OBSERVATIONAL STUDY

OPEN

Role of Terlipressin in Patients With Hepatorenal Syndrome-Acute Kidney Injury Admitted to the ICU: A Substudy of the CONFIRM Trial

Constantine J. Karvellas, MD[1]

Ram Subramanian, MD[2]

Jody C. Olson, MD[3]

Khurram Jamil, MD[4]

IMPORTANCE AND OBJECTIVES: This study assessed the potential advantages of treating hepatorenal syndrome-acute kidney injury (HRS-AKI) with terlipressin versus placebo in the ICU setting.

DESIGN: Patients were randomly assigned in a 2:1 ratio to receive terlipressin or placebo for up to 14 days.

SETTING: A retrospective analysis of data from the phase III CONFIRM study.

PARTICIPANTS: Adult patients with HRS-AKI admitted to the ICU.

MAIN OUTCOMES AND MEASURES: In this substudy, we evaluated outcomes of the ICU stay and the need for organ support, including renal replacement therapy (RRT).

RESULTS: Among 300 patients with HRS-AKI from the CONFIRM study, 45 were treated in the ICU (terlipressin, 31/199 [16%]; placebo, 14/101 [14%]). On ICU admission, baseline demographics were similar across treatment arms, including severity of liver dysfunction. Among patients alive at the end of the ICU stay, those randomized to terlipressin had a significantly shorter median length of ICU stay than placebo (4 vs 11 d; $p < 0.001$). Terlipressin-treated patients had a significantly larger improvement in renal function from baseline versus placebo (−0.7 vs +0.2 mg/dL; $p = 0.001$), including when accounting for the interaction between treatment and day-of-patient-admission to the ICU (−0.7 vs +0.9 mg/dL; $p < 0.001$). Cumulative requirement for RRT through day 90 was improved in the terlipressin arm versus placebo (10/31 [32%] vs 8/14 [57%]; $p = 0.12$), although not significantly. Of 13 patients who received a liver transplant, five out of five (100%) in the placebo arm needed RRT through day 90 versus five out of eight (63%) in the terlipressin arm.

CONCLUSIONS: In this subanalysis of CONFIRM, patients admitted to the ICU with HRS-AKI who received terlipressin were more likely to achieve renal function improvement, based on serum creatinine changes by the end of treatment, and had significantly shorter lengths of ICU stay than patients randomized to the placebo arm.

KEY WORDS: acute kidney injury; acute-on-chronic liver failure; cirrhosis; hepatorenal syndrome; intensive care unit

One of the most common indications for ICU admission for patients with cirrhosis/acute-on-chronic liver failure (ACLF) is acute kidney injury, specifically hepatorenal syndrome-acute kidney injury (HRS-AKI) (1). Rates of acute kidney injury are between 29% and 56% (2–5) in patients with ACLF when using the European Association for the Study of the Liver-Chronic Liver Failure criteria, and the prevalence was 6–28% when

DOI: 10.1097/CCE.0000000000000890

KEY POINTS

Question: Do patients with hepatorenal syndrome-acute kidney injury (HRS-AKI) who were treated in the ICU benefit from terlipressin treatment in terms of length of ICU stay, need for renal replacement therapy, and changes in renal function?

Findings: In a subgroup analysis of the CONFIRM study, surviving patients who were randomly assigned to receive terlipressin had a significantly shorter mean length of ICU stay versus placebo. Additionally, among patients with HRS-AKI admitted to the ICU those treated with terlipressin had significant improvements in renal function.

Meaning: Treatment with terlipressin resulted in meaningful clinical improvements among patients with HRS-AKI in the ICU setting.

the North American Consortium for the Study of End-Stage Liver Disease criteria were used (5). HRS-AKI is characterized by advanced liver disease with splanchnic and systemic vasodilation and renal afferent vasoconstriction leading to a decrease in glomerular filtration rate (6).

