural analogues were created from this group and tested in the cell-culture CPE assay against VACV and CPXV in order to increase potency and metabolic stability. Tecovirimat was selected for further research owing to favourable metabolic stability and low EC50 values that were reported in this experiment [10, 12].

MECHANISM OF ACTION

After attachment and entry through the cell membrane, Orthopoxviruses undergo biosynthesis. Envelopment transforms these immature virus (IV) particles into infectious intracellular mature viruses (IMV). To develop as an internal enveloped virus (IEV), IMV may be further enveloped with a double membrane layer produced from early endosomes or the trans-Golgi network (TGN). The virions are then released as either extracellular enveloped virus (EEV), which spreads from the site of infection, or cell-associated enveloped virus (CEV), which remains attached to the cell membrane, depending on whether these triple membrane-enveloped particles are transported to the cell surface. Several viral proteins, notably the VP37 protein, are necessary for IMV to encapsulate into IEV. So, IEV production from IMV is prevented by...
The majority of these enzyme substrates are not anticipated to be tecovirimat (ST-246), respectively [16]. The effects of tecovirimat on the urine (mainly as metabolites) and faeces (primarily as tecovirimat resulted in 73% and 23% of the dose being eliminated in vs. 55.3 L/h) than fasting conditions [12]. One dose of radio-labelled was 5 h [12]. Tecovirimat is 77-82% bound to human plasma exposure for human effectiveness. At day 14, the mean time to Cmax and AUC0-24h values of tecovirimat in fed volunteers were 1.5, 4.1, and 2.1-fold higher than those associated with efficacy in animals in both animal models, dose exploration to identify the minimal totally effective dose, and studies of treatment delay and duration in non-human primates (NHPs) [18, 19]. In animal studies, tecovirimat was highly protective against lethal challenges with vaccinia virus (VACV), ectromelia virus, and cowpox virus in mice [20]. MPXV [21] and VARV [22] in nonhuman primates (NHP), and rabbitpox virus in rabbits [23]. In small animals, tecovirimat exhibited disease protection when administered up to 72 h after infection, [24, 20, 23] five days post-infection in NHPs challenged intravenously, [17] and up to eight days following aerosol challenge in NHPs [25]. When tecovirimat therapy began before the onset of illness symptoms, 100% survival was seen in all subjects. In the deadly MPXV aerosol challenge model in cynomolgus macaques, Russo et al. assessed the effectiveness of oral tecovirimat treatment when started from 1 to 8 days after challenge, demonstrating considerable efficacy in therapeutics and postexposure prophylaxis. The pharmacokinetics of the oral suspension formulation employed in this study were comparable to those of the capsule formulation in human and mimic human dosage. Treatment started earlier (before development, it is unknown if alteration of the vp37 protein confers a fitness detriment to orthopoxvirus. There is no known cross-resistance between tecovirimat and cidofovir (CDV) or brincidofovir (BCV), and it is active against strains of vaccinia virus that are CDV-resistant [14, 15]. Tecovirimat prevents Rab9 GTPase and TIP47 from interacting with the vp37 envelope-wrapping protein, which is highly conserved across all orthopoxviruses (a Rab9-specific effector protein). This halts the further development of egress-competent enveloped virions, which are necessary for the virus to spread throughout the host [12, 16]. Results from an in vitro investigation specifically revealed that the cowpox virus VP061 gene product, which is identical to the vaccinia virus F13L gene and produces the vp37 envelope wrapping protein, was the target of tecovirimat antiviral activity [10]. Additionally, tecovirimat completely prevented the development of plaques and the virus’s cytopathic effects, and it significantly reduced the production of extracellular vaccinia virus 24 h after infection compared to control. However, it had little impact on the production of intracellular vaccinia virus [15].

