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# BRINCIDOFOVIR (CMX001) FOR THE TREATMENT OF SERIOUS OR LIFE-THREATENING DOUBLE-STRANDED DNA VIRUS INFECTIONS IN PATIENTS RECEIVING LIVER TRANSPLANT AS PART OF MULTIORGAN TRANSPLANTATION

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## INTRODUCTION

Brincidofovir (BCV) is a lipid conjugate nucleotide in Phase 3 clinical development for the prevention of cytomegalovirus (CMV) infection in hematopoietic stem cell transplant (HCT) recipients. BCV is administered orally, circulates as BCV, and is converted to the active antiviral, cidofovir diphosphate (CDV-PP), within cells. BCV shares the *in vitro* broad-spectrum antiviral activity of cidofovir (CDV) against all five families of double-stranded DNA (dsDNA) viruses which cause disease in humans. The 50- to 500-fold improved *in vitro* antiviral activity of BCV versus CDV has been hypothesized to result from more efficient transport of circulating BCV across the cell membrane.

Over 400 patients have received BCV for serious or life-threatening infections with dsDNA viruses under expanded access programs (Study CMX001-350, clinicaltrials.gov ID: NCT01143181 or under emergency investigational new drugs applications [EINDs]). The case series described consists of three EIND cases (4, 5, and 7) and seven cases from Study CMX001-350.

### Case Summaries

Ten multiorgan transplant patients (liver [L] ± kidney [K]/pancreas [P]/small bowel [SB]) were treated with BCV for serious or life-threatening adenovirus (AdV), BK virus (BKV), cytomegalovirus (CMV), Epstein-Barr virus (EBV) or varicella zoster virus (VZV) infections after failing existing antiviral therapies.

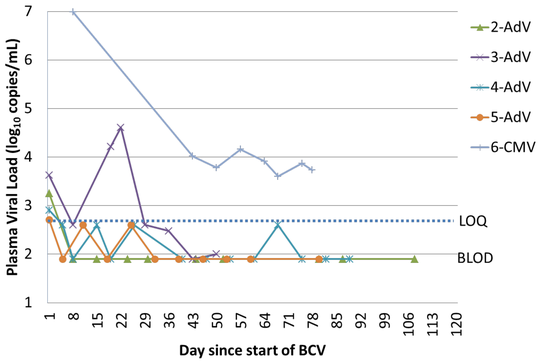
| Case | Age (years)/ Weight (kg)/ Race/Sex | Transplants | Primary Infection | Prior Antiviral Exposure | Initial BCV Dose | Viremia at Start of BCV Treatment ($log_{10}$ copies/mL) |
|---|---|---|---|---|---|---|
| 1 | 4/19.9/W/F | L/K/P/SB | EBV | Ig for CMV prophylaxis* | 4 mg/kg BIW | >7.7 |
| 2 | 3/NC/W/F | L/P/SB | AdV | GCV | ~2 mg/kg BIW | 3.3 |
| 3 | 15/50.4/W/F | L/P/SB | AdV | vACV, CDV, ACV | 100 mg BIW | 3.6 |
| 4 | 1.4 /10.4/NC/M | L/P/SB | AdV | CDV, GCV, ACV, Ig for CMV prophylaxis* | 4 mg/kg BIW | 2.9 |
| 5 | 0.5/4/NC/M | L/P/SB | AdV | CDV | 5 mg/kg BIW | 2.7 |
| 6 | 2/14.9/B/M | L/P/SB | CMV | vGCV, Ig for CMV prophylaxis* | 3.4 mg/kg BIW | 7.0 |
| 7 | 1.8/13.8/NC/F | L/P/SB | EBV | GCV, CDV | 4 mg/kg BIW | 7.7 |
| 8 | 4/14.3/W/F | L/K | BKV | CDV | 4 mg/kg QW | 4.3 |
| 9 | 13/44.5/W/F | L/K | VZV | ACV | ~2 mg/kg BIW | No Viremia |
| 10 | 2/15/B/F | L/SB | AdV | CDV, GCV, Ig for CMV prophylaxis | 2.7 mg/kg BIW | 7.4 |

NC= not collected, *= ongoing; GCV= gangciclovir, vACV= valaciclovir, ACV= acyclovir, Ig= immunoglobulin, BIW= twice a week, QW= once a week

