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Review Article

Monkeypox, a current global health issue: brief review on prevention and treatment

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ABSTRACT

While the COVID-19 pandemic seems to fade away, humanity is currently facing another health challenge risen by the zoonotic orthopoxvirus called monkeypox, with a number of cases that seems to be decreasing for the first time since the beginning of 2022, when the pandemic commenced. This review begins by describing the actual global picture of this phenomenon and progresses, depicting the potential measures of prevention and treatment among monkeypox patients.

After various reports that proved the high transmission of this virus through direct contact with infected patients, the actions that are being taken worldwide revolve around prevention among individuals at high risk, with measures of prophylaxis before and after exposure, while covering immunization with vaccines once used for smallpox (ACAM2000, JYNNEOS or Imvamune). Furthermore, healthcare specialists should address treating infected patients with antiviral therapy, such as tecovirimat, brincidofovir and cidofovir, and without overlooking supportive care and the option of Vaccinia Immune Globulin, the latter still being debatable due to its possible contraindications.

SUMMARY

1. *Introduction*
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Keywords

Monkeypox, ACAM2000, JYNNEOS, Tecovirimat, Vaccinia Immune Globuline, lymphadenopathy, prophylaxis, zoonotic disease, prevention.

Abbreviations

Deoxyribonucleic acid (DNA); Coronavirus Disease 2019 (COVID-19); United States (US); Vaccinia Immune Globulin (VIG); Immunoglobulin A (IgA).

1. Introduction

Although the number of cases of patients infected with the monkeypox virus seems to be globally decreasing by 25.2% since the last World Health

Organization report, the number of countries added to the same list increases[1]. What is known up to this date is the structure of this zoonotic virus, which is made of a double-stranded deoxyribonucleic acid[2], alongside other members of the same Orthopoxvirus genus.

The two main clades of monkeypox virus that have been revealed so far are Central and West African ones[3], with the former being more severe[4]. Symptoms of this disease appear to be similar to the once eradicated smallpox, such as the initial fever, followed by fatigue and headaches, but also the rash associated with maculopapular and vesiculopustular manifestations[5]. However, what differentiates this virus is the surge of multiple lymphadenopathies located in the cervical and submaxillary areas[6].

It appears that even though efforts around the world were made with the purpose of ceasing this virus, the spread amongst countries continues and humanity should pay more attention to this phenomenon[1]. In order to achieve this awareness, through our review, we depict the means of prevention, before and after exposure to the virus, but also the recommended treatment, in regard to supportive care, but also the use of antivirals.

2. Prophylactic recommendations

The data gathered so far shows that the virus can be transmitted through either direct contact with infected patients, but also with their infectious sores, after the rash begins, body fluids or textile materials that they had been using[7]. There is no specific management plan for the prevention of infections with this virus and what proved to be beneficial so far resides in the general schemes used for all Orthopoxvirus infection[8]

Regarding prevention, prior immunization remains the golden standard, with the vaccines once used for smallpox, such as the ones already approved by the United States Strategic National Stockpile (SNS): JYNNEOS, also known as Imvamune, and ACAM2000. Furthermore, the Aventis Pasteur Smallpox Vaccine (APSV) still awaits approval[9]. At the moment, mass vaccination is not required for monkeypox, leaving it dependent on the ongoing public health measures taken so far, which also might change according to the evolution of this pandemic[10]. It also seems that the demand for monkeypox vaccine exceeds the supply in some countries, especially in those that have been affected by this phenomenon since its first appearance amongst human patients, in 1970[11,12].

Firstly, concerning pre-exposure prophylaxis[13], vaccination with either one of the vaccines listed in Table 1 is recommended for individuals at high risk of infection with monkeypox virus, such as research or clinical laboratory personnel working with Orthopoxviruses, as well as health care[14] personnel in charge of patients with orthopoxvirus infections[15].

Secondly, in regard to post-exposure prophylaxis, in the case of a monkeypox viral infection, vaccination is recommended as well[20]. It has been reported that vaccination in the first four days of

Table 1. Vaccines approved by the FDA for Othopoxviruses

Vaccine	Type of vaccine	License
ACAM2000[16]	Live vaccinia virus / replication competent vaccinia virus (a derivative of the original Dryvax)	Licensed in the USA
Modified vaccinia Ankra (MVA)/ Imvamune / Imvanex[17]	Attenuated vaccinia virus / replication-deficient modified vaccinia Ankara	Licensed in the USA and approved by the European Commission
LC16m8[18]	Attenuated vaccinia virus	Licensed in Japan
Aventis Pasteur Smallpox Vaccine (APSV)[19]	Replication-competent live vaccinia virus	Licensed in the USA

infection is highly effective in preventing the disease and clinical manifestation. In case of vaccine administration after four days and up to two weeks, clinical symptoms and disease manifestations may be drastically reduced, but not prevented[21].