Currently, the mainstay of treatment for HRS-AKI that does not respond to volume challenge is vasoconstrictor therapy (e.g., terlipressin) with albumin (7). Worldwide, terlipressin is a widely used vasoconstrictor, followed by norepinephrine, with a small number of studies reporting on the use of midodrine and octreotide (8). Midodrine, octreotide, and albumin can be administered in the general hospital ward but have limited hepatorenal syndrome (HRS) reversal benefits (8). Therefore, patients who fail this therapy require transfer to the ICU for vasopressor infusions with norepinephrine, vasopressin, and albumin, which require ICU monitoring and a central venous catheter.

Terlipressin is a synthetic vasopressin analog with vasoconstrictor activity in the splanchnic and systemic vasculature (9). Its use results in decreased portal blood inflow and reduced portal hypertension, the primary cause of the hemodynamic abnormalities associated with decompensated cirrhosis/ACLF. The resulting redistribution of circulatory volume from the splanchnic to the systemic circulation improves systemic hemodynamics and increases renal perfusion pressure (10). The increased effective arterial volume also decreases compensatory renal and systemic vasoconstrictor activities, further improving renal hemodynamics in these patients (11). Terlipressin has been demonstrated to be associated with improved renal function in patients with cirrhosis/ACLF and HRS-AKI (12–14) and is approved for the treatment of adult patients with HRS and rapidly deteriorating kidney function by the U.S. Food and Drug Administration (FDA) (15). In contrast to norepinephrine, terlipressin does not require a central line and can be given outside the ICU setting.

In this substudy of the CONFIRM trial, we focused on patients with cirrhosis/ACLF who required ICU care. Primary outcomes evaluated the impact of terlipressin therapy on requirements for hospital resources, including ICU and length of hospital stay. Secondary outcomes included renal function and organ failure improvements, as determined by the CLIF definitions (2).

METHODS

Study Aim and Setting

This study is a retrospective post hoc analysis of data from the prospective, randomized, placebo-controlled phase III clinical CONFIRM study (14). It evaluated the effect of terlipressin plus albumin (terlipressin arm) versus placebo plus albumin (placebo arm) in patients admitted to the ICU at randomization and within 72 hours from randomization.

The design and methods for the CONFIRM study were previously described (14). In brief, patients greater than or equal to 18 years old with cirrhosis, ascites, and rapidly progressive renal failure, with a demonstrated doubling of serum creatinine (SCr) to at least 2.25 mg/dL within 14 days, were randomly assigned (2:1) to receive terlipressin (1 mg IV every 6 hr) or placebo with concomitant albumin. If SCr decreased by less than 30% from the baseline value on day 4, the dose could be increased to 2 mg every 6 hours (8 mg/d). Patients were stratified by qualifying SCr (< 3.4 or ≥ 3.4 mg/dL) and pre-enrollment large-volume paracentesis. The primary efficacy endpoint of CONFIRM was number of patients with verified HRS reversal, defined as the percentage of patients with two consecutive SCr values

no greater than 1.5 mg/dL at least 2 hours apart up to day 14 and remaining alive without renal replacement therapy (RRT) for at least an additional 10 days (14). The cumulative need for RRT was also prospectively evaluated (14). Here, HRS-AKI therapy with terlipressin was evaluated in the subpopulation of patients from the CONFIRM study who were admitted to the ICU. In this post hoc analysis, we focused on the improvement of renal function and RRT requirements as the outcomes of great clinical importance for patients with HRS-AKI. Additionally, we assessed mortality and ICU stay duration.

The analyses were based on the intent-to-treat (ITT) population, defined as all randomized patients.

Outcomes

The outcomes were evaluated regarding changes in renal function, the need for organ support, including RRT, the treatment goals, and the duration of the ICU stay. The change in renal function was assessed using repeated measures analysis of SCr level from baseline through the end of treatment (EOT); per the study protocol, SCr values after RRT, transjugular intrahepatic portosystemic shunt placement, liver transplant (LT), or open-label vasopressors were excluded. RRT was defined as any procedure to replace nonendocrine kidney function (i.e., intermittent RRT [IRRT] and continuous RRT [CRRT], including continuous venovenous hemofiltration, continuous venovenous hemodialysis, continuous venovenous hemodiafiltration, peritoneal dialysis, and other dialysis and filtration techniques).

