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Review article

Treatment and prevention of monkeypox

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ABSTRACT

Monkeypox is a zoonosis that is spread mainly through direct contact with fluids and skin lesions of infected people with vesicles still active. Although the virus was isolated for the first time in 1958 and the first human case was identified in a child in 1970, in the Democratic Republic of the Congo, the disease has progressively increased its incidence in Africa reaching in May 2022 sustained transmission outside this continent. As it is a newly introduced virus in our health system, it is necessary to learn the epidemiological pattern in a different environment from that of traditionally endemic areas and to know the available antiviral treatments, as well as the prophylactic measures that could be considered, knowing that as a virus emerging in our regions, scientific evidence is still limited. There are antivirals that have been shown, in animal models, to effectively combat the disease with very good clinical tolerance. This disease has also forced us to review the characteristics of smallpox vaccines, because they have shown a protective effect against monkeypox. For this reason, it is important to have a document that compiles all the scientific information published in this regard.

Tratamiento y prevención de la viruela del mono

Palabras clave:
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RESUMEN

La viruela del mono es una zoonosis que se contagia principalmente a través del contacto directo con los fluidos y las lesiones cutáneas de personas contagiadas con vesículas aun activas. Aunque el virus fue aislado por primera vez en 1958 y el primer caso humano se identificó en un niño en 1970, en República Democrática del Congo, la enfermedad ha aumentado progresivamente su incidencia en África alcanzando en mayo de 2022 trasmisión sostenida fuera de este continente. Al ser un virus de nueva introducción en nuestro entorno sanitario, es necesario aprender el patrón epidemiológico en un medio diferente al de las

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zonas tradicionalmente endémicas y conocer los tratamientos antivirales a nuestro alcance, así como las medidas profilácticas que podrían plantearse, sabiendo que como virus emergente en nuestras regiones las evidencias científicas aun son limitadas. Existen antivirales que han demostrado, en modelos animales, combatir eficazmente la enfermedad con muy buena tolerancia clínica. Esta enfermedad también ha obligado a revisar las características de las vacunas frente a la viruela ya que han demostrado un efecto protector frente a la viruela del mono. Por ello es importante disponer de un documento que recopile toda la información científica publicada a este respecto.

Introduction

Monkeypox is an exanthematous disease, which can have systemic manifestations, caused by infection with a zoonotic orthopoxvirus. It was first isolated in 1958 in monkeys that became ill with a skin disease while being transported from Singapore to Denmark[1]. The first human case was identified in a child in 1970, in the Democratic Republic of the Congo[2], and it is currently endemic in many African countries (Benin, Cameroon, Central African Republic, Democratic Republic of the Congo, Gabon, Ivory Coast, Liberia, Nigeria, Republic of the Congo, Sierra Leone and South Sudan). In 2003, the first outbreak outside of Africa was reported in the USA[3]. Since then, sporadic cases have been reported in several different countries outside endemic areas, most of them travel-related.

Two distinct strains of monkeypox have been identified in different geographical regions of Africa, of which the West African strain causes less virulent disease.

The virus is usually acquired by contact with the body fluids of an infected animal or from a bite, with monkeys and humans being incidental hosts. It cannot be said with certainty, but rodents are thought to be the most likely reservoir. Transmission can also occur from person to person through close contact with infectious skin lesions until the scabs of the lesions fall off, though for any of the strains, contagion through large respiratory droplets cannot be ruled out. Monkeypox (mpox) is not considered contagious during its incubation period[1–5].

After an incubation period of 6–13 days (range 5–21 days), the infected person may develop fever, a maculopapular rash, which progresses into vesicles, pustules and then scabs, lymphadenopathy or myalgia. Mpox is usually a self-limiting disease, but severe cases have been reported, particularly in children and immunosuppressed patients, with a reported fatality rate to date of 3%–6%[2–4,6–8].

On 14 May 2022, the United Kingdom Health Security Agency (UKHSA) reported that two cases of mpox had been identified, neither with any recent history of travel to an endemic area. Since then, the disease has spread to other countries[9]. The Spanish Ministry of Health has drawn up an action protocol against mpox that includes recommendations from international organisations, in order to guarantee detection of cases and adopt immediate control measures. Spain is also following the recommendations of the World Health Organization and European Union bodies, such as the European Centre for Disease Prevention and Control (ECDC). There are no official consensus documents setting out the pharmacological options for treatment and prevention. As such, the aim of this article is to provide a review of the still limited literature based on trials and clinical experience in the field of mpox.

