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A REVIEW ON THE ANTI VIRAL DRUG TECOVIRIMAT PRODUCE PHARMACOLOGICAL ACTIVITY AGAINST THE MONKEYPOX (MPOX)

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ABSTRACT

Monkey pox infection is caused by a virus of the genus *ORTHOPOXVIRUS*, a member of the *Poxviridae* family. Monkey pox virus is transmitted from individual to individual through contact with lesions, body fluids, and respiratory droplets. Monkey pox disease (MPX is currently considered a global threat after COVID 19). European Medicines Agency (EMA) approved Tecovirimat in capsule dosage form (200mg as the first treatment for MPX in january 2022. Tecovirimat was first recognized as an anti *orthopoxvirus* molecule in 2002 and developed by SIGA Technologies. Tecovirimat safety and pharmacokinetic parameters. The patient literature has revealed inventions related to capsule, injection, suspension, crystalline forms, amorphous form, and drug combination Tecovirimat. Cidofovir and process for preparing Tecovirimat. Tecovirimat is believed to handle the current MPX outbreak and is a new hope of biosecurity against the smallpox or *orthopoxvirus* related bioterrorism attack.

KEYWORDS: Tecovirimat, orthopoxvirus, monkeypox, patents, antiviral, COVID-19.

INTRODUCTION

A review on Monkey pox virus an Orthopoxvirus with symptoms similar to smallpox it is an Zoonomicdisease.[1,15] It contain the enveloped double standard DNA virus of (MPXV). Monkey pox family *poxviridae*, sub family *chrodopoxvirinae*, genus *Orthopoxvirus*.[2] The

monkey pox virus was found for the first time in 1958 in monkey pox which were housed in the research institute in Copenhagen, Denmark, hence the disease acquired the name as monkey pox.[6] Monkey pox became the most important OPXV for health, smallpox was eradicated worldwide in 1980. Monkeypox virus has been easily spread among the mammals, including humans. Incubation period of monkey pox it spread human to human transmission in 12 days. The first case several infections were also denoted in other countries including in America, Australia, and Asia.[13] Monkey pox virus can evolve and adapt to the environment in way to allows "species jump" started with animals, and infected humans.[3] Compared with COVID 19infection after the 40 years its is silencing infection, these outbreak are instantaneous report of multiple case in country mainly Europe, USA, Australia (3. The monkey pox virus can spread in a number of ways and to anyone through close, personal, often skin to skin contact.[13] WHO has reported the case fatality rate of monkey pox infection to be around 3 to 6%, which is slightly higher than that of COVID19.[8] On July 23 2022, the WHO declared Monkey pox outbreak as a Public Health Emergency of International Concern(PHEIC).[4] Currently, India has 1 confirmed (5 each in Delhi and Kerala and suspected cases).[1] in Delhi and Telangana each, 2 in Bihar and 4 in Uttar Pradesh only , however, with increasing 'pandemic fatigue' among masses and the rise in number of cases due to another virus could act as hurdle in the planning and execution of public health interventions.[4] First case was reported in India on July 14, 2022, in Kerala, and subsequent reporting of cases within intervals of 1 to2 days In Delhi and Kerala primarily (4. (11 As of 1o December 2022). 82, 474 confirmed cases of monkey pox have been reported in 11 countries in worldwide.[5] We report 528 infection diagnosed between April 27 and June 24, 2022, at 43 sites in 16 countries. Overall, 98% of the persons with infection were gay or bisexual median age was 38 years. Tecovirimat (TPOXX, ST) 246 was created through efforts to develop an orally available antiviral against the smallpox for bio defence.[8] Tecovirimat monohydrate has been approved by the EMA, USFDA. Health Canada to treat the smallpox, however only the EMA has approved Tecovirimat to treatment duration 14 days.[8] Tecovirimat administration demonstrated 100% protection to the infected animal and reduced the viral load and lesion formation.[8] Tecovirimat was approved in 2018 via the Food and Drug Administration (FDA Animal Efficacy Rule or Animal Rule), which allows a pathway for approval of drugs for severe or life threatening conditions when it is not ethical or feasible to conduct efficacy trials in humans.[6]

MATERIAL AND METHODS

Biology and Replication

MPXV belongs to the large enveloped virus family poxviridae double standard liner DNA (dsDNA).[8] The family of these viruses has over ten types including vaccinia virus (VV), (VARV), (CMLV), (CPXV), and several variant isolated from infected Human monkey pox is the typical Zoonamic, Mpox shows the spread animals to humans. (MPXV virus) has been spread to African rodents, and particularly in squirrels.[3] Monkey pox has similar but milder features than smallpox. Polymerase chain reaction (PCR) using swabs of skin lesions (vesicles, ulcers and scabs recommended for confirming infection in symptomatic individuals is used to detect MPXV). In addition, MPXV DNA has been detected by PCR in a wide variety of samples such as throat, nasopharynx, blood, urine, saliva, and semen. Therefore, the present study aims to analyze the detection of the monkey pox virus according to the collection site of samples from confirmed monkey pox cases.