Statistical Analysis

For continuous data, analysis of variance, Kruskal-Wallis tests, and Poisson regression were used to generate *p* values after testing for normality. chi-square or Fisher exact tests were used for categorical data to generate *p* values. The change in renal function was compared between terlipressin- and placebo-treated patients using repeated measures analysis of covariance of SCr level from baseline through the EOT with the factors of "qualifying SCr," "large volume paracentesis use," "treatment," and "day" and with the interaction between "treatment" and "day," as implemented in Statistical Analysis Software (SAS) Proc Mixed (Carey, NC). The analysis was also presented without interaction with the factors of "treatment" and "day" as a sensitivity analysis. The model used a compound symmetry covariance matrix, maximum likelihood estimation, and repeated statement of factor of patient nested in strata. All statistical tests were two-sided with a final significance level of 0.05. Statistical analyses were performed using SAS Version 9.4 (SAS, Cary, NC).

This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for reporting observational studies.

Ethics Approval and Consent to Participate

The CONFIRM trial—a multicenter, randomized, placebo-controlled, double-blind study to confirm efficacy and safety of terlipressin in subjects with HRS type 1 (The CONFIRM study [ClinicalTrials.gov, NCT02770716; Registered May 12, 2016])—was approved by the Western Institutional Review Board, Puyallup, WA (WIRB Pro Number, 20160684; approved June 28, 2016) and was conducted in compliance with the protocol, the Sponsor's standard operating procedures and guidelines, FDA regulations, and the International Council for Harmonisation Good Clinical Practice guidelines that have their origins in the Declaration of Helsinki. Written informed consent was obtained from all patients participating in the CONFIRM study. Consent for publication: Not applicable.

RESULTS

Baseline Demographic and Biochemical Characteristics

The patient-flow (Consolidated Standards of Reporting Trials) diagram is presented in **Figure 1**.

Of 300 patients with cirrhosis and HRS-AKI who underwent randomization in the CONFIRM study (ITT), most patients were treated on a regular floor or liver unit. In total, 31 of 199 patients (16%) randomly assigned to the terlipressin arm were treated in the ICU compared with 14 of 101 patients (14%) randomly assigned to placebo. When comparing patients in the terlipressin arm ($n = 31$) and the placebo arm ($n = 14$) who were admitted to the ICU, no differences in baseline demographics were observed ($p > 0.15$ for all comparisons); in the total population, patient mean age was 53 years, 60% were men, and 91% were White

