

Research Article

Safety, Tolerability, Pharmacokinetics, and Efficacy of Terlipressin Delivered by Continuous Intravenous Infusion in Patients with Cirrhosis and Refractory Ascites

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Background. Terlipressin is a long acting synthetic analogue of vasopressin, which is used to manage variceal bleeding and hepatorenal syndrome. Terlipressin is being developed to treat refractory ascites in cirrhotic patients who are no longer responsive to diuretic drugs and require repeated paracentesis. This study evaluated the safety, tolerability, pharmacokinetics (PK), and efficacy of a continuous intravenous (IV) infusion of terlipressin as an outpatient treatment for refractory ascites in patients with advanced liver cirrhosis. **Methods.** This was an open-label Phase 2a trial. Patients received a continuous IV infusion of terlipressin 2 mg/day escalating to 4 mg/d during an initial 7-day inpatient period, followed by 21 days as outpatients. The PK, safety/tolerability, and effects on the need for and volume of paracentesis were evaluated. **Results.** Four of 6 patients experienced $\geq 50\%$ increase in the interval between large volume paracenteses (LVP) with terlipressin. The volume of ascites removed by LVP in the 28-day treatment period was reduced in all patients by $\geq 30\%$ compared with pretreatment. Terlipressin was rapidly eliminated with a mean half-life of 42.3 minutes, mean clearance of 5.6 mL/min/kg, and volume of distribution of 0.33 L/kg. Average steady state plasma concentrations ranged from 1.69 to 5.55 ng/mL and increased proportionally with increasing dose. Three (50.0%) patients reported treatment-related adverse events, but none were serious. **Conclusion.** Continuous terlipressin IV infusion improved control of refractory ascites with an acceptable safety and predictable PK profile. Further evaluation of terlipressin is warranted in a randomized controlled trial for treating refractory ascites and related complications of cirrhosis.

1. Introduction

Cirrhosis of the liver is one of the leading causes of death in the U.S., accounting for at least 35,000 deaths annually [1, 2]. Ascites is a common complication of liver cirrhosis and often is life-threatening in advanced stages [3, 4] with mortality rates of 50% or more over 5 years [5, 6]. Patients with liver cirrhosis and ascites account for 116,000 hospitalizations each year and incur >10 billion dollars in annual treatment-related costs [7,

8]. The development of refractory ascites, which is defined by resistance or intolerance to diuretics, in patients with cirrhosis is associated with a poor quality of life (QOL) and frequent hospital admissions due to liver-related complications [9–12]. Currently, no pharmacological therapy is approved in the U.S. for refractory ascites in patients with cirrhosis. Terlipressin, a long-acting synthetic analogue of vasopressin, approved and used for the treatment of acute variceal hemorrhage and hepatorenal syndrome in many countries outside

the U.S. [13, 14], is now being developed to treat refractory ascites in patients with cirrhosis. Clinical studies have shown that terlipressin constricts arterial blood vessels in the splanchnic area, and through this effect, it reduces portal hypertension, increases the effective arterial blood volume, and downregulates the sympathetic nervous system and the renin-angiotensin aldosterone system (RAAS). Thus, terlipressin reduces ascites production and increases urinary sodium excretion [15–17]. The initially proposed regimen of terlipressin for hepatorenal syndrome-1 and esophageal varices was intermittent intravenous (IV) bolus doses; however, results from clinical studies indicate high and potentially unacceptable rates of serious adverse events [18–19]. Some evidence suggests that the safety and tolerability of terlipressin may be improved with administration as a continuous IV infusion [17, 18, 20, 21]. This Phase 2a clinical trial evaluated the safety, pharmacokinetics (PK), and preliminary efficacy of terlipressin administered as a continuous low dose IV infusion for treating patients with cirrhosis and refractory ascites.

2. Methods

This study was conducted in accordance with International Committee on Harmonisation Guideline for Good Clinical Practices and the Declaration of Helsinki. The study protocol, amendments, and informed consent form were reviewed and approved by an institutional review board (McGuire Institutional Review Board, Richmond, VA). All patients provided written informed consent prior to any study procedures. This study was registered at clinicaltrials.gov: NCT03107091.