What is more, clinical monitoring is crucial, alongside isolation in order to prevent future outbreaks[9,15].

3. Supportive care

Spontaneous recovery, independent of antiviral or any other type of treatment has been reported in cases of infection with the monkeypox virus[1]. This phenomenon usually occurs amongst non-pregnant adults which tend to experience mild forms of the disease, compared to pregnant or breastfeeding patients who should be treated more catiously[22]

Being considered a self-limiting disease, the infection with the monkeypox virus proved to last for almost 2-4 weeks before achieving full recovery[23]. The incubation period could be considered more impactful for patients, given the fact that it includes symptoms such as fever, lightheadedness, headaches, coughs and the monkeypox-specific lymphadenopathies previously mentioned[24,25]

Moreover, gastrointestinal symptoms have occurred in some cases of monkeypox viral infection, especially those reported during the 2003 outbreak in the United States, which revealed that parenteral exposures had a higher tendency[26–28] to be associated with systemic manifestations demanding massive rehydration in order to compensate for fluid waste either through vomiting or diarrhea[29].

Monkeypox proved so far to have a major impact on other organ systems as well, as shown in Figure 1, given the heavy rash that follows the febrile prodrome[30] and often leaves the patient with significant exfoliation processes that later result in dehydration and protein losses, with a prevalent hypoalbuminemia. Airways can also be affected through inflammation which further leads to congestion and a respiratory complication called bronchopneumonia that many patients are faced with[31–33].

Therefore, it is clearly outlined that patients infected with the monkeypox virus should be treated in regard to all of their symptoms, not only the ones specific to orthopoxviruses, while also paying attention to the fact that there is a prevalent trend among individuals within low-resource settings to be subjects to this matter[29].

4. Antiviral therapy

Several antiviral drugs may be useful and effective in case of a monkeypox infection, although they have been initially studied and researched for their use against smallpox virus[15]Because of the viral similarities between these 2 viruses, monkeypox and smallpox, both being part of the Orthopoxvirus family, antivirals have cross-reactivity for these viruses, making them advantageous in cases of infection with monkeypox virus[34].

4.1. Tecovirimat

Tecovirimat is known[35] to be the first and one of the most effective antiviral drugs against Orthopoxviruses, more specifically smallpox and now the virus of clinical interest, monkeypox[36]Also known as TPOXX or ST-246, Tecovirimat's mechanism of action is inhibiting the release of newly formed enveloped virions in the infected host by inhibiting the viral envelope protein VP37 which mediates the formation of these enveloped virions[37].

Taking into consideration the role of the VP37 protein, it is a target for antiviral drugs of high importance. What is more, Tecovirimat has a massive clinical significance, as it does not present side effects[38]. As mentioned before, by targeting the VP37 protein and thus by inhibiting the release of virions, Tecovirimat is very effective against viral dissemination, but not so much against viral replication, as this process is not inhibited by this antiviral drug[39].

4.2. Brincidofovir and cidofovir

Cidofovir is a nucleotide analogue that is indicated for intravenous administration only, whereas brincidofovir is its oral analogue, a lipid conjugate of cidofovir[40]. Both these drugs have as mechanism of action the inhibition of the DNA polymerase, thus inhibiting the DNA viral replication[41].

Compared to cidofovir, brincidofovir[42] has less renal toxicity, as it is not actively transported in the renal cells by the renal organic anion transporter 1 (OAT1)[43]. However, liver toxicity has been reported in brincidofovir, as it may cause an increase in the serum transaminases and bilirubin, thus making liver function tests a necessity before and during treatment[44]. Between the two drugs,