Treatment

While mild cases are managed with symptomatic treatment, in severe cases of mpox, supportive treatment and treatment of systemic complications and secondary bacterial infections continue to be the cornerstone[4].

At present, no antiviral therapy has been shown to be effective in human clinical trials against mpox[8].

Tecovirimat

Tecovirimat (ST-246[2]) is a derivative of 4-trifluoromethyl phenol, a low-molecular-weight compound. It inhibits the egress of the virus by targeting the VP37 protein, which blocks the final steps in virus maturation, preventing it from leaving the infected cell[10].

First proposed as an antiviral candidate to treat orthopoxvirus infection in 2005, in 2018 it received US Food and Drug Administration (FDA) approval for the treatment of smallpox. Tecovirimat was granted marketing authorisation throughout the European Union on 6 January 2022. Based on animal studies, the European Medicines Agency considered tecovirimat to be effective in reducing mortality rates in smallpox, monkeypox and cowpox. In tests against a panel of various orthopoxviruses, including variola virus strains, tecovirimat showed high antiviral activity and was highly selective for orthopoxviruses, with a significant decrease in mortality rates. In animal models, it has proven effective in terms of survival against mpox when treatment starts after the disease is clinically evident[10–12].

In human cases, there is a published report on the administration of tecovirimat in one of the patients in the first familial outbreak related to a case imported to the United Kingdom, on a two-week regimen of oral tecovirimat 600 mg twice a day. In this case, polymerase chain reaction (PCR) of the blood and upper respiratory tract samples became negative 48 h after starting treatment, and remained negative at 72 h, with no new lesions developing after 24 h of therapy. It has also been used, with good tolerance, in some of the early cases of the 2022 outbreaks outside Africa[9]. It has been administered with promising results on a compassionate-use basis in several cases of orthopoxvirus disease in the USA and Europe, although it was administered concomitantly with other antiviral strategies, such as cidofovir and/or intravenous vaccinia immune globulin[8,10].

It is a drug administered orally in our setting, the intravenous formulation having recently been approved by the FDA[2,13–15].

In *cynomolgus* monkeys, a 10-mg/kg dose of tecovirimat twice daily for 14 days was shown to provide a significant survival benefit, greater if administered within the first five days of virus inoculation. Earlier initiation of treatment was correlated with greater survival benefit and reduced signs of disease[10].

From trials in animal models, a human dose of tecovirimat of 10 mg/kg/12 h (standard adult dose 600 mg twice daily) was predicted to provide plasma exposure several times higher than required to achieve maximum efficacy. Available data suggest that a five-day course is sufficient to confer a clinical response, while a two-week course enables humoral immunity to develop and lasting viral clearance. Tecovirimat may lose efficacy in immunosuppressed patients, and prolonged treatment beyond the 14-day recommendation may be necessary to allow the immune system sufficient time to control an orthopoxvirus infection[8,10].

Over 50 animal studies have been conducted on the efficacy and safety of tecovirimat and no serious adverse effects have been

identified[10]. The United States Centers for Disease Control and Prevention (CDC) have data from clinical trials in humans showing that the drug is tolerable and safe, but with insufficient evidence on its efficacy[1]. The most common side effects with the oral formulation are headache and nausea, and pain at the injection site with the parenteral formulation[13]. There are reports of compassionate use of tecovirimat in cases of complications deriving from the *vaccinia* virus and cowpox, with no significant safety concerns identified. In the case treated in the United Kingdom, the haematological, renal and hepatic profiles remained within normal limits during the first week of treatment and no adverse effects were reported[8]. The pivotal Phase 3 human safety study was conducted using tecovirimat 600 mg twice daily for 14 days, taken with food, and the results showed that this regimen was well tolerated, with no significant adverse events or associated safety problems, the incidence of which being similar in the placebo and treated groups[10].

It is currently not authorised for use in children, as it does not have a standardised dosage in patients weighing less than 13 kg. An oral liquid suspension formulation for paediatric patients is currently being developed. No dose adjustment is necessary for kidney or liver failure[8,10].