1. Incubation: can vary from 7 to 14 days, but, is generally about 13 days.
2. Prodromal Phase: includes fever and lymphadenopathy.
3. Skin rash.

Lymphadenopathy characteristic of the prodromal phase is the essential elements which distinguishes monkey pox from smallpox and chickenpox.[3]

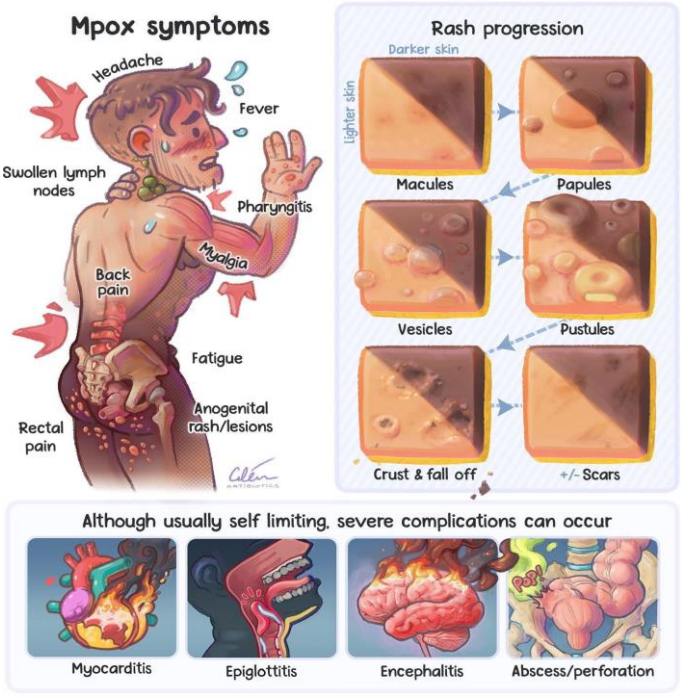


Figure 1: Symptoms of Monkey Pox Infection.

Figure 2:

Figure 3:

Poxvirus encoded DNA replication protein are prime targets for and antiviral. Cidofovir and oral derivatives are acyclic nucleoside analogs that are incorporated into growing DNA stand and inhibit the 5'to3' chain extension and 3'to 5' exonuclease activity of poxvirus DNA polymerase.[7] In 2021, the FDA approved brincidofovir for the treatment of smallpox infection. It is an orally bioavailable lipid conjugate of cidofovir, a viral DNA polymerase inhibitor. It showed improved survival with brincidofovir compared to placebo.[11] Unlike tecovirimat, brincidofovir has activity against an array of double standard DNA viruses, including herpesviruses, and has been studied against cytomegalovirus in hematopoietic stem cell (HSCT) patients. Tecovirimat is not a substrate for cytochrome P450 (CYP) enzymes CYP1A2, CYP2C8, CYP2B6, CYP2C19, or CYP2A4. Tecovirimat inhibits BCRP in vitro but is not an inhibitor of PGP, OATP1B1, OATP1B3, organic anion transporter 1 (OAT1), (OAT3) or organic cation transporter 2(OCT2).[6] There are limited *in vivo* data on the drug interaction potential of tecovirimat. The antiviral Tecovirimat (a protein inhibitor that inhibits the virus's systemic spread to other cells VP37 protein) was recognized as a target of tecovirimat by the mapping of Tecovirimat resistant mutant viruses.[8] Picture shows the mechanism of tecovirimat.

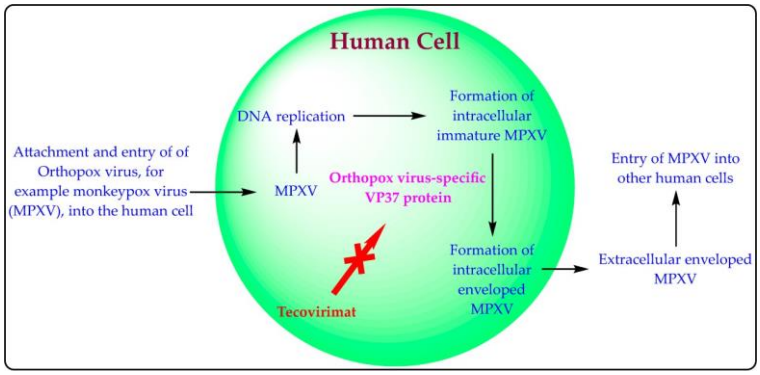


Figure 4: Mechanism of Tecovirimat.

