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Analysis of Published Case Studies Evaluating Brincidofovir as a Potential Antiviral Treatment for Mpox Clade II Infections

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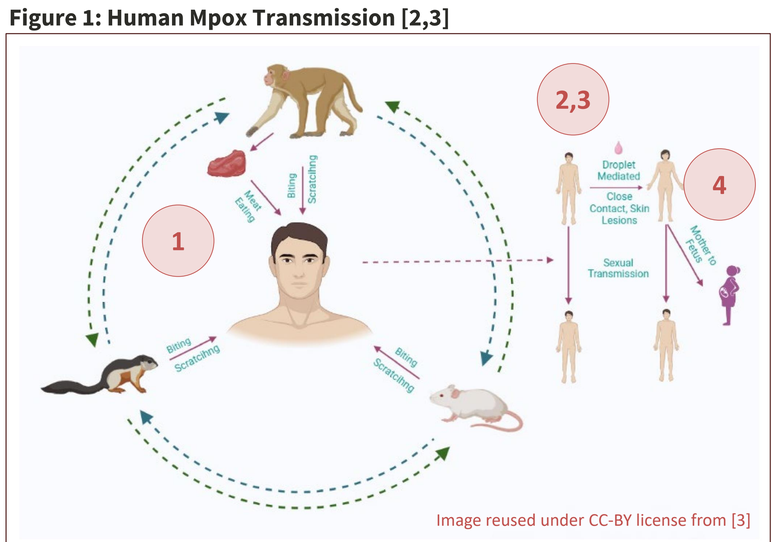
INTRODUCTION

Mpox:

Mpox, a systemic infection caused by monkeypox virus (MPXV), was first described in humans in the Democratic Republic of the Congo (DRC) in 1970 and remains endemic in regions of Africa [1]. Infection can be acquired naturally through the skin, respiratory tract, and mucous membranes, due to exposures to infected humans or animals (**Figure 1**) [2,3]. No antiviral has yet demonstrated efficacy in the treatment of mpox in humans.

Figure 1: Human Mpox Transmission [2,3]



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1. Infected animal transmission. 2. Contaminated material transmission. 3. Human-to-human transmission. 4. Congenital transmission.

Mpox disease course consists of 3 stages: (1) a noncontagious incubation stage following exposure; (2) a contagious prodrome stage, where patients can be symptomatic; (3) the rash stage, where lesions develop and present as macules, papules, vesicles and pustules prior to scabbing and healing [1,2,4,5].

Brincidofovir (BCV):

A DNA polymerase inhibitor and lipid conjugate of the nucleotide analog cidofovir (CDV). The lipid moiety facilitates cell entry of BCV, where it is cleaved into CDV and further phosphorylated to cidofovir diphosphate (CDV-PP), a potent inhibitor of viral DNA synthesis (**Figure 2**) [6,7].

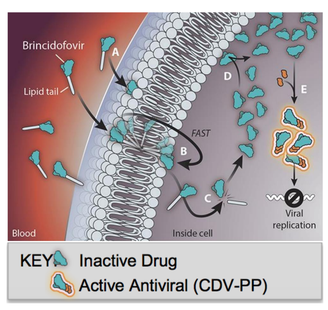

Figure 2: BCV cell entry and metabolism to CDV

BCV is approved in the US and Canada to treat smallpox and is available in two formulations: 100 mg tablets and a 10 mg/mL oral suspension. The approved dose in adults and pediatric patients ≥48 kg is 200 mg (2x 100 mg tablets or 20 mL oral suspension for patients who cannot swallow tablets) once weekly for 2 weeks [6]. The dose is 4 mg/kg oral suspension for adult and pediatric patients 10–<48 kg, and 6 mg/kg oral suspension for pediatric patients <10 kg, both taken once weekly for 2 weeks. BCV contains a Boxed Warning for increased risk for mortality when used for a duration longer than recommended [6].

BCV has shown *in vitro* and *in vivo* activity against MPXV clades I and II [7] and can be made available from the U.S. Strategic National Stockpile to clinicians who request and obtain a U.S. FDA-authorized single-patient emergency use IND (EIND) for mpox disease in adult and pediatric patients with severe illness who meet specific eligibility criteria [8]. The intent of this analysis was to collate all available published human clinical cases of BCV used in mpox Clade II infections in order to evaluate its effectiveness, safety, and impact on patient outcomes.