Tecovirimat is a substrate of the enzymes UGT1A1, 1A3 and 1A4. There are no data on co-administration with strong inhibitors or inducers of these enzymes, but no clinically significant effect on tecovirimat exposures is expected. In addition, tecovirimat is an inducer of cytochrome P450 (CYP)3A and CYP2B6. Although there are currently no data in this regard, the co-administration of other drugs with tecovirimat would reduce the plasma exposure of a substrate sensitive to these enzymes and would therefore reduce its effects. This must be taken into account in particular with drugs such as methadone, maraviroc, rilpivirine, darunavir and phosphodiesterase type 5 (PDE-5) inhibitors[16].

Although it has proved effective against multiple orthopoxviruses in animal models, alteration of a single amino acid in the viral protein involved has been shown to produce resistance to tecovirimat therapy. To date, no orthopoxviruses with naturally acquired resistance have been observed, but resistance to tecovirimat may develop with drug selection or prolonged treatment. Resistance has been reported during the use of the drug in a prolonged treatment cycle of an individual with progressive vaccinia. One option to reduce the risk of emerging resistance to tecovirimat during an outbreak is combination therapy with a second antiviral with a different mechanism of action to that of tecovirimat. Brincidofovir inhibits orthopoxvirus replication at a different stage of the virus life cycle compared to tecovirimat, and *in vivo* studies in mice have shown a synergistic effect when both drugs were administered[10,17].

As yet, tecovirimat has not been approved for post-exposure prophylaxis, although there is preclinical evidence in various animal models of orthopoxvirus disease that tecovirimat administered shortly after orthopoxvirus exposure, but prior to the onset of clear signs of disease, is highly protective against mortality and drastically reduces morbidity. It is approved in the USA for the treatment of smallpox in the event of a potential bioterrorism event[8,10,11].

Brincidofovir

Brincidofovir, also known as hexadecyloxypropyl-cidofovir or CMX001, is a lipid conjugate consisting of a lipid covalently bound to a cidofovir nucleotide analogue. It acts by inhibiting DNA polymerase after incorporation into viral DNA. Compared to cidofovir, it has greater cellular uptake and better conversion to the active form by intracellular enzymes[2,17].

An antiviral with activity against viruses of the herpes family (including those resistant to aciclovir), adenovirus, polyomavirus (JC and BK virus) and poxvirus, brincidofovir has also been used to treat ganciclovir-resistant CMV infections[18] and was approved in June 2021 by the FDA in the treatment of smallpox.

In trials in animal models, it has shown at least 25-times greater efficacy compared to cidofovir. In prairie dogs inoculated with monkeypox virus, brincidofovir produced a modest survival benefit and a reduction in target-organ virus titres. There are no completed clinical trials on the efficacy of brincidofovir for the treatment of mpox in humans. There is very little published on its administration in confirmed human cases, although one team from the United Kingdom has released information on three patients treated with oral brincidofovir, starting treatment in all cases within seven days of the onset of the rash, on a regimen of three 200-mg doses once a week. They found no significant association between brincidofovir doses and the clinical or virological parameters, although the sample was very small[1,8].

It has bioavailability when given orally, which means it can be formulated into tablets and suspensions for administration. It has a very long half-life. The guideline dose for humans is based on its administration in mice in clinical trials, where doses of 5–20 mg/kg gave a significant degree of protection against the development of disease[2,17,18].

It also has a better renal safety profile compared to cidofovir as, unlike cidofovir, brincidofovir is not actively taken up by renal organic anion transporter 1 (OAT1). A common side effect is diarrhoea. In published human cases, alanine aminotransferase (ALT) was elevated, with no other blood test abnormalities of note. The product label includes a warning about an increased risk of mortality in prolonged treatments[8,17,19].

Contraindications include the fact that there are no recommendations for dose adjustment in liver failure and, at present, there is no information on the use of brincidofovir in pregnancy or its presence in breast milk[18].

Brincidofovir concentrations may be increased by the concomitant use of darunavir, rilpivirine and/or sildenafil.

Cidofovir

Cidofovir is a monophosphate nucleotide analogue that inhibits DNA polymerase. It is an approved drug in the treatment of cytomegalovirus retinitis in patients with HIV and is also effective against poxviruses[1,20].

