

Monkeypox: generalities, transmission method and therapeutic approaches

Varíola dos macacos: generalidades, forma de transmissão e abordagens terapêuticas

Viruela del simio: generalidades, modo de transmisión y enfoques terapêuticos

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Abstract

Clinical and epidemiological studies suggest that human-to-human transmission of monkeypox may occur through direct or indirect contact, through secretions through the respiratory tract or through skin lesions, and through contaminated objects. Therefore, this literature review exposes generalities, forms of transmission and therapeutic approaches related to Monkeypox. A survey was carried out on government websites, scientific articles and journalistic websites about ways of prevention and vaccines against the monkeypox virus. It is known that this zoonosis belongs to the Poxviridae family and spreads with greater intensity in underdeveloped countries, due to the unsanitary conditions of these places. Studies indicate that vaccines produced for smallpox are efficient against Monkeypox virus, especially the third generation ones. The vaccine that obtained a better result in the research was the MVA-BN, since it does not leave lesions in the place where it was applied and does not present a threat to a possible transmission, it was also developed for immunosuppressed individuals, facilitating the mass vaccination of the vaccine population. Some drugs have also been shown to be effective against Monkeypox, namely: Brincidofovir, Cidofovir and Tecovirimat, with Tecovirimat in evidence for its efficiency and moderate side effects.

Keywords: Monkeypox; Vaccines; Antivirals.

Resumo

Estudos clínicos e epidemiológicos sugerem que a transmissão do Varíola dos macacos entre humanos pode ocorrer através do contato direto ou indireto, através de secreções pelas vias respiratórias ou por lesões na pele, e por objetos contaminados. Em vista disso, esta revisão de literatura expõe generalidades, formas de transmissão e abordagens terapêuticas relacionadas à Monkeypox. Foi realizada uma pesquisa nos ‘websites’ governamentais, artigos científicos e ‘websites’ jornalísticos acerca das formas de prevenção e vacinas contra o vírus da Varíola dos macacos. Sabe-se que essa zoonose pertence à família Poxviridae e se propaga com maior intensidade nos países subdesenvolvidos, devido a insalubridade desses locais. Estudos apontam que as vacinas produzidas para a Varíola humana apresentam eficiência contra o Monkeypox vírus, principalmente as de terceira geração. A vacina que obteve um melhor resultado nas pesquisas foi a MVA-BN, uma vez que não deixa lesões no local na qual foi aplicada e não apresenta ameaça para uma possível transmissão, ela também foi elaborada para indivíduos imunossuprimidos, facilitando a vacinação em massa da população. Alguns medicamentos também se mostraram eficazes contra a Varíola dos macacos, sendo eles: Brincidofovir, Cidofovir e Tecovirimat, tendo o Tecovirimat em evidência pela sua eficiência e efeitos colaterais moderados.

Palavras-chave: Varíola dos macacos; Vacinas; Antivirais.

Resumen

Los estudios clínicos y epidemiológicos sugieren que la transmisión de la viruela del mono de persona a persona puede ocurrir a través del contacto directo o indirecto, a través de secreciones a través del tracto respiratorio o a través de lesiones en la piel, y a través de objetos contaminados. En vista de ello, esta revisión bibliográfica expone generalidades, formas de transmisión y enfoques terapéuticos relacionados con la viruela del mono. Se realizó una encuesta en sitios web gubernamentales, artículos científicos y sitios web periodísticos sobre formas de prevención y vacunas contra el virus de la viruela del mono. Se sabe que esta zoonosis pertenece a la familia Poxviridae y se propaga con mayor intensidad en países subdesarrollados, debido a las condiciones insalubres de estos lugares. Los estudios muestran que las vacunas producidas contra la viruela son eficaces contra el virus de la viruela del mono, especialmente las vacunas de tercera generación. La vacuna que obtuvo un mejor resultado en la investigación fue la MVA-BN, ya que no deja lesiones en el lugar de aplicación y no presenta amenaza para una posible transmisión, además fue desarrollada para personas inmunodeprimidas, facilitando la vacunación masiva de la población vacuna. También se ha demostrado que algunos medicamentos son efectivos contra la viruela del mono, a saber: Brincidofovir, Cidofovir y Tecovirimat, con Tecovirimat en evidencia por su eficiencia y efectos secundarios moderados.

Palabras clave: Viruela del mono; Vacunas; Antivirales.