Drugs approved by USFDA and CDC for the treatment of Monkey pox cases. Vaccination against the smallpox could be of immense utility in the prevention of monkey pox, because viruses belongs to same family (Orthomyxovirus),by mechanism of cross protection.[10]

RESULT

In this article we have discuss about the how drugs has been discover and they developed to cure the monkey pox. in general most of the people are diagnosed the monkey pox without any treatment. Antiviral drugs have been developed tecovirimat. The first drug with an indication for treatment for smallpox and also the treat the monkey pox infection.

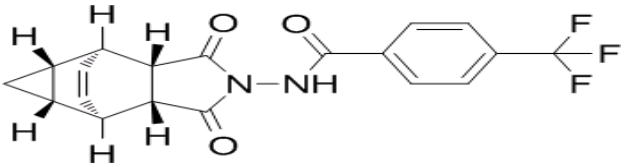


Figure 5: Chemical Structure of Tecovirimat.

TPOXX'S effectiveness against the smallpox by studies has been conducted in animals infected with virus having smallpox and measuring studies has been taken.[12] The *in vitro* Anti viral activity based on concentration of tecovirimat induced cytopathic effect (CPE by 5%). Tecovirimat of (3,10, 30 and100 mg/ kg) once a day. Administration orally to different groups of infection monkey pox after three days of infection (stage of secondary viremia).[8] Treatment during days 14 days. Tecovirimat administrated demonstration 1 % protection to the infected animals reduces the viral load and lesion forming. Tecovirimat is tetracyclic acyl hydrazide compound with a molecular weight of 376.33 g/mol. This drugs exhibits high permeability and low solutions of gastic PH range. Tecovirimat dose selection for treatment of orthopoxviruses is based on the extrapolation of pharmacokinetics in animal models of infection and healthy human volunteers in Germany between the onset of outbreak in may

2022 and march 2023.[12]

Tecovirimat drug tested expensively on cell culture with many orthopoxvirus (OPXV) animal model including in non human primate varida virus (VARV).[10] Tecovirimat drugs only licensed for treatment of smallpox the Center for disease control and prevention(CDC). Hold an expanded access for new drugs protocol for treatment of nonvariola OPXV infection including MPOX.[11] Tecovirimat also authorized for the marketing in the European union on 6 jan 2022. Cidofovir an antiviral union for the treatment of (CMV) in patient acquired immune deficiency syndrome. Further more it shows to be effective against orthopox virus in vitro and animal studies. Cidofovir shows the nephrotoxicity that limits first line treatment. Brincidfovir on it is a prodrug of antiviral cidofovir. In this report 528 infections diagnosed between April 27 and June 24, 2022 at 43 sites in 16 countries. Monkey pox virus DNA was detected in 29 of the 32 persons in whom seminal fluid was analyzed.[9]

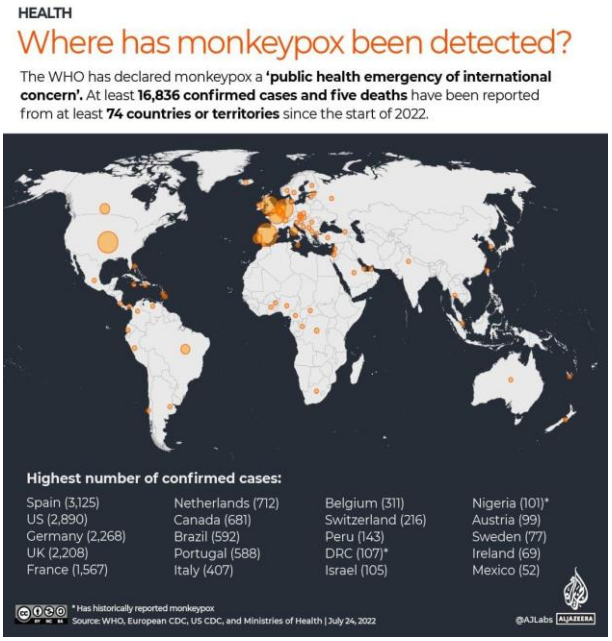


Figure 5: 2022 Human Monkey pox outbreak global map cumulative numbers of confirmed cases, by countries, data as of September 2022 (14).