2.1. Study Design and Treatment. This was an open-label single-arm uncontrolled trial of continuous IV infusion of terlipressin (Figure 1). The study consisted of 3 periods: (1) a pretreatment observation period of up to 28 days, during which patients were monitored without intervention until they required a therapeutic paracentesis; (2) a 28-day treatment period, during which patients received study drug; and (3) a 28-day follow-up period, during which patients were monitored for safety. The study comprised 2 sequential steps: (1) two sentinel patients with cirrhosis and refractory ascites with serum creatinine (SCr) < 1.5 mg/dL were enrolled and completed treatment with study drug, and (2) additional patients with cirrhosis and ascites with SCr < 2.0 mg/dL were enrolled and completed treatment with study drug. Treatment with diuretics was maintained at stable doses throughout the study. Albumin was recommended for all patients per current standard of care after paracentesis to prevent postparacentesis circulatory dysfunction (PPCD) and as clinically indicated. It was recommended (if clinically appropriate) that the albumin dose administered to prevent PPCD (usually 6–8 g/L of ascites fluid removed) was kept constant for each LVP that might be required during the study period.

Within 3 days after a large volume paracentesis (LVP), patients started treatment with terlipressin administered continuously IV via a peripherally inserted central or midline catheter by an ambulatory infusion pump. Step-wise dose escalation from 2 to 4 mg/day in 1 mg/day increments occurred during a 7-day inpatient period, following which

patients continued treatment as outpatients at the highest tolerated dose of terlipressin for a total of 28 days, followed by a 28-day follow-up period. Terlipressin acetate was formulated in 50 mL of 0.9% sodium chloride at concentrations of 0.04, 0.06, or 0.08 mg/mL administered by continuous IV infusion at doses of 2, 3, or 4 mg/day. The solution was administered over 24 hours (infusion rate, 2.1 mL/h).

2.2. Patient Selection Criteria. Adult patients aged 18 to 70 years with a diagnosis of cirrhosis and diuretic-resistant or intractable ascites were eligible if they required at least 3 LVPs in the previous 60 days and with a serum creatinine (SCr) < 2.0 mg/dL (<1.5 mg/dL for sentinel patients). LVP was defined as a paracentesis \geq 4 liters. Diuretic-resistant ascites was defined as ascites that was unresponsive to sodium-restricted diet and high-dose diuretic treatment (increasing doses of spironolactone up to 400 mg/day and addition of furosemide up to 160 mg/day) for at least 1 week. Patients being treated with angiotensin converting enzyme (ACE) inhibitors or beta blockers were on a stable dose for at least 2 months prior to enrollment and maintained that dose for the trial duration.

The diagnosis of cirrhosis was based on liver biopsy (Ishak fibrosis stages 5–6), or on clinical diagnosis based on unequivocal clinical data (splenomegaly, spider angiomas, palmar erythema, gynecomastia, and jaundice), and compatible laboratory, ultrasonography, and endoscopic findings.

Exclusion criteria were as follows: total bilirubin > 5 mg/dL; international normalized ratio > 2.5; current or recent (within 3 months) renal dialysis; hepatic encephalopathy grade 3 or 4; superimposed acute liver failure injury; current or recent (with 7 days) treatment with octreotide, midodrine, vasopressin, dopamine, or other vasopressors; current or recent (within 60 days) episode of respiratory failure requiring positive airway pressure devices or intubation; systemic inflammatory response syndrome (SIRS)/sepsis (documented infection and SIRS) with 2 or more of the following findings: temperature > 38°C or <36°C; heart rate > 90/min; respiratory rate of >20/min or a PaCO₂ < 32 mmHg; white blood cell count of >12,000 cells/ μ L or <4,000/ μ L in the previous 28 days; episode of spontaneous bacterial peritonitis or gastrointestinal hemorrhage in the previous 28 days; ongoing or suspected infection; any severe comorbidity that could interfere with participation in the study such as severe cardiovascular disease or severe chronic kidney disease; active alcohol consumption for the past 12 weeks; transjugular intrahepatic portosystemic shunt or other surgical shunt; or known allergy or hypersensitivity to terlipressin.