1. Introduction

Monkeypox is an infectious disease that emerged in 1958, and had its first case recorded in humans in 1970, in Congo, having the Orthopoxvirus as the transmitting agent, being considered a zoonosis (Pedro Peduzzi, 2022). This disease manifests through vomiting, fever, body and headache pain and mainly by skin lesions, typified as blisters in vesicles, which, inside, present infectious secretion. The contagion of monkeypox is given through contact with bodily injuries, respiratory droplets and infected materials. Suspected cases of the disease are those with symptoms similar to those mentioned. In general, they are people who have traveled in the last 21 days to endemic countries or even who have had sexual intercourse with an infected individual. Cases are only confirmed after testing and obtaining a positive result. Monkeypox: symptoms, transmission, origin and number of cases are updated by OMS (Butantan Institute, 2022).

Monkeypox is already considered a pandemic, as at least 75 countries have reported cases of the disease. The objective of this work is to elaborate a literature review, in order to describe the disease, explain the form of transmission, thus favoring its prevention (Ministry of Health, 2022).

2. Methodology

For the construction of this Literature Review, searches were carried out using descriptors in PUBMED Central, BVS/BIREME, Web of Science, Scielo, The Cochrane Library, Google academic, and the Brazilian CAPES portal. In order to get as much information as possible, we accomplished on-line searches to get information concerning the social-economical situation of the African countries with more cases reported by the local authorities, as well as the health programs implemented by them.

3. Literature Review

Among the various existing diseases, smallpox was the only one to be eradicated worldwide. This virus has a great relationship with Monkeypox, which is evolving in the current world situation, having constituted itself as the newest pandemic to hit humanity after COVID-19. The eradication of smallpox occurred in the last century and led to the suspension of this vaccine for the global population. Due to this fact, the current population does not have immunity against it and, consequently, became more susceptible to Monkeypox, giving rise to an uncontrolled transmission of Smallpox from monkeys (Amy Mckeever, 2022).

Diseases belonging to the family Poxviridae generally consist of complex, large, enveloped, linear, double-stranded DNA viruses. This zoonosis presents itself as a threat to the population in relation to public health, since it spreads in greater quantities in underdeveloped countries, due to the lack of basic sanitation, which leads to the exposure of people to different types of microorganisms responsible for the concomitant development of diseases. various types of disease. Thus, geographically, this disease was detected on the African continent, more precisely in the Democratic Republic of Congo, in the year 1970. There is deficient medical assistance, the presence of hungry people who are exposed to feeding on small mammals, further facilitating the transmission (Marzieh Soheili et al., 2022; Luis G. Sambo, 2007).

Following this line of reasoning, monkeypox spread to other regions of the aforementioned continent, being more present in its western and central parts. Such regions show a low development, in addition to a precarious infrastructure, facts that contribute and are decisive for the proliferation and morbidity of this virus. All of this, associated with the decrease in vaccines against human smallpox, inevitably led to an outbreak of monkeypox in the USA, which began in the 21st century, still in 2003, having as a possible transmitting agent, paradoxically, infected rodents. With the advancement of this virus in several countries, government efforts and measures have focused on the prevention and control of this virus. The most efficient preventive methods for the situation in which endemic countries find themselves are: avoiding contact with animal species that are more susceptible to infection, such as rodents, marsupials and primates. These precautions such as: avoid walking barefoot so as not to come into contact with feces and urine of these animals; the non-consumption of water and food without proper care, and mainly: not eating these wild animals (Daniel B. Di Giulio & Paul B. Eckburg, 2004; Hospital Proncor, 2022). Thus, based on hygiene care, techniques used against COVID-19 in these aspects can also be used for smallpox of the hands, namely: frequent cleaning of monkeys with soap and water or gel alcohol is essential to avoid exposure to the virus, as well as the use of masks by professionals. In this way and 9 contacts in hygiene care, especially in these patients, who are in direct contact with infected patients, otolaryngologists, nurses and mainly general physicians (Ministry of Health, 2022). Although there are still no specific vaccines for the defense of the monkeypox virus, vaccination against smallpox showed a good result in relation to Monkeypox infection, offering an average of 85% protection for the world's populations, thus constituting a promising weapon to fight the virus. In addition to this discovery, three drugs used to treat smallpox also had an effect against monkeypox. This possibility opens the perspective of curing and preventing this newest pandemic that came to devastate the world after the previous one. Such drugs will be described below (Lucas Rocha, 2022).

