Preliminary Data from 13 Liver Transplantation Patients who Received Brincidofovir (BCV) for Adenovirus (AdV) Infection

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ABSTRACT

Background: Adenovirus (AdV) causes significant morbidity and mortality following solid organ transplant, including liver transplant (liver transplantation). The rate of AdV infection in liver transplantation patients varies from 3.5%–38%, with mortality up to 53%. There are no FDA-approved treatments for AdV. Brincidofovir (BCV), a nucleotide analog with broad-spectrum in vitro antiviral activity against double-stranded DNA viruses, is in Phase 3 development for treatment of AdV infection. We present preliminary survival, virologic response, and tolerability data from liver transplantation patients treated with BCV for AdV infection.

Methods: Pediatric and adult patients who received isolated liver transplantation and multi-organ transplantation including liver were identified from studies CMX001-304 (NCT02087306) and CMX001-350 (NCT01143181) (studies of ⩾12 weeks' treatment duration); and emergency INDs. Assessments included change from baseline AdV viral load (VL), time to nadir VL, and safety/tolerability.

Results: Thirteen liver transplantation recipients, including 10 multi-organ patients, received BCV for AdV infection. The majority (n=10) were pediatric patients with a median age of 21 months (range: 6 months, 13 years), and 9 (69%) were male. Three patients (all female) were ⩾15 years of age with a median age of 17 years (15, 31 years). Across the 13 patients, median baseline plasma AdV VL was 3.4 $\log_{10}$ c/mL (undetectable, 10.0 $\log_{10}$ c/mL). Median change from baseline in VL was –1.3 $\log_{10}$ c/mL (–8.0, –0.3 $\log_{10}$ c/mL), and median time to nadir VL was 15 d (4, 96 d). In patients followed for >28 d (n=10), all were alive at time of evaluation, with median change in AdV VL of –1.1 $\log_{10}$ c/mL. In patients (n=3) followed for <28 d, 1 died. In 1 patient (out of 13 patients), treatment was discontinued because of a BCV-related adverse event (AE) (diarrhea). No BCV-related clinical hepatobiliary AEs were reported, with aminotransferase levels remaining stable or declining during treatment. Median change in alanine transaminase was +4 U/L (–507, +106 U/L), aspartate transaminase –1 U/L (–691, +35 U/L), bilirubin –0.05 mg/dL (–15.5, +4.1 mg/dL), and creatinine +0.1 mg/dL (–0.9, +2.5 mg/dL).

Conclusions: Preliminary pooled data from several liver transplantation patients with AdV infection suggest that treatment with BCV can reduce viral burden and is associated with favorable survival. BCV was tolerated, with no clinical hepatobiliary AEs reported in these liver transplantation patients.

INTRODUCTION

- Adenovirus (AdV) causes significant morbidity and mortality following solid organ transplantation (SOT), including liver transplantation.[1–3]
  - The rate of AdV infection in liver transplantation patients is 3.5%–38%,[3] with an associated mortality rate in children of up to 53%.[1]
- There is an unmet need for drugs to reliably treat AdV infection, as there are no current FDA-approved treatments.
- Brincidofovir (BCV) is an orally available lipid conjugate of the nucleotide analog cidofovir.
- BCV has activity in vitro against several types of double-stranded (ds)DNA viruses, including orthopoxvirus, polyomavirus, human herpesvirus, human papillomavirus, and AdV.[4]
- BCV is in development for multiple indications, including the prevention of cytomegalovirus (CMV) and the treatment of AdV infection.
- Data from an ongoing clinical development program suggest that BCV shows potential for treating AdV infection, without significant nephro- or myelotoxicity, and manageable gastrointestinal adverse events (AEs).[4–6]

OBJECTIVE

- To present preliminary virologic response, survival, and tolerability data from liver transplantation recipients who have received BCV for AdV infection.