Fig. 1: Diagram showing the target site of tecovirimat

Pharmacokinetics

Modelling and simulation studies predicted that a 600 mg twice daily dosage of tecovirimat in humans. As this dose would provide a plasma concentration in humans that was required for efficacy but well below the maximum level established as being associated with no adverse events in animal studies [12, 17]. This data was based on the tecovirimat exposure-response relationship in animal models and pharmacokinetic and safety data in human adult volunteers. A 14-day treatment regimen was also chosen based on the kinetics of the humoral immune response to smallpox [12, 15]. The maximum concentration (Cmax) and area under the concentration-time curve from time 0 to 24 h (AU0-24h) values at steady state (reached by day 6) values in humans after successive doses are about 40% greater than after the initial dosage [12, 16]. Additionally, the bioavailability of tecovirimat is affected by food, with fed state resulting in plasma Cmax and AU0-24h values that are up to 50% higher on day 1 and up to 45% higher on day 14 compared to fasting [12]. At day 14, mean steady-state Cmax, minimum concentration, average concentration, and AU0-24h values of tecovirimat in fed volunteers were 1.5, 4.1, 2.1, and 2.1-fold higher than those associated with efficacy in cynomolgus macaques, respectively [5]. The study further revealed that 600 mg twice daily dosage ought to produce the necessary drug exposure for human effectiveness. At day 14, the mean time to Cmax was 5 h [12]. Tecovirimat is 77-82% bound to human plasma proteins and is metabolised via glucuronidation (by UGT1A1 and UGT1A4) and amide bond hydrolysis [16]. At day 14, both fed and fasted conditions produced identical elimination half-life values (23 h), but fed state produced numerically lower clearance values (39.2 vs. 55.3 L/h) than fasting conditions [12]. One dose of radio-labelled tecovirimat resulted in 73% and 23% of the dose being eliminated in the urine (mainly as metabolites) and faeces (primarily as tecovirimat), respectively [16]. The effects of tecovirimat on the majority of these enzyme substrates are not anticipated to be clinically significant despite the fact that it is a weak inducer of CYP3A4 and a weak inhibitor of CYP2C8 and CYP2C19. Although research on animals has suggested that administering tecovirimat along with the live smallpox vaccine (vaccinia virus) concurrently may lessen the immunological response to the vaccine, it is yet unknown whether this interaction will affect vaccine efficacy in humans [16].

Preclinical studies

Among preclinical studies on tecovirimat, there were two pivotal studies on rabbits and four pivotal studies on non-human primates. These studies included pharmacokinetic (PK) parameter in infected animals in both animal models, dose exploration to identify the minimal totally effective dose, and studies of treatment delay and duration in non-human primates (NHPs) [18, 19]. In animal studies, tecovirimat was highly protective against lethal challenges with vaccinia virus (VACV), ectromelia virus, and cowpox virus in mice [20]. MPXV [21] and VARV [22] in nonhuman primates (NHP), and rabbitpox virus in rabbits [23]. In small animals, tecovirimat exhibited disease protection when administered up to 72 h after infection, [24, 20, 23] five days post-infection in NHPs challenged intravenously, [17] and up to eight days following aerosol challenge in NHPs [25]. When tecovirimat therapy began before the onset of illness symptoms, 100% survival was seen in all subjects. In the deadly MPXV aerosol challenge model in cynomolgus macaques, Russo et al. assessed the effectiveness of oral tecovirimat treatment when started from 1 to 8 days after challenge, demonstrating considerable efficacy in therapeutics and postexposure prophylaxis. The pharmacokinetics of the oral suspension formulation employed in this study were comparable to those of the capsule formulation in human and mimic human dosage. Treatment started earlier (before
day 5 postinfection) considerably lessened the severity of the model's secondary endpoints, such as weight loss, clinical symptoms, and viremia. When treatment was started late (as late as 7 d postinfection), it also greatly increased survival. Unexpectedly, treatment initiation on day 7 (100% survival) offered stronger protection from mortality than treatment initiation on day 6 (66% survival), even though survival rates for groups starting treatment on days 6 or 7 both were significantly improved as compared to animals given a placebo. Although this conclusion may seem counterintuitive, it is not surprising given the complexity of the test system and the severity of sickness experienced by animals treated so late in the disease process [25]. Subsequently, researchers showed protection from mortality in a rabbit smallpox model caused by the rabbitpox virus and a nonhuman primate smallpox model caused by the MXPV. In 361 healthy controls randomly assigned to receive 600 mg of tecovirimat twice daily experienced pharmacokinetic and safety levels that were four times higher than those associated with efficacy in nonhuman primates. Incidence of adverse effects were comparable to placebo [26]. Under the "Product Development Under the Animal Rule" an antiviral medication called tecovirimat was authorised for the treatment of smallpox illness. When it is unethical to carry out efficacy studies on humans and animals, it is practical to carry out field trials to assess the efficacy of a drug or biologic product, this approach enables the approval of medications for serious or life-threatening illnesses. The Animal Rule requires that safety be sufficiently assessed in humans, while efficacy is shown on the basis of adequate and well-controlled trials in animal models of the relevant human disease or condition [27].

