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Review Article

A REVIEW OF MONKEYPOX DISEASE AND FUTURE TREATMENT OPTIONS

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ABSTRACT

The Monkeypox virus (MPXV) causative agent for Monkeypox disease resembles a smallpox-like illness and can lead to a number of serious medical issues in humans. It is an enveloped double-stranded DNA virus and belongs to the Orthopoxvirus genus. Monkeypox cases have increased after the smallpox vaccine was no longer administered. Monkeypox did not really receive widespread attention until the 2003 US outbreak. The majority of monkeypox cases connected to the 2022 outbreak are being reported in nations surrounding Europe and in the western world. The neurological, respiratory, and gastrointestinal systems are all known to be impacted. There are currently no standardised or ideal guidelines for the clinical management of patients with monkeypox (MPX), especially in low-resource settings. Patient outcomes may also be poor and their illnesses may last a long time. The range of clinical manifestations, including complications and sequelae, as well as characteristics of the illness that may be indicators of illness severity and poor outcomes, must be better understood in order to improve care. Though more research is required before they can be used in an endemic setting, new therapeutics and vaccines offer hope for the treatment and prevention of monkeypox.

Keywords: Monkeypox, Orthopoxvirus genus, Tecovirimat, Newer therapeutics

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INTRODUCTION

Monkeypox disease is a zoonotic disease caused by the monkeypox virus (MPXV), which belongs to the Orthopoxvirus genus, Chordopoxvirinae subfamily, and Poxviridae family. Smallpox disease and monkeypox disease caused by orthopoxvirusshare many similarities. This virus has linear double-stranded DNA as a genetic material which is present in the cytoplasm of infected cells. Non-human primates and various rodent species serve as a hosts for viruses. Numerous animal species have been found to be susceptible to the MPXVlike dormice, rope and tree squirrels, gambian pouched rats, non-human primates, and other species. The US Centers for Disease Control and Prevention's (CDC) list of biological agents of concern for biosecurity does not include the monkeypox virus, but the matrix created by the EU task force on bioterrorism classifies it as a "agent with high threat for deliberate release" [1, 2]. Following two outbreaks of a disease similar to smallpox in colonies of monkeys confiscated in Malaysia and smuggled through Singapore, Preben Von-Magnus found monkeypox in laboratory cynomolgus monkeys in Denmark in 1958. The name monkeypox originates from the initial discovery of the virus in monkeys in a Danish laboratory. The first case in humans was diagnosed in 1970 in a 9-month-old boy from Democratic Republic of the Congo (DRC). Since that time, monkeypox has become endemic in the DRC, and has spread to other African countries, mainly in Central and West Africa. Outside of Africa, the first reported monkeypox cases in Europe in 2003. Clinical recognition, diagnosis, and prevention still remain challenges in the resource-poor endemic areas where monkeypox is found [2-4]. More than 3000 cases of the MPXV infection have been documented since early May 2022 in more than 50 countries across five regions. Most confirmed cases with a travel history mentioned trips to Europe and North America, as opposed to West or Central Africa, where the monkeypox virus is endemic. Monkey pox disease was declared a global health emergency by WHO on July 23 [5]. MPXV cases and clusters have been reported simultaneously for the first time in both endemic and non-endemic countries across a wide range of geographical areas. Since this is the largest and most pervasive outbreak of monkeypox, there is concern that the infection rate may increase as people huddle together for festivals and gatherings. With a focus on the changes in the epidemiology of human monkeypox since the first cases in the 1970s through the present, the current review only serves to add more information.

