Safety, Tolerability, Pharmacokinetics and Pharmacodynamic Activity of Terlipressin Delivered by Continuous Intravenous Infusion in Patients with Cirrhosis and Refractory Ascites: A Phase 2a Open-Label Trial.

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INTRODUCTION

Patients with cirrhosis and refractory ascites lack long-term pharmacological treatment options and typically suffer poor outcomes with 50% mortality occurring over 6-12 months. The vasoconstrictor terlipressin, which is not approved in the US, may reduce ascites. Where approved ex-US for indications other than the treatment of ascites, terlipressin is administered as bolus dosing with use limited to a hospital setting.

AIM

A Phase 2a trial was conducted to evaluate the safety, pharmacokinetics (PK) and preliminary efficacy of BIV201, terlipressin administered as a continuous infusion, for 28 days, as a treatment for refractory ascites in six cirrhotic patients.

METHOD

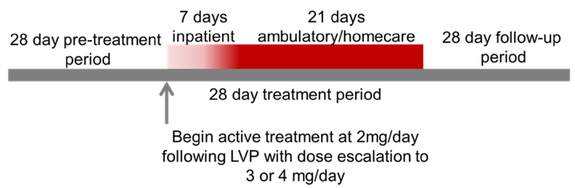
Six adult male patients with decompensated cirrhosis and ascites, requiring at least 3 large volume paracenteses (LVP) in the previous 60 days, and serum creatinine (SCr) < 2.0 mg/dL were enrolled at a single US site. Within 3 days after a large volume paracentesis (LVP), patients started treatment with BIV201 (continuous infusion terlipressin) administered via a PICC line by an ambulatory infusion pump with step-wise dose escalation (2 to 3 and then 4 mg/day over 5 days based on hemodynamic response and clinical safety). Following a 7 day in-house stay, patients continued treatment as outpatients with the highest tolerated dose of terlipressin for a total of 28 days. Serial plasma samples were collected through treatment and assayed for terlipressin and its more active metabolite, 8-lysine vasopressin, by LC-MS/MS.

RESULTS

Terlipressin mean steady state plasma concentrations ranged from 1.69 to 5.55 ng/mL for the 2 mg/day to 4 mg/day dose range. Steady state plasma levels of 8-LVP, the more potent metabolite and full agonist of V1 receptors, ranged from 0.058 to 0.138 ng/mL.

Consistent with low drug exposure, hemodynamic and cardiac tolerance was good during terlipressin infusion treatment and there were no adverse signs of tissue ischemia or clinically significant changes in daily electrocardiograms. Three of the six patients completed 28-day infusion of terlipressin and three discontinued terlipressin infusion early for the following reasons: Recurrence of Grade II hepatic encephalopathy (HE) on day 14, leak from a pre-existing umbilical hernia on day 24, and progressive asymptomatic hyponatremia on day 9 (treatment-related). Four patients reached a maximum dose of 3 mg/day and one patient reached the maximum dose escalation of 4 mg/day.

Four of 6 patients experienced ≥ 50% increase in the interval between LVPs after the start of treatment with terlipressin, two of which experienced extended control of ascites beyond the 28 days of infusion for a total of 72 and 63 days. The volume of ascites removed by paracentesis during the 28-day treatment period was reduced by a minimum of 30% and on average by 66% compared to the 28 days prior to treatment. Four patients (two with SCr > 1.5 mg/dL) experienced a reduction in SCr levels during treatment.



Patient #	101	102	103	104	105	106
Child-Pugh score	10	8	11	7	8	11
MELD-Na	16	12	22	13	9	18
Age	60	64	36	61	61	63
LVP interval, days	7	17	6	14	20	21
SCr, mg/dL	1.6	1.1	2	1.2	0.8	1.1
Terlipressin infusion (max), mg/day	3	4	2	3	3	3
Treatment days	28	14	24	28	9	28
Reason for stopping infusion	NA	Recurrent HE	Leaking hernia	NA	Grade 3 hyponatremia	NA
Terlipressin CL (mL/min/kg)	6.0	5.1	5.7	5.7	6.9	4.1
V (L/kg)	0.29	0.3	0.27	0.68	0.18	0.27
$T_{1/2}$ Ter, (min)	33.4	40.8	32.8	83.1	18.3	45.3
C_{ss} Ter, ng/mL	3.99	5.55	2.91	2.6	3.27	5.48
C_{ss} 8-LVP, ng/mL	0.058	0.108	0.138	0.072	0.11	0.131
Change in LVP interval[a]	0%	+70%	+116%	+414%	+215%	-10%
Total volume ascites removed 28d before treatment[a], L	45	25.8	33	19.7	16.5	17.5
Total volume ascites removed during 28d treatment period, L	29	0	22.6	0	0	12.1
Change in SCr (mg/dL)[b]	-0.4	0	-1.0	-0.4[c]	-0.4[d]	0

a = includes baseline LVP; b = D7-D14; NA = not applicable.

CONCLUSIONS

Consistent with a previous study[1], the data support the safety and feasibility of long-term continuous IV infusion with terlipressin in an ambulatory setting. Early pharmacodynamic data are consistent with terlipressin infusion improving the underlying mechanisms that result in ascites formation. The observed impact on ascites, especially the extended impact in 2 patients, along with the demonstrated feasibility of outpatient management of ascites, warrants evaluation of the efficacy of intermittent treatment cycles of BIV201 as a long-term treatment option for refractory ascites in a larger randomized controlled trial.

REFERENCES

1. Gow et al., Outpatient terlipressin infusion for the treatment of refractory ascites," *American Journal of Gastroenterology*, vol. 111, no. 7, pp. 1041-1042, 2016.

CONTACT INFORMATION

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