The effectiveness of oral tecovirimat for the treatment of smallpox was established in animal models [cynomolgus macaques and New Zealand white (NZW) rabbits] infected with non-vario/a orthopoxviruses because adequate and well-controlled field trials in smallpox-infected humans are neither ethically acceptable nor practical. The survival rates shown in animal research may not be representative of those seen in the real-world [16]. In orthopoxvirus (monkeypox and rabbitpox)-infected cynomolgus macaques and NZW rabbit models, tecovirimat enhanced survival rates in comparison to placebo [12]. In a trial with 24 cynomolgus macaques, tecovirimat 3, 10, and 20 mg/kg once daily for 14 d significantly (p = 0.025) increased survival rates compared with placebo (100, 100, and 100 vs. 0%, respectively) [12]. Another study with 27 cynomolgus macaques reported that tecovirimat 3 and 10 mg/kg (80 and 80 vs. 0%) significantly increased survival rates (p = 0.01) over placebo, but not tecovirimat 0.3 and 1 mg/kg (20 and 0 vs. 0%). Following investigations in 21 cynomolgus macaques were conducted with the 10 mg/kg dose of tecovirimat since it decreased viral load and lesion counts more effectively than the 3 mg/kg dose (i.e., the dose needed to obtain >90% survival rate). When given on day 0 and 5 while administering the following oral tecovirimat 3 mg/kg once daily for 14 d was linked with a significantly (p = 0.05) greater survival rate than placebo (83, 83, and 50 vs. 0%) when compared with other treatments. Survival rates with tecovirimat 10 mg/kg once daily for 3, 5, and 7 d were 50%, 100%, and 80% in a research on treatment duration in 25 cynomolgus macaques, respectively, compared with 25% with placebo. A pooled analysis of the data from the four investigations revealed that 94% of the 33 cynomolgus macaques receiving tecovirimat 10 mg/kg once daily for 14 d survived [compared with 5% of those (n = 20) receiving placebo]. Unless otherwise noted, the cynomolgus macaques in the four experiments received an intravenous fatal dose of monkeypox virus (day 0) before receiving oral tecovirimat or a placebo once daily for 14 d, starting on day 4 [after the beginning of clinical symptoms, such as pox lesions] [12]. Survival rates were considerably (p = 0.025) higher with tecovirimat at 20, 40, 80, and 120 mg/kg once daily for 14 d compared with placebo (90%, 90%, 80%, and 80% vs. 0%) in a study with NZW rabbits (n = 50) [12].

In a different trial, all three doses of tecovirimat (40, 80, and 120 mg/kg) given once daily for 14 d resulted in 100% survival rates. The lowest effective dose (LIED) of tecovirimat was 40 mg/kg, and the dose of 40 mg/kg was chosen as the benchmark for effective dosing. A combined analysis of the data from the two studies revealed that, overall, 94% of the 17 NZW rabbits getting tecovirimat 40 mg/kg once daily for 14 d survived (in contrast to 0% of those (n = 10) receiving placebo). The NZW rabbits received afatal (intradermal) dose of the rabbitpox virus on day 0 and then either tecovirimat or a placebo (for the first trial only) was administered orally once daily for 14 d (i.e., fever and viremia)

To promote the development of tecovirimat as a smallpox treatment, more than 50 animal tests of the drug’s efficacy and safety have been carried out. After three months of repeated dosing with tecovirimat plasma levels up to 23 times the acceptable human dose in mice and 2.5 times the recommended human dose in NHPs, respectively, no major side effects were seen in preclinical animal safety, pharmacology, and toxicology tests [28]. Following a single dose of 300 mg/kg [29], which is four times greater than the greatest documented human exposure based on Cmax at the suggested human dose, seizures were seen in dogs. Following 12 d of treatment with tecovirimat at a high dose (300 mg/kg once daily), a follow-up investigation in NHPs found no incidence of seizures. The important preclinical trials are summarized in table 1.

**Clinical studies**

The only regulatory route for authorising a medicine for the treatment of smallpox was the "Product Development Under the Animal Rule" because smallpox is a disease that has been eradicated and conducting efficacy trials in humans would be neither ethically appropriate nor practical. Variola virus infection in animals does not resemble human smallpox sickness, and animal research using the virus, particularly nonhuman primate models, are not reliably reproducible. Research on variola virus is also restricted to two maximum-containment laboratories in the US and Russia, which creates significant feasibility problems for these studies. Therefore, experiments in animal models employing similar ortho-poxxviruses, notably nonhuman primates infected with the monkeypox virus and rabbits infected with the rabbitpox virus, were used to establish the efficacy of tecovirimat for the treatment of smallpox and to obtain drug approval. In these investigations, tecovirimat-treated animals had significantly greater survival rates than placebo-treated animals. By monitoring negative reactions in healthy volunteers who got tecovirimat, safety in human was evaluated. By comparing the plasma concentrations of the medication in healthy volunteers with those in animal models at levels that had been proven to be fully effective against monkeypox and rabbitpox, the optimal dose of tecovirimat for the treatment of smallpox in humans was inferred. The results of investigations in healthy animals and animals served as the basis for the suggested duration of therapy in humans [27].

