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Original Article

A brief on new waves of monkeypox and vaccines and antiviral drugs for monkeypox

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Received 8 July 2022; received in revised form 19 August 2022; accepted 28 August 2022

Available online 6 September 2022

KEYWORDS

ACAM2000;
Brincidofovir;
Jynneos[®];
Monkeypox;
Smallpox;
Tecovirimat

Abstract Monkeypox virus (MPXV), genetic closely linked to the notorious variola (smallpox) virus, currently causes several clusters and outbreaks in the areas outside Africa and is noted to be phylogenetically related to the West African clade. To prepare for the upsurge of the cases of monkeypox in the Europe and North America, two vaccines, Jynneos[®] in the U.S. (Imvamune[®] in Canada or Imvanex[®] in the Europe) and ACAM2000[®] (Acambis, Inc.) initially developed in the smallpox eradication program, can provide protective immunity to monkeypox, and their production and availability are rapidly scaled up in the response to the emerging threat. So far, these two vaccines are recommended for people at a high risk for monkeypox, instead of universal vaccination. Tecovirimat, an inhibitor of extracellular virus formation, and brincidofovir, a lipid conjugate of cidofovir, both are *in vitro* and *in vivo* active against MPXV, and are suggested for immunocompromised persons, who are at risk to develop severe diseases. However, current general consensus in the response to the monkeypox outbreak among public health systems is early identification and isolation of infected patients to prevent its spread.

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Introduction

Monkeypox virus (MPXV), belonging to the *Poxviridae* family and genus *Orthopoxvirus*, is genetically closely linked to the variola (smallpox) virus, and may cause a febrile illness and rash in humans, milder than smallpox.¹ Regarding the recognized outbreaks of monkeypox in Africa, there were at least two clades identified, one in the Congo (Central Africa) and the other one in the Nigeria (West Africa), leading to varied mortality.² The circulating clade causing current outbreaks in many countries is phylogenetically related to the West African clade.² The surge in the case number and geographic distribution of monkeypox was alarmed in recent years, which was suspected to be due to the waning of the smallpox vaccine-induced immunity in the human society.¹

Monkeypox is notorious to present with dermatological manifestations over face and other parts of the body lasting 2–4 weeks,³ and may first present with constitutional symptoms, such as fever, chills, headache, myalgia, backache, and fatigue.⁴ The ongoing epidemic in West Africa and the areas outside Africa differs greatly from earlier outbreaks in Central Africa, in terms of age (54.3% of individuals in their thirties), gender (mainly male), risk factors, and transmission route with sexual transmission being highly likely.⁵ The overall case fatality rate of monkeypox was 8.7%, with a substantial difference between clades: 10.6% for the Central African clade versus 3.6% for the West African clade.⁶

Vaccination for monkeypox

Vaccines developed in the smallpox eradication program could provide protective immunity to MPXV infection.³ Two vaccines, Jynneos[®] in the USA (Imvamune[®] in Canada or Imvanex[®] in the Europe) and ACAM2000[®] (Acambis, Inc.) are available currently (Table 1).^{4,7} Jynneos[®] is a third-generation live, replication incompetent vaccinia virus to be subcutaneously administered as a two-dose regimen, and is approved for both smallpox and monkeypox in the USA and Canada, but only for smallpox in the Europe.

ACAM2000[®] is a single plaque-purified vaccinia virus derivative of Dryvax[®], aseptically propagated in cell culture.⁸ The supply of Dryvax[®] (Wyeth Laboratories, Inc.) was insufficient, and this vaccine had a questionable safety issue, because it consisted of a pool of vaccinia virus strains with varying degrees of virulence.⁸ In contrast, ACAM2000[®] is a live, replication competent vaccinia virus approved by the U.S. Food and Drug Administration (FDA) for active immunization against smallpox, and is percutaneously administered as one dose via the multiple puncture technique. ACAM2000[®] is recommended for re-vaccination every three years. However, such an infectious vaccinia

virus can be transmitted to unvaccinated persons from the vaccine recipients, if there is close contact with the inoculation lesion or exudate. Therefore, ACAM2000[®] is contraindicated among immunocompromised population, those with chronic dermatological illness (such as atopic dermatitis or eczema), or pregnant women. Routine vaccination with ACAM2000[®] for laboratory personnel who handle cultures or animals possibly contaminated or infected by vaccinia viruses has been recommended.⁹ The rare serious adverse drug reactions (ADRs) of ACAM2000[®] included myopericarditis, auto-inoculation, generalized vaccinia, ocular vaccinia, and post-vaccinal encephalitis.¹⁰