2.3. Study Procedures. Physical examination and weight/abdominal circumference, 12-lead electrocardiogram (ECG), vital signs (heart rate, blood pressure, mean arterial pressure, body temperature), clinical laboratory testing (chemistry, hematology, urinalysis), plasma renin and aldosterone levels, 24 h sodium urine excretion, spot urinary creatinine and sodium, estimated glomerular filtration rate (eGFR), fractional excretions of sodium, and Model for End-stage Liver Disease (MELD) score were performed at

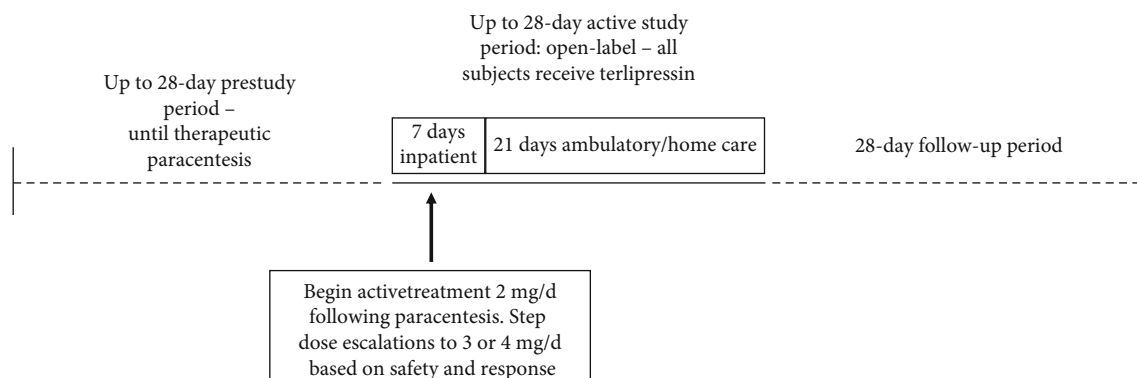


FIGURE 1: Study design.

regular intervals during the pretreatment, treatment, and follow-up periods.

Paracentesis was performed for the following conditions: (1) presence of moderate to severe ascites upon medical examination with patient discomfort (shortness of breath or umbilical hernia or abdominal pain and/or distension and/or limitation of activity) for a repeat LVP, (2) weight regain to 90-100% of previous LVP-related weight loss, and (3) reincrease in abdominal girth to 90-100% of previous LVP-related of abdominal girth.

Serial plasma samples to characterize PK parameters for terlipressin and its metabolite, 8-lysine vasopressin (8-LVP), were collected prior to the start of the infusion on day 1 and at 0.5, 0.75, 1, 1.5, 2, 3, 6, and 24 hours after the start of the continuous infusion; prior to the change in infusion rate and 1, 2, and 8 hours after a dose change to 3 mg and 4 mg; in the morning on days 7, 14, and 28; and prior to discontinuation of terlipressin for an adverse effect. Terlipressin plasma concentration-time data were analyzed by individual and population PK modeling.

Terlipressin and 8-LVP plasma concentrations were analyzed with a validated high performance liquid chromatography and tandem mass spectrometry (LC-MS/MS) assay with a lower limit of quantitation of 0.25 ng/mL for terlipressin and 0.05 ng/mL for 8-LVP. Terlipressin PK data were analyzed using the NONMEM (nonlinear mixed-effects modeling) software (version 7.4.3; ICON plc, Gaithersburg, MD) with a GNU Fortran 95 compiler (version 4.6.3) on a Dell Optiplex® 9020 personal computer running Windows 7.

2.4. Study Analysis. This was a pilot proof-of-concept study and was not powered for inferential statistics. The sample size for the study was selected on the basis of observations of feasibility, data from a recently published study [17], and historical first-in-human studies. Data for baseline characteristics, safety, and PK results were summarized with descriptive statistics.