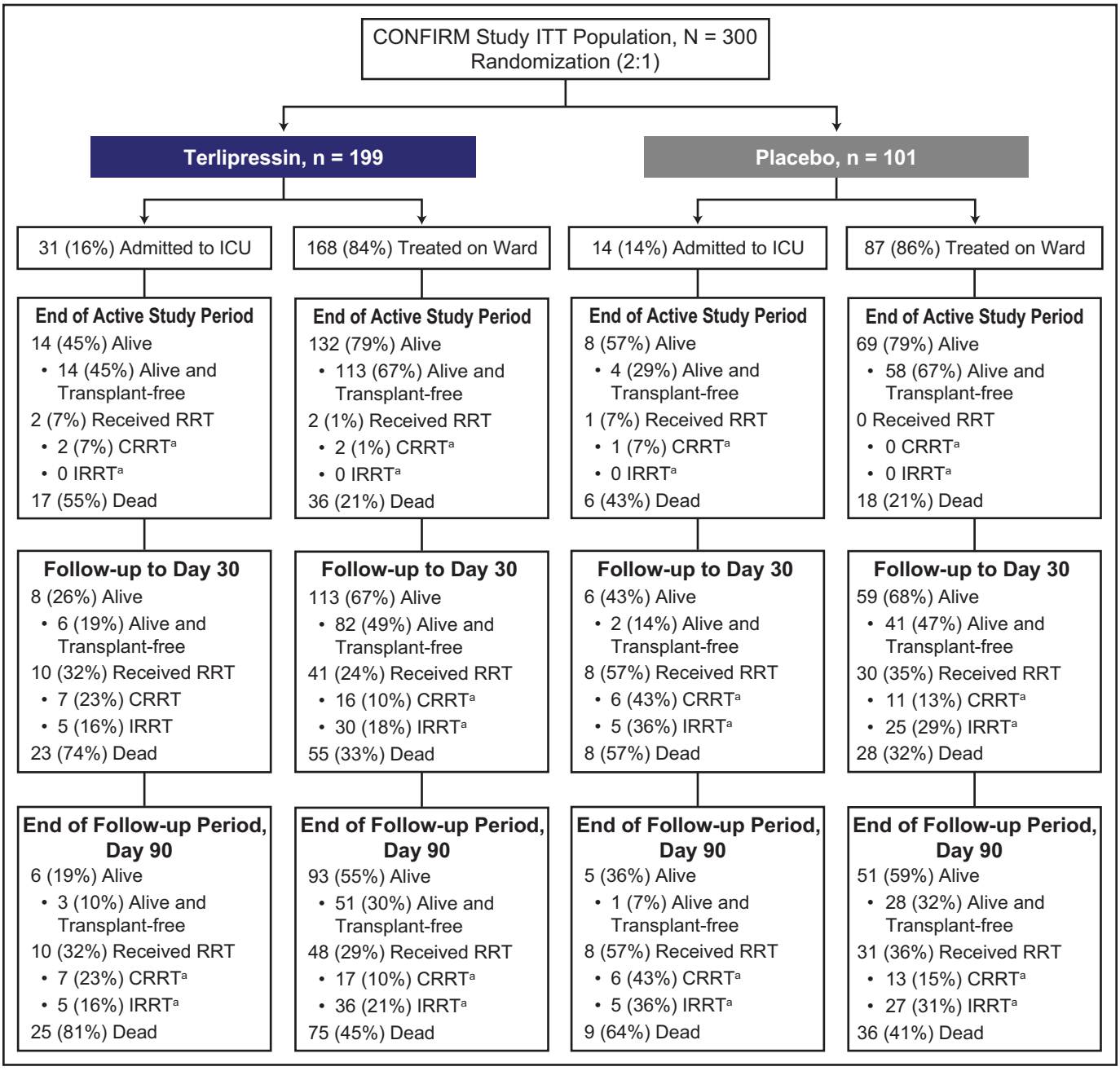

Figure 1. Consolidated Standards of Reporting Trials patient-flow diagram. [a]Continuous renal replacement therapy (CRRT) includes continuous venovenous hemofiltration, continuous venovenous hemodialysis, continuous venovenous hemodiafiltration, and other types of therapy. Intermittent renal replacement therapy (IRRT) includes intermittent dialysis and hemodialysis. A patient may be counted as having both continuous renal replacement therapy (RRT) and intermittent RRT. There was no significant difference in outcomes between terlipressin- and placebo-treated patients among those admitted to the ICU and among patients who were treated on the ward. ITT = intent-to-treat, The CONFIRM Study = a multi-center, randomized, placebo controlled, double-blind study to confirm efficacy and safety of terlipressin in subjects with hepatorenal syndrome type 1.

(**Table 1**). At baseline, there were no significant differences in the severity of liver disease assessed by Model for End-Stage Liver Disease (MELD) score (37 vs 38.5; $p = 0.36$) or by the etiology of cirrhosis. Regarding complications of portal hypertension, more patients in the terlipressin arm than in the placebo arm who were admitted to the ICU had a history of esophageal variceal hemorrhage (26% vs 0%; $p = 0.04$).