The Advisory Committee on Immunization Practices (ACIP) in the U.S. has recommended ACAM2000[®] and Jynneos[®] for pre-exposure prophylaxis against orthopoxvirus, including monkeypox, infections among those at risk of exposure and infection.⁷ Individuals can be considered as fully vaccinated two weeks after the second shot of Jynneos[®] or four weeks after one shot of ACAM2000[®].¹⁰ In the aspect of post-exposure prophylaxis, there has been an animal model of prairie dogs infected by a low-dose challenge of MPXV of the Congo Basin clade at the doses of two fold of lethal dose 50% (LD₅₀), the administration of Imvamune[®] at one day was more effective than at three days post-exposure, but ACAM2000[®] was effective at either post-exposure time-point.¹¹

For the current outbreak, the Centers for Disease Control and Prevention (CDC) in the U.S. recommend that either vaccine be given within four days after the exposure to prevent onset of the disease, and if given between 4 and 14 days after the exposure, post-exposure vaccination may reduce the symptoms of disease, but may not prevent the disease.¹⁰ Some antiviral agents, such as tecovirimat, might affect the immunogenicity of ACAM2000[®], if administered concomitantly,¹² and thus co-administration of tecovirimat and ACAM2000[®] should be avoided so far.

Antiviral treatment for monkeypox

Certain antiviral agents have been prepared for unexpected emergence of smallpox, and these drugs have been then approved in the treatment of monkeypox in recent years.³ Though monkeypox in most patients are mild and self-limited and only need supportive care, antiviral agents are commonly retained for severe illness occurring in immunocompromised patients, pediatrics, pregnant and breastfeeding women, and for complicated lesions, especially those near the mouth, eyes, or genitals.^{4,13}

Tecovirimat

Tecovirimat (Tpoxx[®]; ST-246) was the first antiviral agent approval for smallpox and monkeypox (Table 2).¹³ Over

Table 1 Efficacy and safety of two vaccines of monkeypox recommended by the Centers for Disease Control and Prevention, United States.

Name	Component	Route	Dosage	GMT ^a (95% CI)	Serious adverse drug reactions	Re-vaccination	Contraindication
ACAM2000 [®]	Single plaque-purified, live, replication competent vaccinia virus	Percutaneous (scarification)	One dose	84.4 (73.4, 97.0)	Incidence: events/million Myopericarditis (117.71–519.52) Auto-inoculation (84.86–494.78) Generalized vaccinia (58.86–74.22) Ocular vaccinia (21.90–74.22) Post-vaccinal encephalitis (1.37–24.74)	Recommended, every 3 years	Serious allergy to a vaccine component, history of atopic dermatitis or other exfoliative skin condition, an immunocompromising condition (e.g., due to a disease or therapeutics), pregnancy, breastfeeding, and known underlying heart disease (e.g., coronary artery disease or cardiomyopathy)
Jynneos [®] (Imvamune [®] , Imvanex [®])	Live, attenuated, non-replicating vaccinia virus	Subcutaneous	Two doses (0.5 mL each), 4 weeks apart.	152.8 (133.3, 175.0)	Crohn's disease, sarcoidosis, extraocular muscle paresis, and throat tightness	No data	Serious allergy to a vaccine component

^a Geometric mean neutralizing antibody titer as measured by vaccinia 50% plaque reduction neutralization test in healthy smallpox vaccine-naïve adults 18 through 42 years of age (from package insert of Jynneos[®]. Revised 06/2021).
CI: confidence interval.

300,000 compounds were screened for against orthopoxvirus, and the best activity was observed in tricyclonone carboxamides, and after testing analogues, the lead candidate, a 4-trifluoromethyl phenol derivative, was initially named as ST-246.¹⁴ Tecovirimat inhibits the production of extracellular viruses by interacting with the F13L gene product, which is a phospholipase involved in the formation of a protein complex that catalyzes the envelopment of intracellular mature virus particles.^{14,15} A F13L gene product–protein complex interacts with components of the trans-Golgi that wrap infectious intracellular viral particles to form triple-wrapped viruses prior to transportation to the cell surface and release.¹⁶ In this step, formation of conserved oligomeric Golgi (COG) complex is required; and the COG complex is an eight-protein (COG1-COG8) vesicle tethering complex to regulate membrane trafficking, glycosylation enzymes, and maintaining Golgi structures.¹⁷ So tecovirimat exerts its antiviral effect by inhibiting extracellular virus formation, and thereby preventing cell–cell and long-distance spread.¹⁸ In infected cynomolgus macaques with tecovirimat treatment at 5, 6, 7, or 8 days following MPXV challenge, survival rate was 100%, 67%, 100%, and 50%, respectively.¹⁹ Even with delayed administration for post–challenge therapy, tecovirimat is effective against MPXV infection.