Epidemiology

Infection outbreaks that are sporadic in nature and usually result from contact with wildlife reservoirs have been reported in Africa. The data suggests that African rodents are the natural reservoir, despite the fact that the disease was initially discovered in captive monkeys [6]. Squirrels, rats, mice, monkeys, prairie dogs, and humans have all contracted infections. There are currently two clades of virus that are genetically distinct from one another. In contrast to the West African clade, the Congo Basin (Central African) clade is reported more frequently and has cases of documented human-to-human transmission [3]. The first MPXV outbreak outside of Africa occurred in the United States of America in 2003, and had contact with pet prairie dogs that had the disease was to blame. These pets had been kept with dormice and pouched rats from Ghana that were imported from the Gambia. Over 70 cases of MPXV were reported by this outbreak in the US. Travelers from Nigeria to Israel in September 2018, the UK in September 2018, December 2019, May 2021, and May 2022, Singapore in May 2019, and the United States of America in July and November 2021 have also been reported monkeypox disease. MPXV cases were found in a number of non-endemic nations in May 2022 [7]. Given alleged flaws in disease reporting and confirmation, precise prevalence and incidence are challenging to establish. However, since the routine smallpox vaccination was stopped, both metrics have increased. Living in heavily forested and rural areas of central and western Africa, handling and preparing bushmeat, caring for someone with the monkeypox virus, and not having received a smallpox vaccination are all proven risk factors for monkeypox infection. The risk of infection has also been linked to male gender. The cultural expectation that men frequently hunt and interact with wild animals may, however, complicate this. Direct contact with bodily fluids, skin lesions, or respiratory droplets of infected animals can result in transmission, as can indirectly contact with contaminated fomites. Mathematical modelling in the context of declining herd immunity to orthopoxviruses reflects an increasing threat of disease spread between humans, despite the fact that human-to-human transmission has historically been restricted [8]. Studies are being conducted right now to learn more about the epidemiology, sources of infection, and patterns of transmission.

Virus morphology, genome organization, and morphogenesis

The MPXV virus and other orthopoxviruses have similar morphological traits. Under an electron microscope, MPXV has an intracytoplasmic brick-like appearance with lateral bodies and a central core that is between 200 and 300 nm in size. A lipoprotein outer membrane with geometric corrugations surrounds the virus. The inverted terminal repeats (ITRs) of the MPXV genome are composed of hairpin loops, tandem repeats, and some open-reading frames. The MPXV genome is a linear double-stranded DNA (197 kb) that is covalently joined at its ends by palindromic hairpins. Despite being a DNA virus, MPXV completes its entire life cycle in the cytoplasm of infected cells. The MPXV genome encodes every protein necessary for viral DNA replication, transcription, virion assembly, and egress. While the genes that code for the interactions between the virus and the host are less conserved and are found in the terminal region, the genes that code for housekeeping functions are highly conserved [9].

Pathophysiology

The MPXVreplicates at the inoculation site after viral entry via any route (oropharynx, nasopharynx, or intradermal), then spreads to nearby lymph nodes. An initial viremia then triggers viral spread and organ seeding. This is the incubation period, which can last up to 21 d and typically lasts 7 to 14 d. Before lesions are visible, there are 1–2 d of prodromal symptoms like lymphadenopathy and fever caused by secondary viremia. Patients who are sick now might be infective and spreads the virus to others. Skin lesions develop from oropharyngeal lesions. By the time lesions start to form, serum antibodies are already detectable [10].

Clinical signs and symptoms

Generalized headache and exhaustion follow a febrile prodrome at first. Many patients have maxillary, cervical, or inguinal lymphadenopathy (1–4 cm in diameter) prior to or concurrent with the development of the rash. Large lymph nodes are firm, tender, and occasionally uncomfortable. Lymphadenopathy may be a sign that the immune system recognises and reacts to MPXV infection more effectively than it does to variola virus infection, but more research is needed to confirm this hypothesis. Fever frequently goes down the day after the rash appears or for up to 3 d after. The rash frequently starts out on the face before spreading quickly in a centrifugal pattern throughout the body. The distinctive lesions frequently manifest as macular, papular, vesicular, and pustular in order of appearance. On any given patient, there could be a few to thousands of lesions. Oral lesions are frequently observed and can make eating and drinking difficult. Given the severity of the skin damage, secondary bacterial skin infections are a concern, and it has been found that 19% of unvaccinated monkeypox patients have these infections. Patients' skin has been observed to be swollen, stiff, and painful until crusts formed. Skin lesions that develop into pustules during a second febrile period have been linked to a decline in the patient's general condition [2, 4]. The majority of those who are affected by MPXV experience a self-limited illness that usually lasts two to four weeks before full recovery. When MPXV is clinically present, it can be challenging to distinguish its symptoms and lesions from those of smallpox, other orthopoxvirus and parapoxvirus infections, and, to a lesser extent, chickenpox. The primary distinction between smallpox and MPX is that while smallpox virus and chickenpox virus typically do not cause lymphadenopathy (such as in the cervical or inguinal region), MPXV does. Other orthopoxviruses, such as the buffalopox, camelpox, and orf virus, as well as the pseudocowpox and bovine papular stomatitis viruses, typically cause localised skin lesions in humans. Although, localized skin lesions can also be a presenting symptom of MPX [1].