Antivirals are drugs known to have specificities capable of reducing the action of the virus in the human body. Fighting any infection can be done initially by preventing the invasion of cells or by weakening viral replication, actions that will contribute to preventing the worsening of the disease and its evolution. These drugs are indicated to be used in the initial phase of the infection, in particular, between the first and fifth day of the appearance of symptoms. The effectiveness of antivirals is due to the presence of an increase in the natural viral load in the initial phase of the infection (Manual MSD, 2022). Tecovirimat was developed as a treatment for common smallpox in humans, being licensed by the EMA (European Medicines Agency) for the treatment of smallpox in monkeys, based on studies carried out in animals and humans in 2022. The drug is not yet highly available in the market. Brazil, but the Pan American Health Organization, intends to expand the fight against the outbreak of

the disease and is available in the form of an oral capsule (200 mg) and in an injectable form for intravenous administration. This medication, despite being highly effective, has reverse effects, such as headaches and nausea (European medicines Agency, 2022; Lucas Rocha, 2022; Pharmacy diary, 2022). The second drug is Cidofovir, which initially focused on the treatment of cytomegalovirus retinitis in people with acquired immunodeficiency syndrome (AIDS). Even though it already has this function, there is not enough data available for its efficiency for the treatment of Monkeypox, but it has demonstrated capacity against Orthopoxvirus *in vitro* and animal studies. A restricted access protocol is maintained, made by the CDC (Center for Disease Control and Prevention), for the use of Cidofovir, which must be stored for the treatment of Orthopoxvirus, including monkeypox in the event of an outbreak. As with all medicines, there are possible adverse effects, during treatment with the use of Cidofovir, there are possibilities of fever, asthenia, dizziness, nausea with vomiting, pneumonia, infection, neutropenia, asthenia and an increase in creatinine, which is acquired through tests (Hospital S rio-Liban s, 2019; John G. Rizk et al., 2022). Brincidofovir has few studies with evidence of clinical benefit, but it has been approved for the treatment of Smallpox in adults, pediatric patients and neonates. There are no data available on its effectiveness in the treatment of monkeypox in humans, however, like Cidofovir, it has shown efficacy in *in vitro* and animal studies against Orthopoxvirus (Instituto Butantan (2022), O que   recomendado e o que deve ser destacado no tratamento da var ola causada pelo Monkeypox) . Possessing possible most common side effects such as: diarrhea and nausea, unlike the atypical symptoms that are: stomach pain and cramps, swelling of the hands, feet or legs and vomiting, the indication if you present these unusual symptoms is the follow-up with greater attention. for risks of other diseases (INDICE.eu, 2022).

The means of propagation of smallpox in monkeys occurs through contact between humans, through secretions through the respiratory tract or through skin lesions, and through contaminated objects. Therefore, this disease has a high risk through sexual intercourse between men and between people with HIV. The incubation period after the identification of the disease is about 6 to 13 days, however there is a variation in this period, and a longer time of up to 21 days of isolation may be necessary (Butantan Institute, 2022). There are two methods of testing for monkeypox, the most effective being the collection of the secretion that is present inside the pustules, so the sample is collected and taken for analysis in the laboratory. In some cases, if the lesions are already dry, the material referred is the crusts of the lesions or if the patient does not present lesions on the skin or mucosa, samples will be collected from the oropharynx and the rectal or genital canal. The diagnosis of monkeypox is only in a laboratory way, through molecular testing or genetic sequencing. The molecular test makes it possible to identify the genetic material of a virus or sample, and the genetic sequencing test works by recognizing the nitrogenous bases of the virus's DNA. Using this information, it will be possible to compare the viral genome with the patient's sample available for diagnosis, so that a possible monkeypox infection is known (Ministry of Health, 2022).

The symptoms that are presented in the initial phase of the monkeypox infection are in general and not necessarily in this order: fever, intense headache, asthenia, lymphadenopathy, and generalized fatigue Regarding the groups that should be prioritized for the application of vaccines that are effective against monkeypox are: health professionals who work on the front lines of fighting the virus, laboratory professionals and men who have sex with men (MSM). This vaccination should also be aimed at vulnerable groups, such as immunosuppressed people, children and pregnant women. There is also an interruption of the cutaneous-mucous integrity, that is, the erosion of the skin barrier against biological agents, which can appear in the period of 1 to 3 days after the onset of fever, with an infectious fluid not coming into contact with another individual, with the possibility of symptoms persisting for a period of two to four weeks. Usually, pustules tend to appear more on the facial region than on the trunk, and even so, the infected person after treatment may have possible sequelae such as eye problems and encephalitis, caused by contact with the monkeypox virus and the tissues. affected brains during the active phase of the infection (Butantan Institute, 2022). Infections of viral origin necessarily have the use of immunizing agents as a preventive agent. In ancient times, the practice of vaccination brought some inconveniences, which are relatively diminished nowadays. There are still memories of the first

people who got the smallpox vaccine in the 60s and 70s of the 15th century. Gregory Poland's case is living proof of the unpleasant memories he went through. The vaccine made available against Smallpox for the eradication of the same had the live virus that underwent replication applied directly to the skin of the arm, which resulted in a scar for Poland, in addition to about 1 month away from his wife, isolated in a room to keep your distance from the people you live with. Since the smallpox vaccine had a long recovery process, the number of people who had this vaccine was very small, in addition to the restriction groups: such as pregnant women, immunosuppressed people and those with heart disorders (Amy Mckeever, 2022).