In a phase I study, tecovirimat could be quickly absorbed following oral administration, with the time to maximum concentration of 2–3 h. No obvious adverse effect at single oral dose of 500, 1,000, or 2000 mg to fasting healthy volunteers was observed.²⁰ On the basis of its efficacy in two animal models and pharmacokinetic and safety data in humans, tecovirimat was considered further as a therapy for smallpox, in accordance with the FDA Animal Rule.²¹ Tecovirimat was approved for the treatment of symptomatic smallpox by the U.S. FDA in July 2018 and stockpiled by the US government for emergent use in case of a smallpox outbreak.¹³

In the expanded safety trial, 452 participants were randomization to tecovirimat at a dose of 600 mg twice daily (361 participants) or matching placebo (91 participants) for 14 consecutive days.²¹ The overall adherence rate was 94.4% in the placebo group and 93.6% in the tecovirimat group, and the corresponding rate in the pharmacokinetic part was 100% and 96.9%, respectively.²¹ Adverse events of grade 3 or higher occurred during treatment at 1.1% in both group, and included headache, osteoarthritis, and hidradenitis.²¹ One fatal adverse event was related to pulmonary embolism at one week after completion of tecovirimat treatment in a participant with recent recurrent deep-vein thromboses but no anticoagulant therapy.²¹ With current evidence, tecovirimat is regarded as a safe antiviral agent without obvious adverse events.

Brincidofovir

Brincidofovir (BCV or hexadecyloxypropyl-cidofovir [HDP-CDV]), initially named as CMX001, is a lipid conjugate of cidofovir (CDV).²¹ The therapeutic efficacy of BCV was shown to be higher than that of CDV due to increased cellular uptake and better conversion to the active form by

Table 2 Summary of two potential antiviral drugs for monkeypox.

Name	Tecovirimat	Brincidofovir, BCV
Synonym	Tpoxx [®] , ST-246	Tembexa [®] ; Hexadecyloxypropyl-cidofovir (HDP-CDV), CMX001
US FDA approval	July 2018 for human smallpox	June 2021 for human smallpox
Pharmacological preparation	Capsule: 200 mg Injection: lyophilized powder for reconstitution, 200mg/20 mL	Tablet: 100 mg Oral suspension: 10 mg/mL
Mechanism	Inhibit extracellular virus formation and prevent cell–cell and long-distance spread	A pro-drug of cidofovir conjugated with a lipid molecule; in infected cells, transformed into cidofovir diphosphate to inhibit DNA polymerase-mediated DNA synthesis and incorporate into the growing viral DNA chain, slow viral DNA synthesis rate
Treatment dose and duration	Oral - take within 30 min after eating full meal ● 40 kg to <120 kg: 600 mg BID for 14 days ● ≥120 kg: 600 mg TID for 14 days Intravenous dosing - ● 35 kg to <120 kg: 200 mg over 6 h q12 h for 14 days ● ≥120 kg: 300 mg over 6 h q12 h for 14 days	● ≥48 kg (tablet or oral suspension): 200 mg PO x 2 doses (on Day 1 and 8) ● <48 kg (oral suspension): 4 mg/kg PO x 2 doses (on Day 1 and 8)
Renal or hepatic adjustment	Renal impairment ● Oral: mild, moderate, severe, or patients requiring hemodialysis: no dosage adjustment required ● Intravenous: mild-to-moderate (CrCl 30–89 mL/min), no dosage adjustment necessary; severe (CrCl <30 mL/min), contraindicated Hepatic impairment ● Mild, moderate, or severe (Child-Pugh class A, B, or C): no dosage adjustment required	Renal or hepatic impairment: no dosage adjustment required with any degree of impairment
Pharmacokinetics	● Plasma protein binding: 77.3%–96.3% ● Route of elimination: feces (71–75%) and urine (18–24%) at 96 h post dose	Oral 100 mg tablet: C _{max} , 251 ng/mL; area under curve, 1394 ng h/mL; oral bioavailability: 13.4% in tablet and 16.8% in suspension
Drug–drug interaction	● May induce certain CYP enzymes, including CYP3A4, and its metabolites (M4 and M5) have the potential to produce drug–drug interactions by the induction of CYP2B6 ● Increased effect of repaglinide; decrease effectiveness of midazolam	Concomitant use with OATP1B1 and 1B3 inhibitors increase BCV-associated adverse reactions