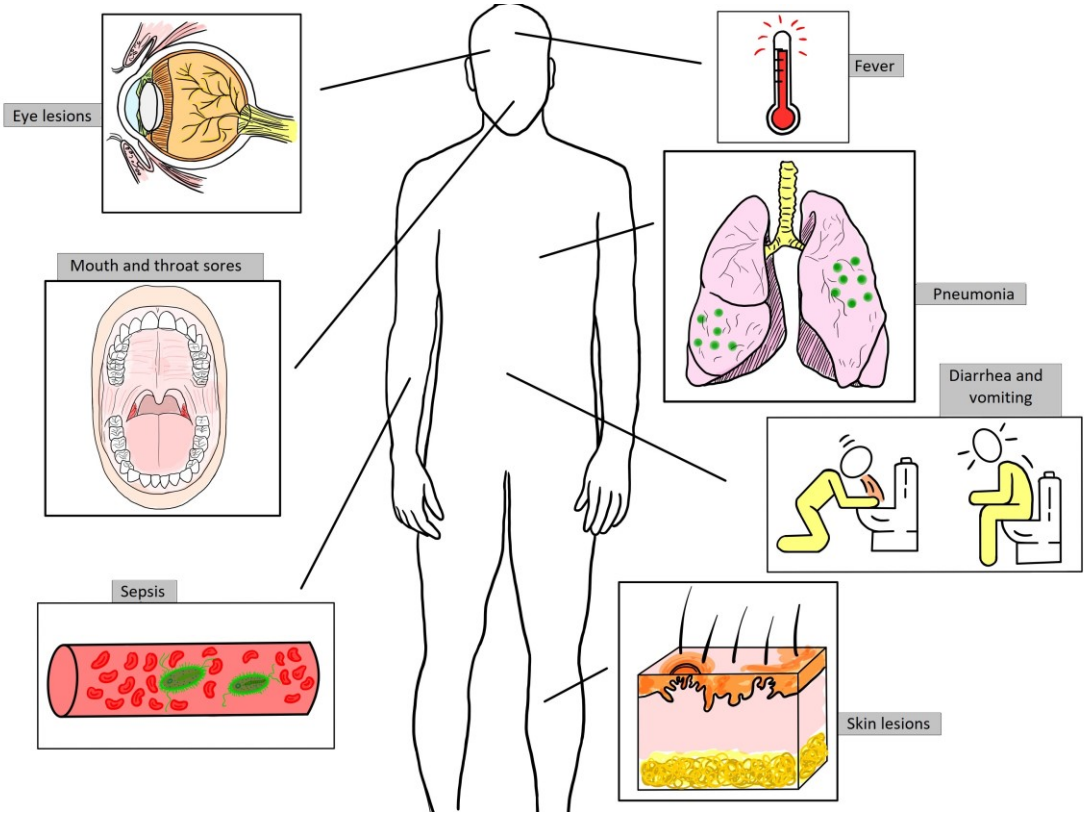

Figure 1. The clinical picture of a monkeypox-infected patient
(created based on the information provided within reference[29])

brincidofovir and cidofovir, the first one is of first choice as it has a higher renal safety profile and can be administered orally, thus being easier to use[42]

What is more, studies show that saline and probenecid therapy are necessary to be used simultaneously with cidofovir[40].

5. Vaccinia Immune Globulin (VIG)

Vaccinia Immune Globulin (VIG) is a hyperimmune globulin that has been approved by the Food and Drug Administration US for use against certain complications, especially cutaneous ones[45] and side effects that may occur post-vaccination[46.] VIG consists of antibodies obtained from individuals that have been immunized with the smallpox vaccine, which makes it highly effective against dangerous side effects of the vaccine[47.]

Due to the fact that the frequency of adverse events in the case of this globulin proved to be almost insignificant, controlled clinical trials were never exerted with the purpose of assessing its efficacy[45]. However, it visibly helped in the case of patients with progressive vaccinia, a phenomenon that occurred as an eczema vaccinatum after a history of exposure to the vaccinia virus[48.] After VIG started being used, the case-fatality rate lowered with approximately 25% to 50%[45.]

Because it is a hyperimmune globulin, VIG is contraindicated in individuals with history of anaphylactic or systemic reactions to human globulins or in individuals with Immunoglobulin A (IgA) hypersensitivity[49.] Although it may sound promising, there is no specific research and there is a massive lack of data regarding human vaccination with the smallpox virus, as it is highly unethical since the eradication of smallpox in 1980, thus making VIG a contraindicated drug at the present moment[47].

6. Conclusion

Monkeypox is a virus with an exorbitant potential of transforming into a pandemic. However, studies and massive research upon viruses from the Orthopoxvirus genus are very useful at the present

moment, when the world is facing a potentially dangerous pandemic situation with this virus. The existence of vaccines and antiviral drugs, such as tecovirimat, cidofovir, brincidofovir and vaccinia immune globulin offers the world hope, as their efficacy against monkeypox has been reported.

With all the historical knowledge regarding smallpox and the Orthopoxvirus genus, humans have plenty of reasons to be optimistic in case of an infection with the monkeypox virus. With proper healthcare, treatment, isolation and prophylaxis, a pandemic could be easily avoided. What is more, the wisdom gained from the most recent global event, the COVID-19 pandemic[50,51] comes in handy to health care personnel, members of the political world and the general public[51–59].

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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