3.1 Smallpox vaccine generations

The MVA-BN vaccine (Imvamune), being a third-generation vaccine, developed in the Danish laboratory Bavarian Nordic, was approved and has a vaccinia virus, however this virus does not replicate, facilitating vaccination and reducing side effects. Vaccination is done with the application of two doses, with an interval of one month between them. In some locations it can be applied within 4 days of contact with infected individuals to prevent disease manifestations, and within 5 to 14 days of contact to reduce monkeypox symptoms. This vaccine, unlike the one described below, does not leave lesions at the site and no risk of contamination for other individuals. It is approved only for people over 18 years of age and restrictions are limited to allergies to vaccine components, covering a greater number of people who are eligible for immunization (Brett W. Petersen et al., 2022; Lara Pinheiro, 2022).

Developed by Sanofi and manufactured by the American laboratory Emergent BioSolutions. ACAM2000 is considered a second-generation vaccine, as it is developed with a live virus and has the ability to self-replicate, causing a lesion that will develop after its application. Like MVA-BN, ACAM2000 has more common side effects, such as pain at the injection site, edema and hyperemia, in addition to fever, erythema and lymphadenopathy. This vaccine is applied in a single dose, in which the individual starts to acquire immunity after an average of 28 days. It is contraindicated for people with congenital or acquired health problems, such as those involving the immune system, people living with HIV, atopic dermatitis, people with allergies to vaccine components, heart disease, eye diseases treated with topical steroids; also in children under 12 months or in pregnant women (Brett W. Petersen et al., 2022; Aysegul Nalca & Elizabeth E. Zumbrun, 2010; Lara Pinheiro, 2022).

The third-generation vaccine is the LC16m8, developed by the KM Biologics laboratory, in Japan, and approved for application in 1975. This vaccine was used during the smallpox pandemic and is a virus that should be applied with caution to people with immunodeficiency, as it is made with a weakened human smallpox virus, the vaccinia virus, with a small capacity for replication, as explained in the paragraph above. This vaccine has symptoms similar to the first generation but less intense. It has shown promise in both animals and humans (Brett W. Petersen et al., 2022; Lara Pinheiro, 2022).

Regarding the groups that should be prioritized for the application of vaccines that are effective against monkeypox are: health professionals who work on the front lines of combating the virus, laboratory professionals and men who have sex with others. men (MSM). This vaccination should also be aimed at vulnerable groups, such as immunosuppressed people, children and pregnant women on the front lines of the fight against the virus, laboratory professionals and men who have sex with men (MSM). This vaccination should also be aimed at vulnerable groups, such as immunosuppressed people, children and pregnant women (Brett W. Petersen et al., 2022; Lara Pinheiro, 2022).

People who had contact with the virus and contracted the disease, in addition to acquiring defense against the virus, may have sequelae. These sequelae can be altered by infected patients who present pathological manifestations, whether hereditary, congenital, acquired or epidemiological. Therefore, as a result of the vaccine, encephalitis, usually caused by an infection, can occur in every one million vaccinated individuals. Just like eczema, being a dermatosis that is capable of spreading smallpox, having high fever and generalized lymphadenopathy. Another sequel is called generalized vaccinia, occurring in

patients who had rejection of the vaccine, with the appearance of new lesions after one week of application of the immunizing agent (Lara Pinheiro, 2022).

4. Discussion

Viral infections are relevant in infectology because they have as an etiological agent a microorganism that is found between the animal and mineral kingdoms: viruses. Thus, such a characteristic implies an indeterminate latency time outside the human organism, as they can crystallize and remain inactive for hundreds of thousands of years (Paulo Roberto Soares Stephens et al., 2009). In this context, viral infections alter lymphocytes, being the necessary condition for preventive treatment to mass vaccination of the population. Thus, the fact that human smallpox was the only viral infection to be eradicated on the planet made its vaccination no longer necessary, favoring the infection and transmission of smallpox from monkeys, as it has a genetic load similar to that of the virus smallpox in humans (Smallpox). Thus, some studies have indicated the possibility of vaccination against smallpox in humans for preventive treatment against monkeypox (Amy Mckeever, 2022).