METHODS

A PubMed search was conducted which identified 27 published case reports involving treatment of Clade II infections with BCV alone or in combination with tecovirimat (TCV), vaccinia immune globulin (VIGIV), cidofovir (CDV) and/or broad-spectrum antibiotics. Published cases from May 2022 (start of the mpox outbreak) to Sep 2025 were analyzed to identify patient demographics, symptomology/complications, and treatment and patient outcomes to support future clinical evaluation of BCV in treating mpox. .

RESULTS

BCV was used as a first- or second-line monotherapy in 18.5% and 25.9% cases, respectively, or as second line combination therapy with TCV, VIGIV, or CDV in 44.4% of cases. The number of 200 mg weekly BCV doses given to patients ranged from 1–6. Of the 27 patients receiving BCV in their treatment, 16 (59.3%) recovered, 5 (18.5%) died, with unknown outcome in 6 patients (22.2%).

TCV was the primary monotherapy provided to 66.7% of patients and BCV was introduced as a second-line monotherapy or combination therapy with VIGIV or CDV; typically, later (average 58.5–72.5 days, respectively) in the disease course. Published cases of BCV first-line monotherapy use were in Saudi Arabia and the UK. All these cases resulted in recovery, and in two renal transplant patients, fever subsided, and lesion crusting was observed within 72 hours of treatment.

Patients had an average age of 34.3 years, were primarily male (88.5%), HIV positive (81.5%), and had CD4+ counts <100 cells/mL (90.0%) (**Table 1**).

Demographics:

Table 1: Demographics of Patients Receiving BCV for Treatment of Mpox

Demographics		
Age, years (N=20)	Average	34.3
	Min	20
	Max	51
Sex, n (%) (N=26)	Male	23 (88.5)
	Female	1 (3.8)
	Transgender Female	2 (7.7)
Underlying Condition, n (%) (N=27)	HIV Positive	22 (81.5)
	Post Renal Transplant	2 (7.4)
	None	3 (11.1)
Immune Status, n (%) (N=20)	CD4+ <200 cells/mL	20 (100.0)
	• CD4+ <100 cells/mL	18 (90.0)
	• CD4+ <50 cells/mL	10 (50.0)
	• CD4+ <25 cells/mL	4 (20.0)
	• CD4+ <12.5 cells/mL	2 (10.0)
Other viral infections, n (%) (N=18)	Herpes Simplex	3 (16.6)
	Syphilis	3 (16.6)
	Varicella zoster	2 (11.1)
	Cytomegolavirus	2 (11.1)
	Hepatitis B	1 (5.6)
	Gonorrhea	1 (5.6)
	None	6 (33.3)
Treatments (N=27)		
BCV (PO), n (%)	First line monotherapy	5 (18.5)
	Second line monotherapy	7 (25.9)
	Second line combination therapy	12 (44.4)
TCV (PO, IV), n (%)	First line monotherapy	18 (66.7)
	First line combination therapy	4 (14.8)
VIG (IV), n (%)	First line combination therapy	4 (14.8)
	Second line combination therapy	12 (44.4)
CDV (IV), n (%)	First line combination therapy	2 (7.4)
	Second line combination therapy	5 (18.5)
CDV (topical/ intralesional), n (%)	Second line combination therapy	4 (14.8)
Case Outcomes (N=27), n (%)	Recovered	16 (59.3)
	Death	5 (18.5)
	Unknown	6 (22.2)

TCV = tecovirimat, BCV = brincidofovir, CDV = cidofovir, VIGIV = vaccinia immune globulin intravenous, HIV = Human Immunodeficiency Virus, N = sample size, n (%) = # of patients within the sample size. Adapted from references 9–25.

Symptomology & Complications:

Of the 27 patients with mpox, 22 were in the rash stage and had:

a) Skin lesions on the face, scalp, arms, hands, fingers, palms, torso, genitals (scrotum, penis, labia), anus, legs, feet, and soles, and;
b) Mucosal lesions on the nasal septum, tongue, pharynx, and oropharynx.

Many of the reported complications were aligned with the prodrome and rash stages of the mpox disease course:

a) Skin complications including conjunctivitis, eye swelling, and deep tissue abscess;
b) Respiratory complications including tonsillitis, compromised airways, pulmonary nodules, pleural effusion, and respiratory failure;
c) Gastrointestinal complications including proctitis and rectal bleeding, and;
d) Genitourinary complications including renal failure, scrotal infection, penile strictures, syphilis and gonorrhea.