3. Results

Six adult male patients were enrolled between September 2017 and May 2019, and 5 completed; one patient discontinued the study for an AE. Three patients completed the full 28-day treatment period, and three patients received terlipressin for

9 to 24 days. Baseline characteristics for individual patients are reported in Table 1. Concomitant furosemide was used by 5 (83.3%) patients, potassium-sparing diuretics by 5 (83.3%) patients, and albumin, administered after LVPs, by 3 (50.0%) patients that required LVPs during the study.

3.1. Efficacy. Three patients received treatment for 28 days; 3 patients discontinued early for recurrent hepatic encephalopathy, leaking hernia, and grade 3 hyponatremia (Table 2). Four patients reached a maximum dose of 3 mg/day, and one patient reached the maximum dose of 4 mg/day. Four of 6 patients experienced $\geq 50\%$ increase in the interval between LVPs after the start of treatment with terlipressin, and two of the four patients experienced extended control of ascites beyond the 28 days of infusion. The volume of ascites removed by paracentesis in the 28 days prior to treatment versus the 28-day treatment period was reduced in all patients by at least 30% and on average by 66.5% (Table 2). The number and volume of LVPs decreased markedly from pretreatment to the end of the 28-day treatment period and remained below pretreatment values at the 28-day follow-up.

Serum creatinine improved in 5 of 6 patients. Mean and median SCr concentrations decreased slightly from baseline to end of treatment, whereas mean and median eGFR values increased from baseline to end of treatment. Plasma renin activity (PRA) decreased in 3 of 4 patients who had pretreatment and treatment values. Decreases in PRA values during treatment compared with baseline suggest a correction of hemodynamic function with terlipressin.

3.2. Pharmacokinetics. Terlipressin PK during continuous IV infusion was best described by a one-compartment model with zero-order input and first-order elimination (Table 3). Terlipressin was rapidly eliminated with a mean elimination half-life of 42.3 minutes. Mean terlipressin clearance (CL) was 5.6 mL/min/kg, and volume of distribution was 0.33 L/kg. Steady state average plasma concentrations (C_{ss-ave}) ranged from 1.69 to 5.55 ng/mL for terlipressin and increased proportionally with increasing infusion rate (dose). The C_{ss-ave} ranged from 0.059 to 0.138 ng/mL for 8-LVP and was similar across infusion rates. Albumin was recommended for all subjects per current standard of care after paracentesis to prevent postparacentesis circulatory

TABLE 1: Baseline characteristics for individual patients.

	101	102	103	104	105	106
Age, years	60	64	36	61	61	63
Race	Black	White	White	White	Black	White
Weight, kg	85.1	89.8	71.2	120.7	75.6	84.0
Cirrhosis etiology	Hepatitis C/alcohol	Hepatitis C	Alcohol	Alcohol	Alcohol	Hepatitis C/alcohol
Child-Pugh score (class)	10 (C)	8 (B)	11 (C)	7 (B)	8 (B)	11 (C)
MELD score	16	12	22	13	9	18
Serum creatinine, mg/dL	1.6	1.1	2.0	1.2	0.8	1.1
Sodium, mmol/L	142	141	132	141	139	135
24 h urinary sodium excretion, mmol/d	0	0	2.6	10.5	150	10.2

TABLE 2: Summary of outcomes from treatment per patient.

Parameter	Subjects					
	101	102	103	104	105	106
Treatment days (dose, mg/d)	28 (3)	14 (4)	24 (2)	28 (3)	9 (3)	28 (3)
Reason for stopping	NA	Recurrent HE	Leaking hernia	NA	Grade 3 hyponatremia	NA
Spirolactone/furosemide, mg/d						
Pretreatment	150/60	200/60	None	100/40	100/20	100/160
Treatment	50/20	200/60	None	100/40	100/20	100/160
LVP interval, days/28-day period						
Pretreatment	7	18	7	14	21	21
Treatment	7	29	13	74	63	20
% change in LVP interval	0	70	116	414	215	-5
Total volume of ascites removed/28-day period, L						
Pretreatment	45.0	25.8	33.0	19.7	16.5	17.5
Treatment	29.0	0	22.6	0	0	12.1
% change in volume	-36	-100	-32	-100	-100	-31
Change in SCr (mg/dL)	-0.4	0	-1.0	-0.4	-0.4	-0.1

HE: hepatic encephalopathy; NA: not applicable; SCr: serum creatinine.