METHODS

- Pediatric and adult patients who underwent isolated liver transplantation or multi-organ transplantation, including liver allograft, were identified from studies CMX001-304 (AdVise; NCT02087306) and CMX001-350 (NCT01143181), and among patients treated under emergency use (EIND) regulations.
- CMX001-304 (AdVise) is a Phase 3, open-label, parallel-group, multicenter study that included recipients of allogeneic hematopoietic cell transplant and SOT, and is assessing BCV for the treatment of AdV infection.
  - Patients were eligible to enroll if they were aged 2 months or older with asymptomatic AdV viremia or symptomatic AdV infection (local infection or disseminated disease).
  - The study comprised a 12-week treatment period in which patients weighing ⩾50 kg received BCV 100 mg twice weekly (BIW), and patients weighing <50 kg received weight-based doses of 2 mg/kg BIW, not exceeding 200 mg of BCV weekly.
    - This was followed by a post-treatment follow-up period of ⩾12 weeks.
- CMX001-350 was an open-label, multicenter, expanded-access study.
  - It included patients aged 1 month or older with immediately life-threatening or serious disease caused by ⩾1 dsDNA virus infections, including CMV, AdV, and BK virus, and no other therapeutic options.
  - BCV was administered until clinical disease was resolved or stabilized and/or viral DNA testing was negative for 4 consecutive weeks, whichever was longer, for up to 6 months. Initially, BCV was administered at 200 or 300 mg BIW (adults and adolescents 13–17 years) or 4 mg/kg BIW (pediatric patients ⩽12 years), depending on clinical condition; in April 2011 dosing was standardized to the currently recommended doses of 100 mg BIW (adults and adolescents 13–17 years) or 2 mg/kg BIW (pediatric patients ⩽12 years).
- EIND patients were dosed as described above for CMX001-350 patients, including the dose change, except that mg/kg dosing was used for all pediatric patients <18 years.
- Assessments included changes from baseline in AdV viral load (VL), time to nadir VL, survival, and safety and tolerability.
- The lower limit of detection for the AdV DNA qPCR assay was 2.00 $\log_{10}$ or 100 copies/mL; the lower limit of quantification (LLOQ) was 2.28 $\log_{10}$ or 190 copies/mL (304 and 350 patients). For continuous analyses and plots, these values were imputed for target not detected (TND) and <LLOQ values, respectively.

RESULTS

Baseline characteristics

- Baseline characteristics for each individual patient are shown in **Table 1**.
- Thirteen liver transplantation recipients, including 10 multi-organ transplant patients, received BCV for AdV infection.
  - The majority (n=12) were <18 years old with a median (range) age of 3.1 (0.6, 17.2) years. One adult patient was 31.9 years old.
  - Seven patients (54%) were male.
  - Eight patients had disseminated AdV disease.
  - Five patients had prior exposure to cidofovir.
- Median baseline plasma AdV VL was 3.4 $\log_{10}$ copies/mL (range: TND to 10.0 $\log_{10}$ copies/mL).

Antiviral activity

- Median reduction (range) from baseline in VL was –1.19 (–0.28, –8.00) $\log_{10}$ copies/mL and median (range) time to nadir VL was 15 (4, 96) days.
- All patients with AdV viremia or localized infection (n=5) survived; 1 of 8 patients with disseminated AdV disease died.
- Treatment duration and virologic response are summarized in **Table 2**, while the change from baseline in AdV VL with BCV treatment is shown in **Figure 1**.
- Ten of the 11 patients with available data had a last on-treatment AdV VL below LLOQ.

Table 1. Baseline characteristics.