It has shown *in vitro* activity against monkeypox virus. Cidofovir can only prevent death when administered prior to the onset of the rash. In human cases, administration has been considered in high-risk contacts of confirmed cases and in very early stages of symptoms, always in well-hydrated patients due to its nephrotoxic effects[2,20].

Cidofovir has no formulation for oral administration[17]. It is also used currently in topical administration for mpox, despite the lack of data on its efficacy in this formulation[9].

The most common adverse effects are headache, asthenia, fever, skin rash, nausea, vomiting and eye abnormalities. The main dose-limiting toxicity associated with cidofovir administration is its nephrotoxicity, which is dose-dependent. In addition, treatment must be accompanied by the administration of oral probenecid and prior adequate intravenous hydration with saline solution[21].

The administration of cidofovir is contraindicated in patients who have hypersensitivity to the active substance or to other medicinal products containing sulfonamides.

Interactions of cidofovir/probenecid and antiretroviral drugs have not been investigated in clinical trials. It is important to consult the probenecid summary of product characteristics when prescribing. Co-administration of cidofovir and tenofovir disoproxil fumarate may increase the risk of Fanconi syndrome.

Other treatments under investigation

Ribavirin and tiazofurin are dehydrogenase inhibitors and have been shown to inhibit orthopoxvirus replication, with monkeypox virus being one of the most susceptible to them[1].

Adenosine N1-oxide (ANO) showed significant activity in blocking the movement of viral mRNA and thus inhibiting viral replication[1].

Immunoglobulin administration is also a therapy being studied for mpox[2,9].

Prevention

Early suspicion is critical in order to interrupt the chain of transmission, along with taking a complete medical history, which includes information on factors of exposure to the virus, activities participated in during the period of infection, possible protection measures adopted and high-risk contacts[22].

Prophylactic intervention in exposed asymptomatic individuals would further improve outbreak control by reducing virus dissemination and disease transmission[10].

Control and epidemiological surveillance

The CDC recommends isolation in a negative pressure room for hospitalised cases of monkeypox, particularly in medical interventions with increased risk of generating aerosols, caring for the patient with standard contact and droplet precautions, with escalation to airborne precautions if possible[2,3]. The Spanish Ministry of Health recommends that staff attending to a case of mpox use personal protective equipment for contact and airborne transmission precautions: gown, gloves, eye protection and FFP2 masks (filtering face piece level 2, corresponding to a filtration capacity of 92%); disposable shoe coverings are not recommended, but staff should wear footwear that can be decontaminated. If medical procedures that generate aerosols are performed, an FFP3 mask should be worn[23].

Infected patients with active skin lesions should be isolated at home, with maximum precautionary measures taken in terms of contact with their surroundings and their pets. The infected individual should wear a surgical mask and keep the lesions covered, whenever possible, until the scabs have fallen off and a new layer of skin has formed[1,23].

Contacts should be monitored for 21 days, with temperature taken at least once a day. As transmission only occurs during florid symptoms, close contacts do not need to isolate themselves while asymptomatic[1,3].

Infected animals must be quarantined for at least six weeks[4].

Prophylactic interventions

The official smallpox response plan does not currently allow for the prophylactic use of antiviral drugs in the event of an outbreak[10].

Classically, the smallpox vaccine induces both a humoral and cell-mediated response against orthopoxviruses, targets a wide range of viral particles and prevents viral replication. Studies have shown that vaccination against smallpox provides cross-protection against other orthopoxvirus species. Infection with an orthopoxvirus or immunisation with an orthopoxvirus vaccine provides immunological cross-protection against other viruses of the same genus. It has not been determined whether licensed vaccines would provide effective protection against monkeypox in endemic areas[1,24,25].

Residual IgG and neutralising antibodies have been shown to persist in people vaccinated against smallpox. More than 90% of volunteers vaccinated 25–75 years ago who participated in a study published in *Nature Medicine* in 2003 maintained significant humoral and/or cell-mediated immunity against the *vaccinia* virus contained in the smallpox vaccine[26]. Antiviral antibody responses were stable from 1 to 75 years after vaccination, whereas antiviral T-cell responses slowly declined, with a half-life of 8–15 years. If these levels of immunity are considered to be at least partially protective, then the morbidity and mortality rates associated with a smallpox outbreak would be substantially reduced among previously vaccinated individuals. Of the infected patients in the US outbreak, smallpox vaccine recipients showed immune activity against orthopoxvirus (IgG and memory B cells) after exposure to monkeypox. Those previously vaccinated against smallpox have been found to have 85% protection against monkeypox. However, although vaccination against smallpox can provide partial protection, a sufficiently large infectious inoculum can overcome such protection and manifest itself symptomatically through prolonged or frequent contact with infected animals or people[24,26].