TABLE 3: Summary of terlipressin PK parameters.

	CL (L/min)	CL (mL/min/kg)	V (L)	V (L/kg)	K (min ⁻¹)	$t_{1/2}$ (min)
Mean	0.49	5.6	31.6	0.33	0.020	42.3
Median	0.49	5.7	23.5	0.29	0.019	37.1
%CV	24.2	16.7	80.2	53.2	49.2	52.1
Range	0.34, 0.69	4.1, 6.9	13.8, 82.3	0.18, 0.68	0.008, 0.038	18.3, 83.1

CL: clearance; %CV: percent coefficient of variation; K: elimination rate constant; $t_{1/2}$: half-life; V: volume of distribution.

dysfunction (PPCD) and as clinically indicated. It was recommended (if clinically appropriate) that the albumin dose administered to prevent PPCD (usually 6-8 g/L of ascites fluid removed) was kept constant for each LVP that might be required during the study period.

Good agreement was observed between observed and population model-predicted terlipressin plasma concentrations (Figure 2). Good agreement also was shown between the observed and model-predicted terlipressin plasma concentrations for individual patients, with the regression line mirroring the line of identity in 5 of the 6 patients (Data Supplement). A simulation of plasma concentrations of

terlipressin based on IV bolus injection every 6 hours [14] vs. continuous IV infusion at 3 doses from this study demonstrated that continuous infusion provided low, consistent plasma concentrations compared with high intermittent peak concentrations with IV bolus injection (Figure 3).

3.3. Safety/Tolerability. Consistent with this patient population with advanced cirrhosis, all 6 patients reported at least one treatment-emergent adverse event (TEAE), including 4 (66.7%) patients with serious TEAEs (Table 4). A total of 19, 19, and 2 TEAEs occurred at doses of 2 mg/d, 3 mg/d, and 4 mg/d, respectively. Four patients experienced 5 serious

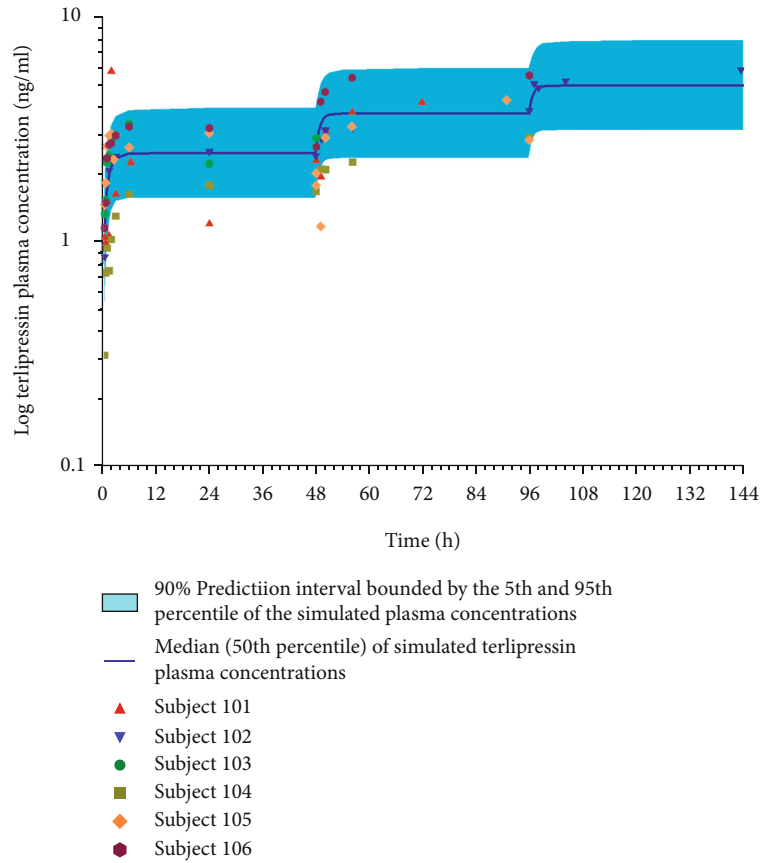


FIGURE 2: Observed and simulated terlipressin plasma concentrations from population PK modeling.