Patient	Study	Transplant	Age (years)	Sex	Race	Time from transplant to first dose (days)	Baseline disease status	Prior CDV exposure	BCV dosing schedule
1	304	Liver, pancreas, small bowel	0.7	Male	White	35	Asymptomatic viremia	No	2 mg/kg BIW
2	304	Liver, pancreas, small bowel	6.2	Female	Black	1102	Disseminated disease	No	2 mg/kg BIW
3	304	Liver, small bowel	4.9	Male	Black	832	Asymptomatic viremia	No	2 mg/kg BIW
4	304	Liver, pancreas, small bowel	31.9	Female	White	32	Disseminated disease	No	100 mg BIW
5	304	Liver, pancreas, small bowel	1.5	Male	Other	59	Asymptomatic viremia	No	2 mg/kg BIW
6	304	Liver	17.2	Female	White	48	Disseminated disease	No	100 mg BIW
7	304	Liver	1.2	Male	White	25	Disseminated disease	Yes	2 mg/kg BIW
8	304	Liver	13.8	Male	White	21	Localized infection	Yes	2 mg/kg BIW
9	350	Liver, pancreas, small bowel	15.1	Female	White	433	Localized infection	Yes	100 mg BIW, then 90–100 mg BIW (based on weight)
10*	350	Liver, small bowel	2.6	Female	Black	17	Disseminated disease	No	40 mg, then 20 mg
11	350	Liver, pancreas, small bowel	3.7	Female	White	957	Disseminated disease	No	2 mg/kg BIW
12	EIND	Liver, pancreas, small bowel	1.5	Male	White	110	Disseminated disease	Yes	3.8 mg/kg BIW†
13	EIND	Liver, pancreas, small bowel	0.6	Male	Other	41	Disseminated disease	Yes	5 mg/kg BIW†

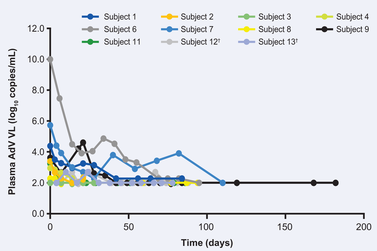
*Patient died as a result of hepatic failure, which was assessed as unrelated to BCV.
†Doses are higher than currently recommended as treatment began prior to April 2011 when BCV dose was still standardized at 200 or 300 mg or 4 mg/kg BIW.
BCV: brincidofovir; BIW: twice weekly; CDV: cidofovir; EIND: emergency investigational new drug application.

Table 2. VL over time with BCV treatment.

Patient	BCV treatment duration (days)	Number of BCV doses	Baseline AdV VL ($\log_{10}$ copies/mL)	Nadir on-treatment AdV VL ($\log_{10}$ copies/mL)	Time to nadir on-treatment AdV VL (days)	Last on-treatment AdV VL ($\log_{10}$ copies/mL)	Change in VL to last on-treatment day ($\log_{10}$ copies/mL)
1	57	16	4.39	<LLOQ	43	<LLOQ	–2.11
2	15	5	3.40	TND	15	<LLOQ	–1.12
3	26	8	TND	TND	5	TND	0
4	8	3	2.95	<LLOQ	15	<LLOQ	–0.68
5	12	4	TND	ND	ND	ND	ND
6	91	26	10.00	TND	96	TND	–8.00
7	82	16	5.74	<LLOQ	29	3.91	–1.83
8	88	25	<LLOQ	TND	8	TND	–0.28
9	180	42	3.62	TND	42	TND	–1.63
10*	4	2	7.40	ND	ND	ND	ND
11	80	17	3.26	TND	7	TND	–1.26
12	89	22	2.91	TND	7	TND	–0.91
13	79	20	2.72	TND	4	TND	–0.72
Median (min, max)			3.40 (TND, 10.00)	TND (TND, <LLOQ)	15 (4, 96)	TND (TND, 3.91)	–1.19 (–8.00, –0.28)

*Patient died as a result of hepatic failure, which was assessed as unrelated to BCV.
For continuous analyses, 2.00 and 2.28 were imputed for values that were TND and <LLOQ, respectively.
AdV: adenovirus; BCV: brincidofovir; LLOQ: lower limit of quantification; ND: no data available; TND: target not detected; VL: viral load.

Figure 1. Change in AdV VL* in plasma through the end‡ of BCV treatment.



*Data not available for patients 5 and 10.
†Data are for change in whole blood VL.
‡Last data entry was 7 days after end of treatment if available.
AdV: adenovirus; BCV: brincidofovir; VL: viral load.