Treatment & Outcomes:

Pre-treatment CD4+ counts were <200 cells/mL in all 20 reported cases. Levels <200 cells/mL in mpox patients have been associated with severe disease, necrosis, pulmonary spread, hospitalization and increased mortality [26, 27]. The risk of mortality is increased in HIV positive patients [28–30].

When BCV is introduced as the 1st line monotherapy (n=5) or combination therapy (n=3) early in the disease course, the associated survival is 100%. When treatment is delayed and BCV is introduced after 1st line TCV monotherapy has failed, survival outcomes range from 33.3 to 58.3% (**Table 2**). This underpins the importance of further evaluation of early 1st line treatment with BCV.

Table 2: Summary of BCV Treatment, Dosing and Outcomes

N (% of total)	Location	Treatment		200 mg Weekly BCV Doses	Days from Rash Onset, mean (min, max)	Outcome, %
		1st Line	2nd Line			
5 (18.5)	UK, Saudi Arabia	BCV Mono	n/a	1 to 2	8.8 (6, 14)	Survival: 100.0 Death: n/a Unknown: n/a
3 (11.1)**	United States	BCV Combo	n/a	3	35	Survival: 100.0 Death: n/a Unknown: n/a
1 (3.7)**	United States	TCV Combo	BCV Mono	2	43	Survival: 0.0 Death: 100.0 Unknown: n/a
7* (25.9)	United States	TCV Mono	BCV Mono	2 to 4	58.5 (56, 61)	Survival: 33.3 Death: n/a Unknown: 66.7
12 (44.4)	United States	TCV Mono	BCV Combo	1 to 6	72.5 (11, 230)	Survival: 58.3 Death: 25.0 Unknown: 16.7

*This patient group includes 1 patient that also received BCV combo therapy as a first line treatment. ** these two rows include TCV use as a 1st line treatment and total up to 4 (14.8%) to align with Table 1. TCV = tecovirimat, BCV = brincidofovir, Mono = monotherapy, Combo = combination therapy with either VIGIV, TCV Oral or IV, or CDV IV/topical, IV = intravenous, min = minimum, max = maximum, n/a = not applicable. Adapted from references 17 – 33.

Safety:

Adverse events following BCV treatment were reported in 5 patients (18.5%), and all were transient elevations of liver enzymes (**Table 3**). Three of these cases were where BCV was used as a first line monotherapy within 7 days of rash onset. The other two cases were where BCV was used as a second line monotherapy, one of which was after 56 days of rash onset. Of the 5 patients who experienced adverse events, 1 (3.7%) had elevations after a single dose, 3 (11.1%) had elevations after 2 doses, and 1 (3.7%) had elevations after an unknown number of doses.

Table 3: Adverse Events Following BCV Treatment

BCV Adverse Events, n (%) (N=27)	
Total Reported Transaminitis	5 (18.5)
Transaminitis after 1 dose	1 (3.7)
Transaminitis after 2 doses	3 (11.1)
Transaminitis after unknown doses	1 (3.7)
No AEs reported	22 (81.5)

AE = adverse event, BCV - brincidofovir.

CONCLUSIONS

- Patients identified (N=27) had an average age of 34.3 years, were primarily males (88.5%), were HIV positive (81.5%), and had CD4+ counts <100 cells/mL (90.0%).
- BCV was used as a first line monotherapy in 5 patients (18.5%) and initiated in an average of 8.8 days after rash onset. All patients given BCV as first line monotherapy survived, with improvements in lesion crusting and fever within 72 hours.
- BCV was used as a first line combination therapy in 3 patients (11.1%) and initiated within an average of 35 days of rash onset, resulting in 100% survival.
- Adverse events following BCV treatment were reported in 5 patients (18.5%) and 80% of these adverse events were transient transaminitis reported after 1 or 2 doses. Transaminitis is an expected adverse event based on the labelling.
- Survival was lower in later treatment (33% – 58%), reinforcing the need for early treatment of antivirals.
- BCV monotherapy is currently being evaluated in a randomized, double-blind, placebo-controlled Phase 3 trial in the Democratic Republic of Congo.

LIMITATIONS

The number of cases analyzed is a small sample size and details on each case were not consistently reported. Where feasible, data for common variables has been collated to aid in interpretation.

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