TABLE 1.
Baseline Demographic and Clinical Characteristics of Patients Admitted to the ICU in CONFIRM, Intent-to-Treat Population

Characteristic	Terlipressin (*n* = 31)	Placebo (*n* = 14)	Total (*n* = 45)	*p*[a]
Age (yr), mean (SD)	54 (10)	50 (9)	53 (10)	0.20
Male, *n* (%)	21 (68)	6 (43)	27 (60)	0.19
Race, *n* (%)				
Asian	1 (3)	0	1 (2)	Not estimable
Black or African American	1 (3)	1 (7)	2 (4)	0.53
White	28 (90)	13 (93)	41 (91)	1.00
Etiology of cirrhosis, *n* (%)				
Alcohol	20 (65)	8 (57)	28 (62)	0.74
Hepatitis C	5 (16)	4 (29)	9 (20)	0.43
Nonalcoholic steatohepatitis	6 (19)	3 (21)	9 (20)	1.00
Autoimmune hepatitis	3 (10)	1 (7)	4 (9)	1.00
Cryptogenic	2 (7)	0	2 (4)	1.00
Other	2 (7)	0	2 (4)	1.00
Alcoholic hepatitis, *n* (%)	14 (45)	7 (50)	21 (47)	1.00
Systemic inflammatory response syndrome subgroup, *n* (%)	14 (45)	12 (86)	26 (58)	0.02
Esophageal varices, *n* (%)				
Prior history	8 (26)	0	8 (18)	0.04
Received banding	11 (36)	1 (7)	12 (27)	0.07
Received prior transjugular intrahepatic portosystemic shunt	5 (16)	0	5 (11)	0.31
Prior infections, *n* (%)	13 (42)	8 (57)	21 (47)	0.52
Spontaneous bacterial peritonitis	7 (23)	4 (29)	11 (24)	0.72
Urinary tract infection	6 (19)	2 (14)	8 (18)	1.00
Pneumonia	1 (3)	1 (7)	2 (4)	0.53
Other	5 (16)	1 (7)	6 (13)	0.65
Mean arterial pressure (mm Hg)	80 (11)	79 (11)	80 (11)	0.67
Sodium (mmol/L)	134.0 (6.7)	134.1 (5.0)	134.0 (6.2)	0.93
Creatinine (mg/dL), median (Q1–Q3)	3.5 (2.7–3.9)	3.5 (2.7–4.7)	3.5 (2.7–4.0)	0.79
Bilirubin (mg/dL), median (Q1–Q3)	13.4 (5.1–26.0)	24.6 (7.6–33.0)	18 (5.1–29.9)	0.26
Albumin (g/dL), mean (SD)	3.6 (0.8)	3.4 (0.7)	3.6 (0.8)	0.32
Child-Pugh score, *n* (%)				0.48
Class B (7–9)	7 (23)	3 (21)	10 (22)	
Class C (10–15)	24 (77)	10 (71)	34 (76)	
Model for End-Stage Liver Disease score, median (Q1–Q3)	37 (32–40)	38.5 (36–40)	37 (33–40)	0.36
Chronic Liver Failure-Sequential Organ Failure Assessment score				
n	19	10	29	
Median (Q1–Q3)	12.0 (10.0–15.0)	12.0 (12.0–14.0)	12.0 (11.0–15.0)	0.42

Q1–Q3 = 25th–75th percentile.

[a]*p* value is for the comparison between terlipressin and placebo treatment arms. For continuous data, analysis of variance or Kruskal-Wallis tests were used to generate *p* values after testing for normality. For categorical data, a Fisher exact test was used to generate *p* values.

TABLE 2.
Summary of Hospitalization and ICU Admissions in CONFIRM, Intent-to-Treat Population