| Case | Histories |
|---|---|
| 1 | L/K/P/SB transplants; pancytopenia; liver failure from total intestinal aganglionosis (Hirschsprung's disease); and renal dysplasia due to novel mutation of RET gene; multi-drug-resistant *Pseudomonas* pneumonia, peritonitis, bacteremia, and fungemia; and EBV viremia. Commenced BCV at 4 mg/kg BIW, then decreased to 2 mg/kg BIW (at Day 14 post BCV start). **BCV Trt Duration: 3 weeks** |
| 2 | L/K/P transplants; meconium peritonitis, inferior vena cava stenosis, hypertension, renal tubular acidosis type IV, grade 2 acute cellular rejection of intestinal graft, gastrointestinal bleeding, bowel resection, fever, dehydration, and transplant rejection. **BCV Trt Duration: 12 weeks** |
| 3 | L/K/P transplants; posterior reversible encephalopathy syndrome with seizures; grade I graft versus host disease of the colon; hemolytic anemia; *Candida* esophagitis; acute renal failure; *Pseudomonas* bacteremia; and sepsis. Prior to treatment with BCV, vACV and ACV were used to treat herpes oral lesions and disseminated VZV infection. IV CDV was also adminstered for AdV infection prior to BCV. **BCV Trt Duration: 26 weeks** |
| 4 | L/K/P transplants; AdV viremia; respiratory syncytial virus upper respiratory infection; renal failure requiring dialysis; lethargy and seizures, aseptic/viral meningoencephalitis. Because of a persistently positive blood AdV by PCR despite ongoing treatment (77-days) with IV CDV, there was a concern that there might be encephalitis due to AdV resistant to CDV. Since condition deteriorated while on treatment with IV CDV, emergency access to BCV treatment was granted. **BCV Trt Duration: 13 weeks** |
| 5 | L/K/P transplants; decreased renal function and urine output; *Pseudomonas* infection; AdV viremia (~2,800 copies/mL). Initiated IV CDV 5 mg/kg/week and after one week AdV viremia increased to ~10,800 copies/mL with no clinical improvement. BCV was requested due to lack of response to high-dose IV CDV and concern that continuing treatment may have promoted virus resistance. **BCV Trt Duration: 12 weeks** |
| 6 | L/K/P transplants; mild cellular rejection (small bowel); respiratory distress; CMV and possible AdV pneumonia. Prior treatment with vGCV for CMV infection. Commenced BCV 50 mg BIW for CMV and AdV infection, but then decreased to 25 mg BIW (at Day 56 post BCV start). **BCV Trt Duration: 12 weeks** |
| 7 | L/K/P transplants; EBV D-/R+ and CMV D+/R+; EBV viremia was 170,000 copies/mL; cervical, axillary and inguinal lymphadenopathy; respiratory failure. Initiated GCV and repeat EBV viremia was >50 million copies/mL; leukopenia without neutropenia and thrombocytopenia; renal failure. Prior to BCV treatment, GCV and IV CDV were used without response. **BCV Trt Duration: 4 weeks** |
| 8 | L/K transplants; atypical hemolytic uremic syndrome. IV CDV was administered QW for 3 weeks for BK viremia and uremia prior to treatment with BCV. **BCV Trt Duration: 10 weeks** |
| 9 | L/K transplants; polycystic kidney disease, bilateral nephrectomy, peritoneal dialysis, sepsis secondary to bacteremia, idiopathic hepatic fibrosis with recurrent cholangitis, seizure disorder, urinary incontinence, chronic rejection, chronic kidney disease, anemia, hyperglycemia, VZV infection. ACV was used to treat the disseminated skin VZV infection for 20 days prior to BCV treatment. **BCV Trt Duration: 1 week** |
| 10 | L/SB transplants; premature birth at 26 weeks, short gut syndrome, necrotizing enterocolitis, AdV infection, and persistent respiratory failure. Hypoxic respiratory failure secondary to AdV pneumonitis and *Enterococcus* superinfection. For CMV prophylaxis, Ig and GCV were used prior to and intermittently with BCV. Prior to BCV, IV CDV was used to treat AdV infection for 10 days. Commenced BCV 2.7 mg/kg BIW, then decreased to 1.3 mg/kg BIW (at Day 3 post BCV start). **BCV Trt Duration: 1 week** |

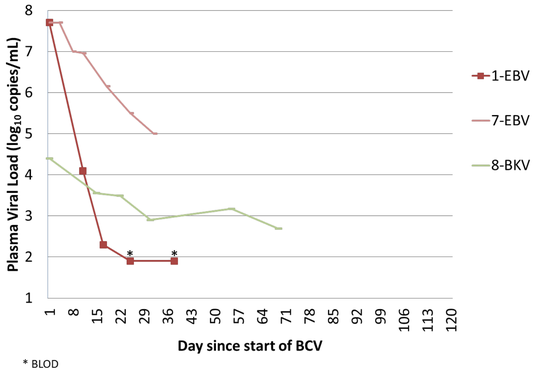
## RESULTS

**Figure 1.** Change in AdV or CMV Viremia during and after BCV Treatment for Cases 2, 3, 4, 5, and 6



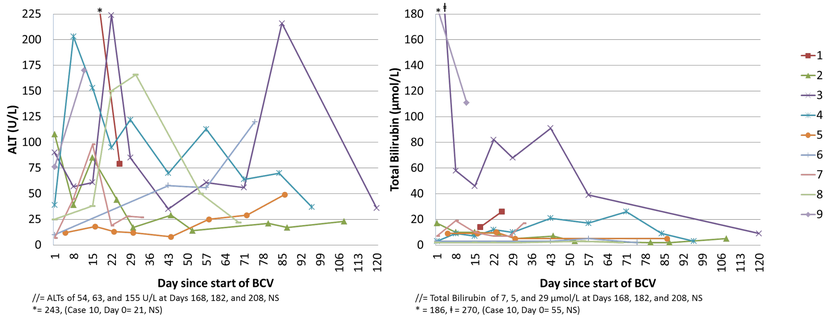

**Case 10-AdV**/Day 0 = 7.4, Not Shown (NS); No post-baseline viremia assessments
LOQ = Limit of Quantitation, BLOD = Below Limit of Detection