Complication

Typically, the rash only lasts for 10 d. Affected people may experience illness for 2 to 4 w. After the lesions have healed, they may leave behind pale traces before developing into scars. Possible side effects include pneumonia, encephalitis, secondary bacterial skin infections, dehydration, conjunctivitis, keratitis and vision loss. Infections during pregnancy increase the risk of stillbirth or abnormal birth outcomes. Those who received the smallpox vaccine as children may experience a milder case of the illness [1, 3]. In outbreaks in endemic areas, the case fatality rate for MPX ranges from 0% to 11%, with mortality disproportionately affecting young childrens [1].

Diagnosis

The disease can be diagnosed using genetic and immunological methods. Real-time PCR (RT-PCR) is a technique used in genetic methods and it targets conserved regions of the extracellular-envelope protein gene (B6R), DNA polymerase gene, E9L, DNA-dependent RNA polymerase subunit 18, rpo18, and F3L gene, is frequently used to detect MPXV DNA from clinical and veterinary specimens as well as from MPXV-infected cell cultures. In order to detect MPXV DNA, restriction length fragment polymorphism (RFLP) of PCR-amplified genes or gene fragments is also used; however, RFLP is time-consuming and necessitates virus culture. The gold standard for characterising MPXV and other OPVs continues to be whole-genome sequencing using next-generation sequencing (NGS) technologies, but the technology is expensive and downstream processing of sequencing data requires a lot of processing power. In Immunological methods, the detection of IgG and IgM antibodies as well as viral antigens, are done by using immunohistochemistry and the enzyme-linked immunosorbent assay (ELISA). Using polyclonal or monoclonal antibodies against all OPVs, immunochemistry analysis can be used to distinguish between poxvirus infection and herpes virus infection. It is known that T-cell responses and antiviral antibodies both rise at the beginning of a disease. IgM and IgG, however, are found in serum five and more days, respectively, after the onset of the rash. If IgM and IgG antibodies are present in an unvaccinated person with a history of rash and severe illness, an indirect MPXV diagnosis may result [11]. The diagnostic tests and samples that is used for the detection of MPXV is elaborated in table 1.

Table 1: Diagnostic tests for monkeypox disease

S. No.	Tests	Description	Type of samples
1	Genetic method-PCR	Based on NAAT, Rt-PCR-Gold standard	Lesion fluid
2	Viral culture	Virus grown and isolated from patient sample	Lesion fluid
3	Electron microscopy	To morphologically identify pox viruses.	Biopsy specimen, lesion fluid, scab material
4	Immunological methods-Immunohistochemistry	Detect the presence of Orthopoxvirus-specific antigens.	Biopsy specimen
5	Immunological methods-Antibodies (IgM and IgG)	Assess a acute or chronic exposure to Orthopoxvirus	Blood sample

Prevention

There are currently no known, effective treatments for monkeypox infection. The method of treatment for viral illnesses is supportive management. However, there are precautions that can be taken to avoid an outbreak. Until all lesion crusts have naturally fallen off and a new skin layer has formed, the infected person should stay in isolation, wear a surgical mask, and keep lesions covered as much as is practical [10].

Vaccination

According to studies, the smallpox vaccine offers cross-protection against other OPV species, including MPXV. The data that are currently available indicate that 90% of the cases that have been identified are naive to OPV infection, with many of them having been born after the smallpox eradication program's termination. It was found that people who had previously received the smallpox vaccine had 85% protection against MPXV. [12-14] ACAM2000 and

IMVAMUNE have neither been authorised for use in the general population as of yet.

1. During the 2003 USA, MPXV endemic, the Centers for Disease Control and Prevention (CDC) recommended the smallpox vaccine (ACAM2000TM), which reduced symptoms but did not prevent disease. Due to issues like the vaccine's unknown effects on people with immune systems that are suppressed and the safety of the vaccine that contains live vaccinia virus, this vaccination is neither accessible to the general public nor used in MPXV endemic areas. Includes a live vaccine virus as well. In August 2007, the The Food and Drug Administration (FDA) granted it a licence, displacing the earlier orthopoxvirus vaccine Dryvax®. For people who have been found to have a high risk of contracting smallpox, ACAM2000® is recommended for active immunisation against the disease. During an outbreak, the CDC has an emergency access IND protocol that permits the use of ACAM2000® for non-variola orthopoxvirus infection (such as monkeypox) [15].