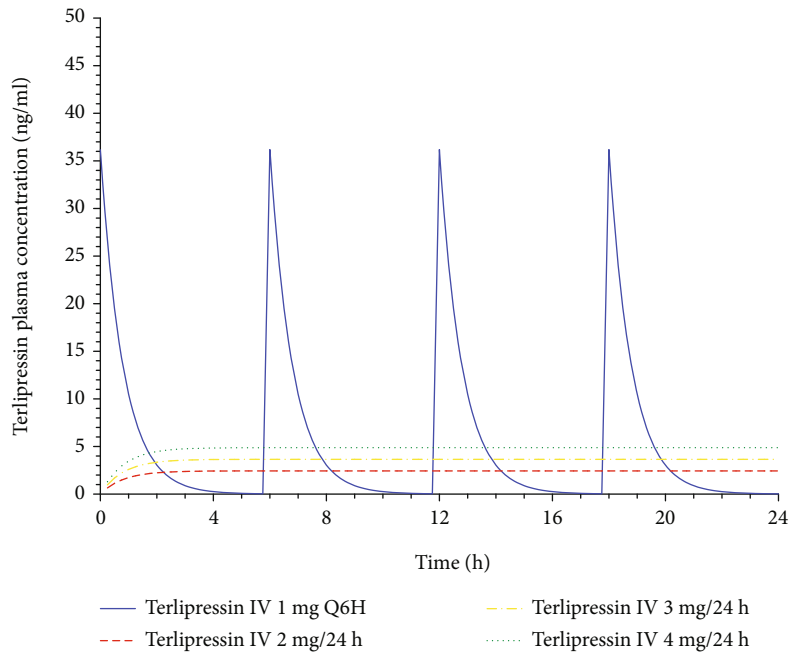


FIGURE 3: Simulated plasma concentrations of terlipressin with IV bolus 1 mg every 6 hours [14] vs. IV continuous infusion of 2, 3, or 4 mg/d in current study.

TABLE 4: Incidence of treatment-emergent adverse events (TEAEs).

Parameter	N (%) N = 6
At least one TEAE	6 (100)
Related TEAE	3 (50.0)
Serious TEAE	4 (66.7)
Serious-related TEAE	0
TEAE leading to drug withdrawal	3 (50.0)
Grade 3-4 TEAE	4 (66.7)
Fatal TEAE	0
Individual TEAEs	
Diarrhea	3 (50.0)
Vomiting	2 (33.3)
Hypokalemia	2 (33.3)
Headache	3 (50.0)

TEAEs (bacteremia, hepatic encephalopathy (2), ruptured umbilical hernia, partial bowel obstruction); all considered unrelated to treatment. Three of these serious TEAEs occurred during treatment (bacteremia from leg cellulitis on day 27, a recurrence of grade 2 hepatic encephalopathy on day 14, and a leak from a preexisting umbilical hernia on day 24); the latter two resulted in treatment discontinuation. One patient experienced two serious AEs (hepatic encephalopathy and intestinal obstruction) during follow-up considered unrelated to treatment. One patient discontinued treatment on day 9 for treatment-related progressive asymptomatic hyponatremia. Of note, hemodynamics and cardiac performance were quite stable during treatment, and no adverse signs of tissue ischemia were observed. Sinus bradycardia and sinus arrhythmia were reported as TEAEs in 2 patients but considered not related to treatment. A prolonged QT interval was reported in 1 patient on day 21 that was not related to treatment. The QTc prolongation was concomitant to a very large paracentesis (12L), was transient for <48 hours, and the change remained below 60 ms (elevation vs. study day 1 was only 20 ms). This effect was thought to be related to the post LVP hemodynamic change but with no obvious hyponatremia and a slight concomitant increase with liver enzymes. No concomitant medication was identified as a potential cause. One patient experienced hypotension (day 2), sinus bradycardia (day 5), and tachycardia (day 27), but only tachycardia was considered treatment-related.