During the WHO eradication campaign, first-generation smallpox vaccines based on different virus strains produced from animal models were initially used. These vaccines were associated with adverse reactions, ranging from a mild rash and fever to more serious conditions such as progressive vaccinia and post-vaccination encephalitis. Second-generation vaccines are produced in cell cultures and elicit similar levels of immune response. They can also cause serious adverse reactions, including myocarditis, particularly in immunocompromised patients. Lastly, so-called third-generation vaccines have been developed, based on attenuated strains with altered replication of the *vaccinia* virus, which are safer in vulnerable populations[24,25].

Vaccines

From 2015 to 2019, ACAM2000®, a second-generation vaccine, was the only FDA-licensed orthopoxvirus vaccine. In November 2021, the US Advisory Committee on Immunization Practices accepted the JYNNEOS® vaccine as an alternative to ACAM2000® for pre-exposure prophylaxis against orthopoxvirus infection among persons at risk, so as to have two vaccines available for this purpose[25].

The ACAM2000® smallpox vaccine, recommended by the CDC during the mpox outbreak in the USA in 2003, was shown to reduce symptoms but not prevent the disease. ACAM2000® is a second-generation vaccine against *vaccinia* virus with the ability to replicate derived from a purified clone used to manufacture the Dryvax® vaccine, one of those used to eradicate smallpox. This gives it the advantage of being a vaccine practically identical to one already applied in actual clinical practice, with demonstrated efficacy and therefore knowledge of how it behaves in human administration. ACAM2000® is administered percutaneously using a multiple puncture (scarification) technique, through 15 punctures with a bifurcated stainless-steel needle which has been pre-immersed in the reconstituted vaccine; a vaccination technique unique to vaccines against orthopoxvirus. This produces a lesion-like skin reaction at the vaccine administration site, which is often used as a marker of successful vaccination. This skin lesion contains infectious *vaccinia* virus capable of transmission to close contacts of those vaccinated. A vaccine dose is administered, eliciting maximum protection at 28 days. For personnel working with more virulent orthopoxviruses, ACAM2000® boosters are recommended every three years. If ACAM2000® has been received, the JYNNEOS® vaccine can subsequently be administered as a booster dose[1,25].

ACAM2000® has a risk of serious adverse events, such as progressive vaccinia, eczema vaccinatum and myopericarditis (estimated rate of 5.7 per 1000 vaccinated)[25].

ACAM2000® is contraindicated in people with a severe allergy to any of the vaccine's components, a history of atopic dermatitis

or other exfoliative skin condition, immunocompromised status, pregnancy, lactation and known underlying heart disease, and is also contraindicated in infants under one year of age or if the vaccine recipient cannot be sufficiently isolated from household contacts who have a history of active exfoliative skin disease, immunocompromised status or pregnancy. Concerning underlying heart conditions, it should be noted that the presence of three or more of the following factors contraindicates primary vaccination with ACAM2000®: hypertension; diabetes; hypercholesterolaemia; heart disease at age ≤ 50 in a first-degree relative; and smoking[1,25].

JYNNEOS® (also known as IMVAMUNE® or IMVANEX®) has also been approved by the FDA and the European Medicines Agency (EMA) for the prevention of smallpox and mpox in people over the age of 18 years. A vaccine based on the replication-deficient strain of vaccinia Ankara poxvirus, it has been modified into a third-generation, attenuated, non-replicating vaccine. The US Advisory Committee on Immunization Practices (ACIP) currently recommends the use of JYNNEOS® for primary vaccination as an alternative to ACAM2000®. Although a robust antibody response has been observed after a single dose of JYNNEOS® in clinical trials, the recommended regimen is to administer two doses by subcutaneous injection 28 days apart. The safety of JYNNEOS® has been assessed in 20 clinical trials on 5261 people. The most frequently reported adverse reactions were local reactions at the injection site and typical systemic reactions to vaccines (headache, myalgia and nausea), which were mild to moderate in intensity and resolved without intervention within seven days. It does not cause the residual skin lesion produced by injection with ACAM2000®. The protection provided by the vaccine is not effective until two weeks after receiving the second dose. People who are at continual risk of occupational exposure to more virulent orthopoxviruses (*variola* virus and monkeypox virus) should receive a booster dose every two years; and those at continual risk of occupational exposure to less virulent orthopoxviruses (vaccinia virus or smallpox vaccine virus) should receive booster doses at least every 10 years.