2. US-FDA and the European Medicine Agency (EMA) have also granted licences to IMVAMUNE. This is a replication-deficient, attenuated third generation modified vaccinia Ankara (MVA) vaccine for the prevention of smallpox and monkeypox in adults (18 y of age and older). In contrast to ACAM2000, this vaccine is not contraindicated for use in patients with immunodeficiencies like AIDS and atopic dermatitis [9]. According to historical data, vaccinia virus smallpox vaccination was about 85% effective against monkeypox [15]

Treatment

Supportive care

The majority of monkeypox patients recover without any medical assistance. To reduce gastrointestinal fluid losses, those with gastrointestinal symptoms (such as vomiting or diarrhoea) will need oral or intravenous rehydration [16].

Antiviral drugs

Cidofovir

It shows its antiviral property by blocking viral DNA polymerase enzyme. There are no available statistics on cidofovir's efficacy in treating monkeypox in humans. In the US, it is prescribed for cytomegalovirus. Although *in vitro* and animal studies have shown that cidofovir has activity against poxviruses, it is unknown whether or not a patient with a severe monkeypox infection will benefit from treatment. The CDC has expanded access investigational new drug (EA-IND) that permits the use of stocked cidofovir to treat orthopoxviruses (including monkeypox) during an outbreak [17, 18]. The nephrotoxicity associated with cidofovir has been reduced in the modified cidofovir compound known as CMX-001 [4].

Brincidofovir

An oral analogue of the intravenous medication cidofovir, brincidofovir, may have a better safety profile than cidofovir, such as less renal toxicity. Since June 2021, brincidofovir has been authorised in the US for the treatment of smallpox. This drug shows its antiviral property by blocking viral DNA polymerase enzyme. The effectiveness of brincidofovir against orthopoxvirus infections has been established, despite the paucity of studies examining its use in treating monkeypox infections in animal models. However, *in vitro* activity and effectiveness against lethal monkeypox virus infections in animals have been reported. As brincidofovir may result in increases in serum transaminases and serum bilirubin, liver function tests must be performed both before and during treatment. These treatments are accessible through an IND or EUA [15]. As compared to cidofovir, treatment for cytomegalovirus infections with brincidofovir has not been associated with severe renal toxicity or other adverse events, suggesting that brincidofovir may have an improved safety profile. The CDC is currently working on an EA-IND to make it easier to use brincidofovir as a monkeypox treatment [17-19]. Brincidofovir has a greater selective index due to its better efficacy, which was at least 25-fold higher than cidofovir's, despite having higher cellular toxicity and superior antiviral activity than cidofovir against VARV, MPXV, VACV, and CPXV *in vitro*. Brincidofovir has better efficacy because it is taken up by cells more readily and is better converted by intracellular enzymes into the active form. After Brincidofovir has entered the cells through the endogenous liquid uptake pathways, it is converted by intracellular kinases and released by cleavage as phosphorylated cidofovir [9].

Tecovirimat (also known as TPOXX or ST-246)

Tecovirimat is an antiviral drug that was approved for the treatment of smallpox disease under a regulation known as the "Animal Rule."This rule allows for the approval of drugs for serious or life-threatening conditions when it is not ethical to conduct efficacy studies in humans and not feasible to conduct field trials to study the effectiveness of a drug or biologic product. Under the Animal Rule, efficacy is established on the basis of adequate and well-controlled studies in animal models of the human disease or condition of interest; safety must be adequately evaluated in people [20]. The first antiviral approved for the treatment of smallpox in adults and children weighing at least 3 kg is tecovirimat and it is regarded as the preferred method of care. Dual therapy with tecovirimat and brincidofovir may be used in patients with advanced disease. This drug targets the viral envelope protein VP37. It prevents the virus from spreading within an infected host by blocking the final steps in viral maturation and release from the infected cell. Although the effectiveness of this medication against monkeypox in humans has not been investigated, studies on animals have shown that tecovirimat treatment improved survival from lethal monkeypox virus infections when compared to placebo treatment at various disease stages. In an expanded safety study involving 359 human volunteers the safety profile of the tecovirimat was similar to placebo group. According to the CDC's Emergency Access Investigational New Protocol, tecovirimat can be used to treat infections caused by non-variola orthopoxviruses, like monkeypox [15, 18]. Additionally, the CDC is in possession of expanded access investigational new drug (EA-IND), also known as compassionate use, that permits the use of tecorvirimat that has been stored to treat monkeypox when an outbreak occurs [21].