Healthy human volunteers participated in a phase I clinical trial to evaluate the safety, tolerability, and clinical pharmacokinetics (PK) of tecovirimat given orally as a single dosage of 500, 1,000, or 2,000 mg while fasting. The volunteers were not allowed to consume food for 5 h before dosing. The four dosages were selected based on the drug was well tolerated and safe at these dosing levels. Over 50% and 1,000 mg dose levels, but not over 1,000 and 2,000 mg dose levels, the pharmacokinetics in plasma demonstrated dose proportionality. Non-fasting subjects had higher apparent maximum drug concentration in serum (Cmax), duration to maximum drug concentration in serum (Tmax), and area under the curve from zero hour to infinity (AUC∞) than did fasting subjects at the 1,000-mg dosage level. It has been predicted that doses of 400 mg and 800 mg for humans who are non-fasting will encompass plasma drug exposure levels comparable to those that provide protective efficacy in the nonhuman primate model of ortho-poxxvirus disease based on these results and given the variability in exposure levels in both monkeys and humans in the non-fasting and fasting states [30].

The purpose of this phase I, double-blind, randomised, placebo-controlled, ascending multiple-dose trial was to evaluate the safety, tolerability, and pharmacokinetics of tecovirimat when given orally once day for 21 d to healthy human volunteers who were not fasting. This drug was proved to be well tolerated, and there were no significant side effects (AEs). The most frequently reported adverse events (AEs) in all treatment groups was headache, which caused one event (AE) in all treatment groups was headache, which caused one significant side effects (AEs). The most frequently reported adverse

Drug's multiple-dose pharmacokinetics were thoroughly studied. The 250, 400, and 800-mg/day dosage groups' respective mean concentration in serum (Cmax), duration to maximum drug concentration in serum (Tmax), and area under the curve from zero hour to infinity (AUC∞) than did fasting subjects at the 1,000-mg dosage level. It has been predicted that doses of 400 mg and 800 mg for humans who are non-fasting will encompass plasma drug exposure levels comparable to those that provide protective efficacy in the nonhuman primate model of ortho-poxxvirus disease based on these results and given the variability in exposure levels in both monkeys and humans in the non-fasting and fasting states [30].

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day 21. By day 6 (within 3 to 5 half-lives), a steady state was attained, saturable absorption was seen at the 800-mg dose level, and there was very little parent drug excretion in the urine. Based on these findings, 400 mg/day of drug treatment is anticipated to result in plasma concentrations that are higher than those that were effective in nonhuman monkey models in earlier investigations [31].

A phase 2, double-blind, randomised, placebo-controlled, multicentre trial was carried out to evaluate the safety, tolerability, and pharmacokinetics (PK) of tecovirimat when given as a single oral dose per day (400 mg or 600 mg) for 14 d to fed adult volunteers. The drug’s PK and dosage proportionality were established. For the 400-mg treatment group, the PK study revealed that a steady state was reached by day 5 and by day 6 for the 600-mg group. According to the dose proportionality study, the 400- and 600-mg ratio of dose-normalized peak drug concentration in plasma (C_{max}) and relative exposure for each dosage interval (AUC) ranged from 80% to 85%. Drug was safe and well tolerated and no deaths or significant adverse events were reported during the research.

Treatment-emergent adverse events (TEAEs) were uncommon, with moderate nausea and headache being the most frequent occurrences [32]. Desai et al. conducted clinical trial on tecovirimat patients following laboratory confirmation of orthopoxvirus infection from skin lesions by polymerase chain reaction, who had lesions in face or genital area, or who had disseminated disease. For enhanced absorption, oral tecovirimat therapy for adult patients was weight-based, given every 8 or 12 h, and administered within 30 min of a meal with moderate to high-fat content. On day 7 of therapy, complete remission of lesions was observed in 10 patients (40%), while by day 21, complete resolution of lesions and discomfort was documented in 23 patients (92%). No patient discontinued therapy while receiving tecovirimat treatment, which was typically well tolerated. On day seven of therapy, the following side effects were most commonly reported: fatigue in 7 patients (28%), headache in 5 patients (20%), nausea in 4 patients (16%), itching in 2 patients (8%), and diarrhoea in 2 patients (8%) [33].