Within the spectrum of treatment of viral infections, two forms of treatment stand out: one being merely symptomatic, and the other preventive. In this context, we have antivirals and vaccines divided into several generations. In this way, existing vaccines have promising efficacy against Orthopoxvirus. However, they can present with varying symptoms, and ACAM2000 can cause an injury at the applied site. Thus, a comparison is necessary to identify which one has the best result, with a short period of time, and without causing many side effects that harm the affected individual. First-generation vaccines are characterized by the use of a replication-competent live pathogen. The second-generation ones are produced through tissue cell culture, thus presenting a lower risk of spreading the virus. Still, these vaccines have the live virus, with the ability to self-replicate, having the same risks as first-generation vaccines. It is then evident that the vaccines considered of third generation are the most modern and least harmful to health, as they present the viruses based on preclinical studies and that do not have the ability to replicate, reducing the chance of injury by individuals who received the vaccine and consequently attenuating the symptoms suffered by them (Brett W. Petersen et al., 2022). The vaccine that has the Modified Vaccinia Ankara Virus (MVA) becomes the most competent against Monkeypox, since even though it competes with LC16m8 in the third generation of vaccines, LC16m8 still has a low amount of virus replication, being harmful. Consequently, MVA-BN does not leave lesions at the site where it was applied and does not pose a threat to possible transmission, it was also developed for immunosuppressed individuals, contributing to greater immunization of the population.

The vaccine mechanism is an important factor for prevention in which it aims to defend the body against critical infections or that can lead to death. Encouraging the immune system to identify the invading organism that is in the infected patient and destroying the virus faster. However, treatment is performed, as already mentioned in the literature review, by means of antivirals: Cidofovir, known as Vistide, Brincidofovir, also called CMX001 or Tembexa and Tecovirimat or TPOXX, ST-246. Such forms of treatment have the objective of total recovery or reduction of symptoms (The United Nations Children's Fund, 2019).

Although these drugs are for a therapeutic process of the disease, they can imply several side effects. However, the antivirals mentioned in the above paragraph have similar adverse symptoms like nausea. On the other hand, Brincidofovir and Cidofovir are the ones that cause greater similarity, such as tiredness or weakness, malaise, stomach pain, colic, skin changes, asthenia, anemia. However, Cidofovir is the one with the greatest diversity of implications resulting from the use of the antiviral, being leukocytosis, leukopenia, lymphadenopathy, reaction lymphoma, pancytopenia, thrombocytopenia, thrombocytopenic purpura, amnesia, anxiety, seizures, hallucinations, insomnia, gingivitis, gastrointestinal hemorrhage, urinary incontinence some of its individual side effects.

Next, on the effectiveness of drugs approved by the Federal Drug Administration, the US government agency that controls drugs, a study was carried out in which it showed that Cidofovir did not have data specifically aimed at common smallpox and monkeypox in humans, because the study was performed on animals. However, it is not known whether the use of the drug is effective for the total treatment of Smallpox. Cidofovir has an updated second generation, with a greater defense action, indicated for newborns, children and adults, for the intervention of Smallpox symptoms, its name being Brincidofovir. There is not enough knowledge about its effectiveness against Orthopoxvirus, however, it is known that under no circumstances should it be used together with Cidofovir, with precautions to avoid adverse effects (Centers for Disease Control and Prevention, 2022; National Commission for the Incorporation of Technologies in the Unified Health System, 2022). Like the drugs mentioned above, Tecovirimat does not have total proven effectiveness, but tests were carried out on animals that prove its positive effects in its therapeutic process against Orthopoxvirus, and, if used at the beginning of the infection, human smallpox. It is understood that the drug considered safer for the treatment of Smallpox and Monkeypox would be Tecovirimat, as it is the antiviral with the chemical substance with the least damage to the human body, that is, with the lowest rate of side effects (CNN Brasil, 2022).

5. Conclusion

Viral infections demand a great demand from the host organism on the elements that structure the immune system, as they require the concomitant activation of both types of immunity: innate and adaptive. The treatment modalities are based on the use of antivirals and the use of immunizing agents that can give the body the conditions to produce effective antibodies against the onset and development of diseases, and it would be no different with Monkeypox. The access of the poorest populations to better adapted medical centers, as well as an increase in per capita income, would certainly increase the chances of a more adequate and effective recovery.

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