NIOCH-14

An analogue of tecovirimat is an investigational oral antiviral agent with *in vitro* and *in vivo* activity against orthopoxviruses. NIOCH-14's effectiveness in *in vitro* studies against VARV, MPXV, and ECTV was comparable to that of Tecovirimat, but NIOCH-14 is still a viable antiviral candidate for the future due to its strong antiviral activity against many OPVs and its simpler production process [22].

KAY-2-41 (N-Methanocarbathymidine)

Due to their antiviral activity, nucleoside analogue inhibitors (N-Methanocarbathymidine, 4′-thio derivative of idoxuridine, and KAY-2-41) were also tested as potential medications. The effectiveness of N-methanocarbathymidine (N-MCT) against herpesviruses, Balb/c mice infected with CPXV Brighton, and a mouse model infected with VACV was noted. The drug's antiviral activity is mediated by the N-MCT triphosphate metabolite, which is formed in a viral thymidine kinase-dependent manner. According to one, *in vitro* research, the 4′-thio derivative of idoxuridine (also known as 4′-thioIDU) was effective against the CPXV, VACV, and viral strains that were resistant to cidofovir or Tecovirimat. In comparison to Brincidofovir and Tecovirimat, KAY-2-41 OR 1′-Carbon-substituted 4′ thiothymidine derivative was said to have higher efficacy than cidofovir. KAY-2-41 had been demonstrated to offer defence against VACV, CPXV, and CMLV *in vitro* [23].

Miscellaneous

In order to test potential medications against OPVs, Baker *et al.* divided these medications into five categories based on their antiviral activities: S-adenosylmethione, Inosine monophosphate (IMP) dehydrogenase, DNA polymerase inhibitors, reverse transcriptase (RT) and protease inhibitors, and other compounds. Other targets which have shown promising results in *In silico* and *in vitro* studies are C-ca3-Ado and C3-Npc A. These drug shows antiviral property by inhibiting S-adenosylhomocysteine (SAH) hydrolase enzymes. Ribavirn and tiazofurin have shown antiviral effects by inhibiting IMP dehydrogenase. Adenosine N1-oxide (ANO) demonstrated notable anti-OPV activity by preventing the translation of viral mRNAs and preventing viral replication [9].

Vaccinia immune globulin (VIG)

The FDA has approved the hyperimmune globulin VIG for the treatment of vaccinia infections in people who have skin conditions, progressive vaccinia, severe generalised vaccinia, and aberrant infections brought on by the vaccinia virus (except in cases of isolated keratitis, e. g., ocular infections). The use of VIG for monkeypox or smallpox has not been tested in humans, despite the fact that it is a potential treatment. Data on the effectiveness of VIG against monkeypox and smallpox are largely lacking [15, 22, 24]. Newer molecules are summarized in table 2.

Table 2: Potential new drug molecules for monkeypox disease

S. No.	Name	MOA	Status
1	CMX-001 Modified cidofovir compound [25]	inhibits DNA polymerase	Phase II/III trials
2	Ribavirin and ribavirin analogs antiviral [26]	IMP DEHYDROGENASE inhibitor	*in vivo* efficacy studies
3	Tiazofurin antiviral [25]	IMP DEHYDROGENASE inhibitor	
4	C-ca3-Ado Antiviral [25]	SAH HYDROLASE INHIBITOR	*In vivo* studies
5	C3-Npc A Antiviral [25]	SAH HYDROLASE INHIBITOR	*In vivo* studies
6	HPMA Antiviral [25]	DNA polymerase inhibitor	*In vivo* studies
7	ANO (Adenosine N1 oxide) Antiviral [25]	Blocks the translation of viral mRNAs	*In vivo* studies
8	Mitoxantrone [26]	DNA ligase	In silico studies
9	Rifampin [26]	Viral capsid protein	In silico studies

CONCLUSION

More pharmacopoeia research is imperative due to the growing threat posed by zoonotic illnesses like monkeypox and other poxviruses to human survivability. Additional research should be conducted using the novel potential targets mentioned in this paper in order to reduce fatalities caused by viruses.

ETHICS STATEMENT

Not applicable

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All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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