Efficacy in animal study	Survival rate of cynomolgus macaques with tecovirimat treatment at 5, 6, 7, or 8 days following monkeypox virus challenge: 100%, 67%, 100%, and 50%	Survival rate of prairie dogs intranasally challenged by monkeypox virus on the day of BCV therapy relative to inoculation day: 57% on ID-1, 43% on ID0, and 29% on ID1
Adverse drug reactions	<ul style="list-style-type: none"> ● Oral: headache, osteoarthritis, and hidradenitis ● Intravenous: infusion site pain, swelling, erythema, extravasation; headache 	Mild gastrointestinal events, such as diarrhea, nausea, vomiting, abdominal pain
CrCl: creatinine clearance; CYP: cytochrome; ID-1: 1 day prior to viral challenge; ID0: the day of challenge; ID1: one day after viral challenge. US FDA: Food and Drug Administration, United States.		

intracellular enzymes.²² In contrast to CDV, HDP-CDV is orally active and lacks the nephrotoxicity of CDV.²² Increased oral bioavailability and increased cellular uptake of BCV is facilitated by its lipid portion, which is responsible for the improved activity profile.²²

BCV showed antiviral activity against double-stranded DNA viruses, including poxviruses.²³ Of the infected prairie dogs, which have been used to investigate the therapeutic efficacy of antiviral agents against poxviruses, divided into three groups based on the first day of BCV treatment relative to inoculation day, *i.e.*, ID-1, ID0, or ID1, the trend in efficacy was noted dependent upon the timing of treatment initiation: 57% on ID-1, 43% on ID0, and 29% on ID1.²³ Therefore, early administration of BCV for monkeypox is suggested. Phase II and III studies performed in immunocompromised adults and children at risk of infection with cytomegalovirus or adenovirus showed similar adverse events and good safety profile.²⁴ In October 2016, the European Drug Agency gave favorable opinions for BCV as an orphan treatment for smallpox,¹⁵ and later BCV received the Orphan Drug Designation from the FDA in June 2018.¹⁵ So BCV might be another useful compound against monkeypox, besides tecovirimat.

Cidofovir

Cidofovir (CDV) has used to treat infections due to human cytomegalovirus (HCMV), human herpesvirus, adenovirus, and other DNA viruses.²⁵ *In vitro* and in animal models, cidofovir has been shown to exhibit antiviral activity against the genus Orthopoxvirus, including monkeypox and smallpox.²⁶ However, significant renal toxicity, hypersensitivity, and other adverse events discourage the popular prescriptions of parenteral cidofovir.¹⁰ Clinical data of cidofovir treating or preventing smallpox or monkeypox in human are lacking. Therefore, it is unknown whether or not a person with severe monkeypox infections will benefit from treatment with cidofovir, a potentially nephrotoxic agent.¹⁰

Recombinant immunoglobulin

Recombinant immunoglobulin (rVIG) has demonstrated potential efficacy against several orthopoxviruses, including MPXV *in vivo* in both prophylactic (protect mice from infection when given up to 14 days before viral inoculation) and therapeutic (6 days after viral challenge) fashion.²⁷ However, its role in human orthopoxvirus infection requires further clinical data.

Novel agents under investigation

Host Golgi-associated retrograde proteins play a role in EV formation from MPXV and vaccinia virus.¹⁸ Inhibition of the retrograde pathway by small molecules, such as Retro-2, was found to be able to decrease vaccinia virus infection.¹⁸ PA104, a new compound containing a benzodiazepine scaffold similar to that of Retro protein, could inhibit 90% viral spread at 1.3 μM with a high selectivity index.¹⁸ PA104 strongly inhibited two distinct tecovirimat-resistant viruses, demonstrating its potential benefit for use in

Table 3 Five clinical trials registered at *ClinicalTrials.gov* related to monkeypox, posted from March 2014 to July 2022.