Table 1: Some important preclinical studies

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Authors/year</th>
<th>Animals tested/Objective</th>
<th>Results</th>
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<tr>
<td>1</td>
<td>Grosenbach DW et al. [12]/2018</td>
<td>Efficacy of tecovirimat in nonhuman primate (monkeypox) and rabbit (rabbitpox) models</td>
<td>-For testing in humans, a dosage of 600 mg twice daily for 14 d was used, providing doses greater than those in nonhuman primates. (mean steady-state C_{max}, C_{min}, and C_{avg} of 2209, 690, and 1270 ng per milliliter, respectively)</td>
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<td>2</td>
<td>Quenelle DC et al. [20]/2007</td>
<td>Evaluated for activity against mice infected with cowpox virus (CV), vaccinia virus (VV), and ectromelia virus (ECTV)</td>
<td>-In vitro 50% effective concentration (EC_{50}) of 0.48 μM against CV, 0.05 μM against VV, and 0.07 μM against ECTV.</td>
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<td>3</td>
<td>Jorden R et al. [21]/2009</td>
<td>Antiviral Efficacy in a Nonhuman Primate (NHP) Monkeypox Model</td>
<td>-NHP received a 14-day course of therapy that provided 100% protection from the deadly monkeypox virus infection and decreased viral load and lesion formation.</td>
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<td>4</td>
<td>Mucker EM et al. [22]/2013</td>
<td>Efficacy of tecovirimat in nonhuman primates infected with variola virus (Smallpox)</td>
<td>-Regardless of whether therapy began two or four days after infection, no animals treated with tecovirimat perished from infection, in contrast to 50% of placebo-treated controls. -Additionally, the number of cutaneous lesions, oropharyngeal virus shedding, and viral DNA circulating in the blood all significantly decreased after tecovirimat treatment. In a deadly aerosolized rabbitpox model utilised as a substitute for smallpox, once daily for 14 d beginning 1 h postexposure (p.e.), resulted in 100% survival.</td>
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<td>5</td>
<td>Nakca A et al. [23]/2008</td>
<td>Evaluation of orally delivered tecovirimat as postexposure prophylactic and antiviral therapeutic in an aerosolized rabbitpox rabbit model</td>
<td>Drug inhibited virus replication by 50% (conc. = 0.010 μM) and active against multiple orthopoxviruses, including vaccinia, monkeypox, camelpox, cowpox, ectromelia (mousepox), and variola viruses. Up to 5 d after the challenge, survival in animals starting therapy was 100%.</td>
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<td>6</td>
<td>Yang G et al. [24]/2005</td>
<td>Tecovirimat Inhibits Extracellular Virus Formation and Protects Mice from Lethal Orthopoxvirus Challenge</td>
<td>Drug inhibited virus replication by 50% (conc. = 0.010 μM) and active against multiple orthopoxviruses, including vaccinia, monkeypox, camelpox, cowpox, ectromelia (mousepox), and variola viruses. Up to 5 d after the challenge, survival in animals starting therapy was 100%.</td>
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<tr>
<td>7</td>
<td>Russo AT et al. [25]/2018</td>
<td>Efficacy of Tecovirimat Following Lethal Aerosol Monkeypox Virus Challenge in Cynomolgus Macaques</td>
<td>Drug inhibited virus replication by 50% (conc. = 0.010 μM) and active against multiple orthopoxviruses, including vaccinia, monkeypox, camelpox, cowpox, ectromelia (mousepox), and variola viruses. Up to 5 d after the challenge, survival in animals starting therapy was 100%.</td>
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CONCLUSION

Monkeypox disease, in contrast to smallpox, is still prevalent in part of world (mainly West and Central Africa). Despite case reports of tecovirimat being used to treat patients with infections due to monkeypox and other non-variola orthopoxviruses, there are no robust evidence for its efficacy in humans. Instead of only healthy participants, people with monkeypox disease could provide safety data for tecovirimat. Although tecovirimat has been found to be effective against monkeypox in animal models and have a good safety profile in healthy individuals, it is still crucial to carry out more RCTs to ascertain tecovirimat efficacy and safety in the treatment for monkeypox disease.

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CONFLICT OF INTERESTS
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