2014 World Transplant Congress
San Francisco, California USA

D2364

Brincidofovir (CMX001) Experience in Renal Transplant Patients for Treatment of Refractory CMV Infection

Kathleen Mullane[1] DO, Diana Florescu[2] MD, Jo-Anne Young[3] MD, Eun Kwak[4] MD, Maggie Anderson[5] BS, Tom Brundage[5] MS, Herve Mommeja-Marin[5] MD
[1]Univ of Chicago, [2]Univ of Nebraska, [3]Univ of Minnesota, [4]Univ of Pittsburg, [5]Chimerix, Inc.

ABSTRACT

Brincidofovir (CMX001, BCV) is an oral nucleotide analog, in Phase 3 development for prevention of cytomegalovirus (CMV) and treatment of adenovirus (AdV) infections. BCV has broad-spectrum *in vitro* antiviral activity against double stranded DNA (dsDNA) viruses, including CMV, AdV, BK virus and herpes simplex viruses. BCV was administered in patients with refractory or resistant dsDNA viral infections, including CMV infections, in an expanded access protocol (Study 350).

Renal transplant patients with refractory CMV infection who received BCV ≥ one week were evaluated for safety and efficacy. Five transplant patients (4 renal and 1 renal/pancreas) with resistant or refractory CMV infection received BCV 100-200 mg twice weekly.

Five adult patients (44-56 years of age) were treated with BCV for CMV viremia (3/5 viremia only) and/or CMV syndrome (2/5). Three patients received 2 or more renal transplants prior to BCV treatment. All patients received immunosuppressants (IS) and one had an increase in IS therapy during BCV treatment. All received previous treatments for CMV (foscarnet 2/5, GCV 1/5, vGCV 3/5). Initial BCV doses ranged from 100 to 200 mg twice weekly with a median duration of treatment of 91 days (10-171). At the completion of treatment, three patients had a complete virologic response (<LOD, 100c/mL), one had a -2.4 $\log_{10}$ response, and one had an increase of +0.4 $\log_{10}$. Resistance testing confirmed pre-existing viral resistance to GCV in 4/5 patients with one patient developing CDV resistance on therapy. The most common adverse event was diarrhea (3/5 patients); one of the patients with unresolved viral infection was withdrawn due to diarrhea on day 10. The other patient with unresolved viral infection was withdrawn due to worsening CMV viremia at day 147 after an increase in IS therapy. CMV viral infection resolved while receiving BCV monotherapy in 3 of 5 patients.

Patients with resistant and refractory CMV, who have failed standard therapies, may respond to BCV treatment. Further evaluation of BCV for treatment and prevention of dsDNA viral infections, especially CMV, is warranted.

INTRODUCTION

Brincidofovir is a lipid conjugate of the nucleotide analog, cidofovir (CDV). Lipid conjugation results in higher intracellular concentrations of the active antiviral *in vitro* and lower peak plasma concentration of CDV. This significantly lowers the risk of CDV-like nephrotoxicity, particularly important in the renal transplant population. Over 1000 individuals have received BCV in Phase 1-3 clinical trials and through emergency request (EIND or foreign equivalent).

Brincidofovir was provided through expanded access to a total of 210 subjects with life threatening or serious disease/condition caused by dsDNA viral infection(s) (Study 350). The most common primary dsDNA viral infection in study 350 was CMV (107/210, 51%).

This subset of 5 adult subjects (ages 44-56 years of age) received renal or renal/pancreas transplants prior to BCV treatment with 3/5 subjects receiving two or more transplants. These subjects had received prior antiviral therapy and were considered to have resistant or refractory CMV by the investigator. Each subject had confirmed CMV syndrome and/or viremia at the start of dosing and received at least four doses (two weeks) of BCV. Initial BCV doses were 100-200 mg administered BIW with the mean duration of treatment of 91 days (range 10 -171 days).

Table 1. Baseline Characteristics

Sub #	# Renal Transplants	Underlying Condition	Reason BCV Requested
027	3	Chronic kidney disease, TX rejection, nephropathy	Viremia, resistant to GCV
100	1	ESRD, hypertensive nephrosclerosis	Viremia, acute renal failure on FOS, resistant to GCV, UL97 mutation
154	2	Polycystic kidney disease	Viremia, CMV syndrome, pancytopenic on GCV, thrombocytopenia
170	3	Post urethral syndrome	Persistent CMV viremia during vGCV
230	1	Polycystic kidney disease	CMV syndrome on vGCV, UL97 mutation, GFR <50 mL/min

RESULTS

ADVERSE EVENTS

Adverse events were reported in 4/5 subjects with one subject reporting no AEs. The most common AE was diarrhea reported in three subjects. Nine AEs, all GI related, were assigned by the investigator as probably related to BCV. Two subjects were withdrawn from the study due to adverse events. Subject 027 was withdrawn at D147 due to a Grade 5 SAE of worsening CMV viremia. Genotypic analysis confirmed emergence of resistance to CDV. Subject 230 was withdrawn at D10 due to an SAE of Grade 3 diarrhea and abdominal cramping. These adverse events resolved approximately 1 week following drug discontinuation.