<i>ClinicalTrials.gov</i> identifier	Study Title	Location	First Posted	Study Design	Included Population	Intervention	Outcome Measures	Status
NCT02080767	Tecovirimat (ST-246) Treatment for Orthopox Virus Exposure	America	March 6, 2014	No data	ND	Tecovirimat oral 600 mg daily	ND	Available
NCT02977715	IMVAMUNE [®] Smallpox Vaccine in Adult Healthcare Personnel at Risk for Monkeypox in the Democratic Republic of the Congo	Congo	November 30, 2016	Single group assignment	1600 healthcare personnel at risk of monkeypox infection	Imvamune [®]	Prevention of monkeypox	Active, not recruiting
NCT03745131	Cohort Study of Healthcare Workers Receiving Imvanex [®]	United Kingdom	November 19, 2018	Cohort	120 participants	Imvanex [®]	Serological responses to vaccine	Completed
NCT05058898	A One Health Study of Monkeypox Human Infection (AFRIPOX)	Central African Republic	September 28, 2021	Observational, case–control	280 participants	No	Proportion of monkeypox cases after exposure	Recruiting
NCT05438953	Follow-up of Contact at Risk of Monkeypox Infection: a Prospective Cohort Study (MonkeyVax)	France	June 30, 2022	Prospective cohort study	post-monkeypox exposure	Monkeypox vaccine (Imvanex [®] and Jynneos [®])	Proportion of vaccine failure	Not recruiting

combination therapy with tecovirimat.¹⁸ Even with excellent antiviral effect *in vitro*, the effect of PA104 against MPXV *in vivo* needs more solid evidence.

N-methanocarbathymidine (N-MCT), a thymidine analogue, was first described for antiviral activity against herpesviruses,¹⁵ which is mediated by the formation of a triphosphate metabolite of N-MCT, which is dependent on a viral thymidine kinase.¹⁵ Treatment by intraperitoneal route with N-MCT (100 mg/kg/day) reduced vaccinia virus titers in liver, spleen, kidney, lung, and brain in a mouse model during virus infection.²⁸ More studies are warranted for its effect against human MPXV or orthopoxvirus infections.

Clinical trials related to monkeypox

There were at least five clinical trials registered at *ClinicalTrials.gov* related to monkeypox posted from March 2014 to July 2022 (Table 3).²⁹ Three trials were related to the efficacy of monkeypox vaccines, including preventing 1600 healthcare personnel at risk of monkeypox at Congo with Imvamune[®] (NCT02977715), the serological response of healthcare workers receiving Imvanex[®] in the United Kingdom (NCT03745131), and the efficacy of monkeypox vaccines (Imvanex[®] and Jyneos[®]) in France (NCT05438953). One clinical trial focuses on the proportion of monkeypox cases developing after exposure at Central African Republic and is not a true clinical trial with any intervention (NCT05058898). There is only one clinical trial related to monkeypox treatment: tecovirimat treatment for orthopoxvirus exposure in America (NCT02080767), but there is no detailed study design disclosed.

Conclusions

In the COVID-19 era, the emergence of another infectious disease, the monkeypox, is really a challenge. However, unlike COVID-19, it is fortunate that due to the fear of re-emerging smallpox, there had been several vaccines and antiviral agents readily available for smallpox and monkeypox. Monkeypox, though milder than smallpox, may present with three distinct phases, *i.e.*, incubation phase ranging from 7 to 14 days, prodrome phase with fever and lymphadenopathy, and rash phase evolving through papular, vesicular, and pustular lesions to crust formation.¹ The transmission ability and mutation ability of MPXV is not as worrisome as that of COVID-19. So far, the vaccines of monkeypox are only suggested for people with a high risk for monkeypox, instead of universal vaccination. The antiviral drugs, including tecovirimat and brincidofovir, are recommended for those potentially at risk of severe diseases. The general consensus facing the monkeypox outbreak is early identification and isolation of infected patients to prevent further spread from specific risky individuals to general population. With rapid initiation of infection control measurements and appropriate pre-exposure or post-exposure use of vaccines or antiviral agents, the control of the ongoing monkeypox outbreak needs international collaboration of public health institutions, and effective communications or

information sharing among surveillance networks in the countries and continents.

Funding

The present study was supported by research grants from the Ministry of Science and Technology, Taiwan (MOST 108-2320-B-006-043-MY3, 111-2314-B-675-001-MY3, 111-2321-B-006-009 and 111-2740-B-006-003).

Declaration of competing interest

The authors declare that they have no conflicts of interest.

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