4. Discussion

The aim of this Phase 2a clinical trial was to evaluate PK, efficacy, and safety of terlipressin administered as a continuous low dose IV infusion for treating patients with cirrhosis and refractory ascites. The PK profile of terlipressin by continuous IV infusion was predictable with rapid elimination and a dose proportional increase in exposure as the dose was up-titrated. Observed vs. predicted terlipressin plasma concentrations were highly correlated in 5 of 6 patients. Terlipressin CL varied from 4.1 to 6.9 mL/min/kg and V

from 0.18 to 0.68 L/kg. These values are similar to those previously reported in patients with hepato-renal syndrome (6.25 mL/min/kg for CL and 0.43 L/kg for V) [14] but less than values in healthy volunteers (9 mL/min/kg for CL and 0.7 to 0.9 L/kg for V) [22]. A simulation of terlipressin plasma concentrations during continuous IV infusion at doses used in this study demonstrated low, consistent plasma concentrations compared with high intermittent peak concentrations observed with IV bolus injection. The rapid $t_{1/2}$ supports the administration of terlipressin as a continuous infusion to prevent potentially harmful high maximum plasma concentrations and wide fluctuations between peak and trough concentrations, and the dose proportionality of terlipressin C_{ss-ave} and relatively prompt achievement of steady-state facilitates the titration of terlipressin infusions. Accordingly, with the PK data, the results of the study suggest that the administration of terlipressin by continuous IV infusion is associated with a low rate of adverse effects, confirming what has been observed previously in the setting of type 1 HRS [18]. In regard to the efficacy, the study proved that the administration of terlipressin is capable to induce significant reductions in the number of LVPs and in the volume of ascites removed, confirming previous evidence of a positive effect of the drug on the pathophysiology of ascites [23]. These results are well in keeping with those of Gow et al. who showed, in a pilot study, that the continuous IV infusion of terlipressin in outpatients with refractory ascites was associated with a significant reduction in the number of LVP and volume of ascites removed [17, 21].

Because this was a proof-of-concept study, it has some limitations such as small sample size, open label design, and short follow-up. Nevertheless, its results support the need and the effort to evaluate the use of terlipressin given by a continuous IV infusion in a larger, well-defined patient population with adequate follow-up. A Phase 2 study to evaluate the efficacy, safety, and tolerability of terlipressin in patients with refractory ascites for up to 180 days is already ongoing (ClinicalTrials.gov Identifier: NCT04112199).

In summary, continuous IV infusion of terlipressin provides a consistent and predictable PK profile in patients with cirrhosis and refractory ascites. This could improve safety and tolerability of the drug in these patients. Importantly, continuous IV infusion of terlipressin offers the facility to provide treatment on an outpatient basis. These results support further randomized, controlled studies to evaluate outpatient use of continuous IV infusion of terlipressin in a larger cohort of patients with refractory ascites and other conditions.

Data Availability

All relevant data are included in the manuscript and data supplement. Requests in writing for additional data should be sent to the corresponding author.

Ethical Approval

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been

adhered to, and the appropriate ethical review committee approval has been received. The study conformed to the US Federal Policy for the Protection of Human Subjects.

Conflicts of Interest

JF is a consultant who received compensation from BioVie. EG and AF received none. PA is a clinical advisor who received honorarium from BioVie and from Grifols. GG-C is a clinical advisor who received honorarium from BioVie. JSB, JA, and PM are BioVie employees.

Authors' Contributions

PM, PY, JA, PA, and G G-C are responsible for the substantial contributions to the conception, design, and planning of the work. JSB, PM, PY, JF, AF, EG, PA, and G-GC are responsible for the acquisition, analysis, or interpretation of data for the work. JSB, PA, JF, PM, and JA are responsible for drafting the work or revising it critically for important intellectual content. JSB, PY, JF, EG, AF, PA, GG-C, and JA are responsible for the final approval of the version to be published.

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Supplementary Materials

Supplemental Figure 1: observed vs. predicted terlipressin plasma concentrations for individual patients. (*Supplementary Materials*)

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