Table 2. Adverse Events During Treatment

Sub #	AEs	SAEs
027	diarrhea, CMV colitis, ESRD, hypokalemia, nausea, hypotension, fever, altered mental status, emesis, hypocalcemia, candiduria, neutropenia, Klebsiella, malnutrition, hypervolemia, bacteremia	worsening CMV viremia
100	nausea[1], GI viral infection	none
154	Diarrhea[1], dyspepsia[1], c. diff . diarrhea, hypokalemia	DVT, malabsorption
170	none	none
230	diarrhea[1], retching[1], nausea[1], vomiting[1], chills, fatigue, worsening GERD, abdominal pain/tenderness, gray sputum, asthenia, decreased appetite	diarrhea[1], abdominal pain[1]

1. Investigator assigned AE as probably related to treatment.

VIROLOGY

All five renal transplant subjects had resistant or refractory CMV infections and had received antiviral therapy prior to beginning BCV. Four subjects had confirmed pre-existing viral resistance to GCV.

- Three subjects who had failed other antiviral therapy achieved a sustained and complete virologic response while on therapy with BCV monotherapy.

Table 3. Virologic Response

Sub #	Prior AV	BCV Dosed (days)	Viremia (BL, c/mL)	Viremia (LOT, c/mL)	Virologic Response (LOT)
027	FOS	147	428,000	1800 (D124)	-2.38 $\log_{10}$
100	vGCV, FOS	171	1000	ND (D140)	< LOD
154	GCV	91	ND[1]	ND (D76)	< LOD
170	vGCV	91	1900	ND (D90)	< LOD
230	vGCV	10	62,000	157,000 (D7)	+0.4 $\log_{10}$

ND=undetectable, BL=baseline/D1, LOT=last on-treatment viral load, LOD=limit of detection, AV=anti-viral
1. Subject 154 had detectable viremia w/ CMV syndrome at the time of the Investigator's request for BCV (local lab CMV PCR 3000 c/mL). VL was undetectable at D1 and remained undetectable through the M1 follow-up visit.

Subject 027 showed a -2.38 $\log_{10}$ response at the last measured VL while on treatment (D124). Subject was withdrawn at D147 due to worsening CMV viremia. During BCV treatment, this subject also received foscarnet (D58 through EOS) and an increase in IS therapy. Genotypic analysis confirmed emergence of CDV resistance 4 months following start of treatment with BCV.

Subject 230 had a +0.4 $\log_{10}$ increase on D7 following 2 doses of BCV (last measured VL while on treatment). The subject received a total of 4 doses (two weeks) of BCV and was withdrawn on D10 due to diarrhea.

LABORATORY

Table 4. Renal Function Laboratory Results

Sub #	Cr (BL, umol/L)	Cr (LOT, umol/L)	GFR (BL, mL/min/1.73m^2)	GFR (LOT, mL/min/1.73m^2)	BUN (BL, mmol/L)	BUN (LOT, mmol/L)
027	248	124	19	43	16.8	2.5
100	354	248	15	23	15.7	4.6
154	159	310	41	19	15.0	6.1
170	88	106	106	85	5.4	5.7
230	115	141	46	36	6.4	7.5

BL=baseline/D1, LOT=last on-treatment lab evaluation

SUMMARY

In clinical studies to date, antiviral activity of Brincidofovir has been observed against a wide range of dsDNA viruses including CMV, ADV, BK virus and herpes simplex viruses. Brincidofovir was provided through expanded access to 210 patients with life threatening or serious disease caused by dsDNA infections (Study 350)

Five CMV infected renal transplant recipients who had exhausted other therapeutic options, including pre-existing viral resistance to GCV in 4 of 5 subjects, received BCV monotherapy.

- Investigators reported the CMV infection resolved in 3/5 subjects during BCV monotherapy.
- There were 9 treatment emergent adverse events reported which were attributed as related to BCV therapy (3 diarrhea, 2 nausea, 1 retching, 1 vomiting, 1 dyspepsia, and 1 abdominal pain).
- The most common adverse event was diarrhea which is also the most prevalent adverse event in clinical studies to date.
- There were no remarkable shifts in renal function laboratory findings in subjects treated with BCV for a mean duration of 91 days (10-171).
- One subject discontinued for drug-related adverse events.
- One subject developed CDV resistance following 4 months of treatment with BCV.

CONCLUSIONS

- Patients with resistant and refractory CMV, who have failed standard therapies, may respond to BCV.
- Further evaluation of BCV for treatment and prevention of dsDNA viral infections, especially CMV, is warranted.

The authors gratefully acknowledge the patients who participated in this study, the hardworking study staff at these institutions and the funding of this study through BARDA Contract HHSO10020110013C.