Antiviral treatment was given to 5%of the persons overall, and 70 (13%) were hospitalized.[9] There is two types of complications were reported; one of epiglottises and two cases of myocarditis. The epiglottises occurred in a person with HIV infection who had a CD4 cell count of less than 200 per cubic millimeter; the person was treated with tecovirimat and recovered completely. The myocarditis cases were self-limiting (< 7 days) and resolved without Antiviral therapy.[9]

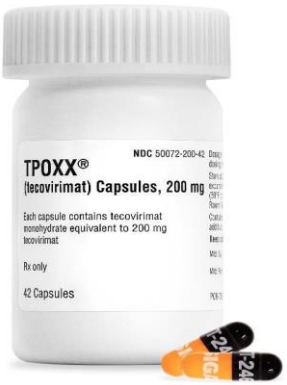
DISCUSSION

In this monkey pox most commonly occur rash, but most serious complication can arise according to research monkey pox in human published in 2009. According to the guidelines by MOHFW, patient isolation at home or hospital and symptom alleviation are essential principles in management of monkey pox cases. Isolation is advised till complete resolution of all lesions and falling of scabs. Transmission of the virus should be curbed with help of usage of triple- layers marks by the patient, practising good hand hygiene, covering the skin lesion to the maximum extent possible. Three types of precaution, i.e., standard, droplet and contact precautions need to be made applicable to all healthcare settings for further limiting potential spread.[10] The Central Basin clade (Central African clade) is more lethal, with a mortality rate of up to 10% in unvaccinated children. The Central African clade is reported most frequently than the West African clade and has documented cases of person- to person transmission, whereas the West African clade does not.[9] Since early May 2022, more than 3000 monkey pox virus infection have been reported in more than 50 countries across five regions, prompting the World Health Organization to declare than monkey pox is"evolving threat of moderate public health concern" on June 23, 2022.[9] Overall 98% of the persons with infection were gay or bisexual men, and 75% were White. Median age was 38 years.[9] Dose adjustment is not require for mild or moderate renal impartment (creatinine clearance [CrCl] >30 ml/ min).

Table 1: Recommended Pediatric and Adult Dosage and Preparation Instructions

Body Weight	Dosage	Number of Capsules	Drug-Food Preparation
13 kg to less than 25 kg	200 mg twice daily	Contents of 1 Capsule twice daily	Mix 1 capsule of TPOXX with 30 mL of liquid or soft food. Administer the whole mixture.
25 kg to less than 40 kg	400 mg twice daily	Contents of 2 Capsules twice daily	Mix 2 capsules of TPOXX with 30 mL of liquid or soft food. Administer the whole mixture.
40 kg and above	600 mg twice daily	Contents of 3 Capsules twice daily	Mix 3 capsules of TPOXX with 30 mL of liquid or soft food. Administer the whole mixture.

Figure: 6. Recommended pediatric and adult dosage forms.



Figture 7: Tecovirimat.

However, IV Tecovirimat is contraindicated in those with several renal impairment (CrCl<30ml/min).[11] In the Tecovirimat drugs are having two phase to demonstrated the safety and efficacy, and limited adverse drug events. In phase 1 trials examined the safety of single -dose Tecovirimat daily for to21 days. The initial trial contained 38 healthy volunteers who received 500mg, 1000mg, or 2000mg daily for 21 days. The most common adverse event reported across all interventions was a headache, gastrointestinal disorders(dry mouth, flatulence, and nausea) were noted in those receiving the higher dose of 800mg.[6] The phase 2 trials examined a single oral dose of either 400mg or 600 mg of Tecovirimat for 14 days. The safety study was a randomized, double- blind, multicenter phase 3 trial of 499 healthy volunteers. Common adverse drug event included headache (12%) of those receiving Tecovirimat and 8% of those receiving placebo) and nausea (5%) of participants receiving Tecovirimat and 4% of participants receiving placebo.[6]

CONCLUSION

The present study identified human monkey pox previously classified as a rare zootomic disease, raised awareness within the worldwide.[6] As of august 9, 2022, nearly 32,000 confirmed cases of monkey pox has been reported across 82 no endemic countries.[5] However smallpox vaccine is highly effective in preventing the monkey pox disease.[6] Tecovirimat is a new hope against the MPX outbreak and bio security against smallpox-related bioterrorism attacks. Tecovirimat was only approved by the EMA to treat to treat MPX.[7] Rapid initiation of infection controls measures and the use of vaccines and antiviral agents are important strategies for controlling the monkey pox epidemic.[1] Currently, Tecovirimat is approved only for the treatment of smallpox infection via the FDA Animal Rule. In international health care authorities must implement global preventive policies to control the burden of the disease both at regional and international levels.[15]

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