Adverse events and laboratory parameters

- One of 8 patients with disseminated AdV disease died as a result of hepatic failure that was assessed by the investigator as related to an aortic conduit clot and unrelated to BCV.
- As expected in this population, patients had numerous AEs, which were not related to study drug but rather to the underlying condition.
  - A summary of treatment-related AEs is shown in **Table 3**.
  - Two treatment-related AEs were assessed as serious (Grade 3 diarrhea in 1 patient and Grade 2 increased stool volume in 1 patient). Both events resolved.
- No BCV-related clinical hepatobiliary AEs were reported, with transaminase levels generally remaining stable or declining during treatment (**Figure 2**).
  - Median (range) changes from baseline until last on-treatment value were: alanine aminotransferase (ALT) +2.5 (–507, +51) U/L, aspartate transaminase (AST) –5 (–691, +81) U/L, bilirubin 0 (–15.5, +7.9) mg/dL, and creatinine +0.1 (–0.9, +2.5) mg/dL.

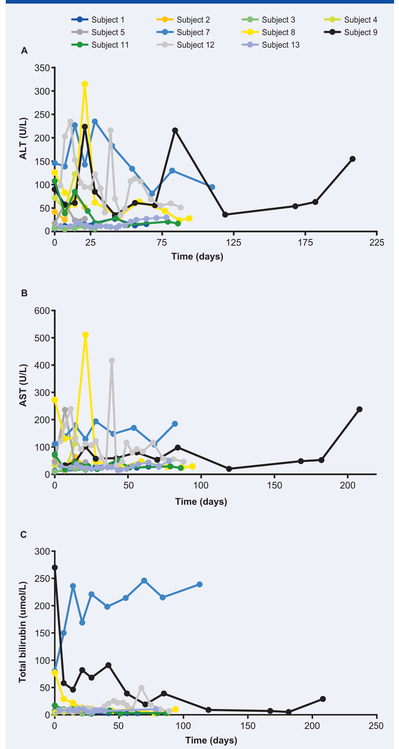
Table 3. BCV-related AEs.

Treatment-related AEs	Diarrhea (n=1), increased stool volume (n=1), leukopenia (n=1)
Treatment-related serious AEs	Diarrhea (n=1), increased stool volume (n=1)
Treatment-related AEs of ⩾Grade 3 in severity	Diarrhea (n=1)
Treatment-related AEs requiring discontinuation of BCV therapy	n=1*
All deaths	n=1†
All deaths related to BCV therapy	n=0

*BCV therapy was interrupted owing to increased stool output. However, BCV treatment was not restarted, because the patient's AdV infection had resolved/improved.
†Patient died of hepatic failure assessed by the investigator as being related to underlying disease (aortic conduit clot) and unrelated to BCV.
AdV: adenovirus; AE: adverse event; BCV: brincidofovir.

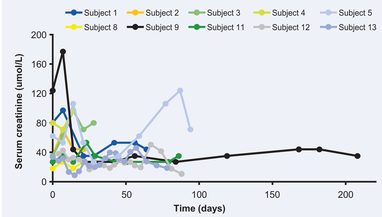
- Changes from baseline in serum creatinine are shown in **Figure 3**.
- No clinically relevant drug-related neutropenia or myelosuppression was reported during treatment.

Figure 2. Serum aminotransferase and bilirubin levels (A) ALT,* (B) AST,* and (C) total bilirubin* through the end‡ of BCV treatment.



*Data not available for patients 6 and 10.
‡Last data entry was 7 days after end of treatment if available.
ALT: alanine aminotransferase; AST: aspartate transaminase; BCV: brincidofovir.

Figure 3. Serum creatinine* through the end‡ of BCV treatment.



*Data not available for patients 6, 7, and 10.
‡Last data entry was 7 days after end of treatment if available.
BCV: brincidofovir.

CONCLUSIONS

- **Although uncontrolled, the preliminary data from these 13 liver transplant patients with AdV infection suggest that treatment with BCV can reduce AdV viral load and may be associated with favorable outcomes.**
  - **In particular, 7 of 8 patients with disseminated AdV disease survived, with a median reduction in AdV viral load of –1.2 $\log_{10}$ copies/mL.**
  - **Survival in this predominantly pediatric liver transplant cohort with AdV compares favorably to published data (up to 53% mortality).[1]**
- **No BCV-related clinical hepatobiliary AEs were reported in these patients.**
- **These data support the continued study of BCV for the treatment of AdV infections in SOT, including liver transplantation.**

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