**Figure 2.** Change in EBV or BKV Viremia during and after BCV Treatment for Cases 1, 7, and 8




* BLOD

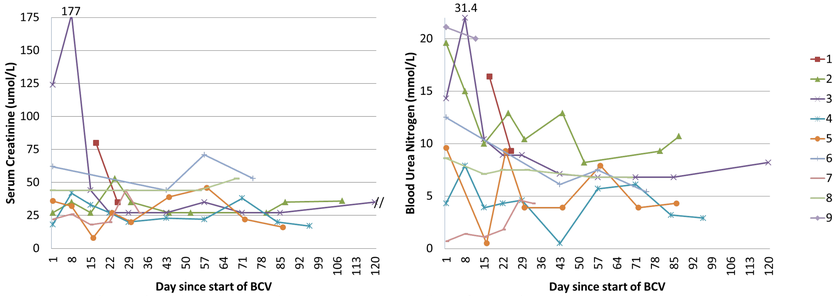
**Figure 3.** Liver Function during and after BCV Treatment as Measured by Alanine Aminotransferase (ALT) and Total Bilirubin




//= ALTs of 54, 63, and 155 U/L at Days 168, 182, and 208, NS
*= 243, (Case 10, Day 0= 21, NS)

//= Total Bilirubin of 7, 5, and 29 µmol/L at Days 168, 182, and 208, NS
* = 186, † = 270, (Case 10, Day 0= 55, NS)

**Figure 4.** Kidney Function during and after BCV Treatment as Measured by Serum Creatinine and Blood Urea Nitrogen (BUN)




//= Creatinine of 35, 44, and 44 µmol/L at Days 168, 182, and 208, NS
(Case 9, Day 0= 265, Day 11=275, NS), (Case 10, Day 0= 55, NS)

//= BUN of 7.1, 4.6, and 8.6 mmol/L at Days 168, 182, and 208, NS
(Case 10, Day 0= 8.9, NS)

**Table 1.** Drug-related Adverse Events and Outcome*

| Case | Initial BCV Dose | Adverse Event (Preferred/verbatim) | Serious | Duration (days) | CTCAE Grade (Severity) | Action | Outcome |
|---|---|---|---|---|---|---|---|
| 2 | ~2 mg/kg BIW | Diarrhea/Worsening diarrhea | Yes | 13 | 3 (Severe) | Dose not changed | Recovered |
| 3 | 100 mg BIW | Leukopenia/Leukopenia | No | 6 | 1 (Mild) | Dose not changed | Recovered |
| 8 | 4 mg/kg QW | Alanine aminotransferase increased/ Elevated ALT | No | 16 | 2 (Moderate) | Dose interrupted | Recovered |
| 8 | 4 mg/kg QW | Gamma-glutamyltransferase increased/Elevated GGT | No | 39 | 2 (Moderate) | Dose interrupted | Recovered |

* Causality not assessed for EIND patients (Cases 4, 5, and 7)

## SUMMARY

- BCV reduced dsDNA viremia in multiorgan transplant patients (liver ± kidney/pancreas/small bowel)
  - 4/4 patients with AdV*
  - 1/1 patients with CMV
  - 2/2 patients with EBV
  - 1/1 patients with BKV

  (* with at least one post-baseline viremia assessment)
- BCV resolved VZV skin lesions in one patient (Case 9)
- Overall, liver function improved or remained stable as assessed by ALT and total bilirubin
- Renal function improved or remained stable as assessed by BUN and serum creatinine
- There were no serious drug-related hepatic adverse events or drug-related adverse events that lead to discontinuation of BCV
- Two patients died while receiving BCV; both deaths assessed as unrelated to BCV
  - Case 7- intracranial haemorrhage
  - Case10- hepatic failure secondary to aortic thrombus
- Two patients died >30 days after receiving BCV
  - Case 1- post-transplant lymphoproliferative disease / *Pseudomonas* pneumonia
  - Case 3- septic shock

## CONCLUSIONS

- BCV demonstrated antiviral activity against dsDNA virus infections in these 10 cases
- BCV appeared to be safe and well tolerated in this small, uncontrolled liver ± kidney/pancreas/small bowel transplant patient population
- These data support the continued study of BCV for the treatment of dsDNA virus infections in SOT and other immunocompromised patients.

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