Data from studies in animal models indicate that a single dose of JYNNEOS® may provide protection against orthopoxvirus infection when administered before or shortly after (one day) exposure to the virus. A prospective observational study was carried out in Great Britain during the 2018 monkeypox outbreak, with the aim of evaluating the efficacy of the JYNNEOS® vaccine as a measure of pre-exposure and post-exposure prophylaxis in healthcare personnel. However, although the study is completed, the results were not yet available at the time of writing this article[1,25,27,28].

Fewer serious adverse events are expected, as it is a replication-deficient virus vaccine. People with risk factors for receiving ACAM2000® could be given JYNNEOS®. It seems safer than ACAM2000® for people with atopic dermatitis, eczema or other exfoliative skin conditions. Patients with atopic dermatitis developed local reactions at the injection site and mild systemic reactions more often. Clinical studies have not detected an increased risk of myopericarditis in JYNNEOS® recipients. However, the mechanism of myopericarditis after receiving ACAM2000® is an immune-mediated phenomenon, and it is not known whether the antigens that precipitate autoantibodies are also present in JYNNEOS®. Safety in a vulnerable population was evaluated in a clinical trial on people with HIV with a CD4 lymphocyte count at inclusion between ≥200 and ≤750 cells/μl. The percentage of adverse effects was no different compared to people with no HIV infection[1,10,25].

JYNNEOS® has not been assessed in the under-18s and is therefore not authorised for this population. Data on its administration in pregnant women are insufficient to determine the associated risks. However, animal models have shown no evidence of harm to the developing foetus. It is not known whether JYNNEOS® is excreted in human milk, so the impact on milk production or safety for breastfeeding infants is therefore unknown[25].

Indications

In summary, the smallpox vaccine could be considered for contacts if given within an ideal time, which would be within four days of exposure. However, a margin of up to two weeks could be allowed, such that, where it has not been possible in the first few days, at least if administered later, while not preventing the disease, it may reduce the severity. The JYNNEOS® vaccine would be recommended as the first option in this scenario[2–4].

Among the target population, we should consider people with occupational risk of exposure to orthopoxvirus infections, certain military personnel, personnel who care for patients infected with orthopoxvirus (people in contact with the skin, mucous membranes, body fluids, respiratory droplets or scabs of an infected patient) and, if the competent health authorities consider it appropriate, to control outbreaks of orthopoxvirus[2].

Routine antibody titre testing after vaccination (to confirm successful vaccination) is not recommended[25].

Combined use with other strategies

Due to the documented risk of myocarditis after receiving ACAM2000® and JYNNEOS® vaccines, consideration should be given to waiting four weeks after orthopoxvirus vaccination before giving a COVID-19 mRNA-based vaccine, particularly among adolescent or young adult males. If there is an active outbreak of orthopoxvirus with public health impact, protection should prevail and vaccination not be delayed. There is no minimum interval required after COVID-19 mRNA-based vaccination and vaccination with orthopoxvirus[25].

In animal trials assessing the potential benefit of combining vaccination and an antiviral, the protective efficacy of the vaccine was not affected by concomitant treatment with tecovirimat, but the humoral response to the vaccine may be adversely affected. This suggests that in a pre-exposure prophylaxis (PrEP) scenario, with near-zero risk of orthopoxvirus exposure, tecovirimat should not be administered at the same time as the smallpox vaccine, as it may slightly reduce its protective efficacy. If variola virus exposure is suspected, even before clinical signs of disease, tecovirimat is probably the best intervention option, as the efficacy of post-exposure vaccination decreases rapidly as the infection progresses, while tecovirimat remains effective after clinical disease is evident. However, further interaction studies between tecovirimat and vaccine should be carried out, in order to determine the degree of interference with the establishment of vaccine-induced immunity[10,11].

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Conflicts of interest

There are no conflicts of interest.

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