Parameter	Terlipressin	Placebo	*p*[a]
Intent-to-treat population	*n* = 199	*n* = 101	
Length of hospital stay (d), median (Q1–Q3, 25th–75th percentile)	19 (14–29)	21 (14–28)	0.66
Time from randomization to hospital discharge (d), mean (SD)	18 (19)	19 (17)	0.25
Admitted to the ICU, *n* (%)	31 (16)	14 (14)	0.69
ICU patient subgroup	*n* = 31	*n* = 14	
Intubated, *n* (%)	19 (61)	6 (43)	0.25
DNR/DNI, *n* (%)	6 (19)	2 (14)	1.00
DNR/DNI/comfort care, *n* (%)	17 (55)	4 (29)	0.10
Listed for transplant at baseline, *n* (%)	8 (26)	5 (36)	0.17
Length of ICU stay for patients alive at the end of stay (d)			< 0.001[b]
n	14	8	
Median (minimum–maximum)	4 (2–14)	11 (3–59)	
Time from randomization to ICU discharge (d)			0.16
n	18	9	
Median (minimum–maximum)	9 (3–29)	12 (2–60)	
Time from ICU admission to death (d)			0.74
n	25	9	
Median (minimum–maximum)	9 (1–52)	8 (2–38)	
Alive at day 14, *n* (%)	14 (45)	8 (57)	0.46
Alive without RRT or transplant, *n* (%)	9 (29)	1 (7)	0.14
Alive at day 30, *n* (%)	8 (26)	6 (43)	0.25
Alive without RRT or transplant, *n* (%)	4 (13)	0	0.29
Alive at day 60, *n* (%)	6 (19)	5 (36)	0.24
Alive at day 90, *n* (%)	6 (19)	5 (36)	0.24

DNI = do-not-intubate order, DNR = do-not-resuscitate order, RRT = renal replacement therapy.
[a]For continuous data, analysis of variance or Kruskal-Wallis tests were used to generate *p* values after testing for normality.
[b]From Poisson regression.
For categorical data, χ^2 or Fisher exact tests were used to generate *p* values.

Organ Support in the ICU and RRT

There were no significant differences in the number of patients requiring intubation/mechanical ventilation between the terlipressin and placebo arms (61% vs 43%; $p = 0.25$; **Table 2**). There were no significant differences in goals of care between treatment arms (Table 2). At the EOT among patients admitted to the ICU, there were no significant differences in additional vasopressor use after the EOT between the treatment and control arms (32% vs 36%; $p = 0.82$; **Table 3**). RRT requirements and outcomes in the ICU and on the ward by treatment are presented in Figure 1. By day 30 of follow-up, 10 of 31 ICU patients (32%) in the terlipressin arm received RRT ($n = 7$ CRRT, $n = 5$ IRRT) compared with eight of 14 (57%) in the placebo arm ($n = 6$ CRRT, $n = 5$ IRRT; $p = 0.12$; **Table 4**). There were no differences in infection rates between the treatment arms (Table 1).

Short-Term Outcomes and ICU/Hospital Discharge

While hospitalized, a minority of ICU patients were listed for LT at baseline: (8/31 [26%] in the terlipressin arm and 5/14 [36%] in the placebo arm; $p = 0.17$;

TABLE 3.
Concomitant Vasopressors and Changes in Chronic Liver Failure-Sequential Organ Failure Assessment Score and Acute-on-Chronic Liver Failure Grade From Baseline to the End of Treatment

Parameter	Patients Admitted to ICU			*p* (Terlipressin vs Placebo)
	Terlipressin (*n* = 31)	Placebo (*n* = 14)	Total (*n* = 45)	
Any vasopressor use after the EOT, *n* (%)	10 (32)	5 (36)	15 (33)	0.82[a]
Vasopressin	6 (19)	2 (14)	8 (18)	1.00[a]
Norepinephrine	8 (26)	5 (36)	13 (29)	0.50[a]
Epinephrine	1 (3)	1 (7)	2 (4)	0.53[a]
Phenylepinephrine	2 (7)	0	2 (4)	1.00[a]
Chronic Liver Failure-Sequential Organ Failure Assessment score, median (Q1–Q3)				0.76[b]
n	15	9	24	
EOT	14 (10–15)	14 (13–14)	14 (11–15)	
Baseline	12 (10–13)	12 (12–14)	12 (11–14)	
Change	1 (–1 to 3)	1 (–1 to 2)	1 (–1 to 2)	
p: within-treatment-arm change	0.40	0.23	0.76	
Acute-on-chronic liver failure grade, median (Q1–Q3)				0.40[b]
n	26	14	40	
EOT	2 (2–3)	2 (2–3)	2 (2–3)	
Baseline	2 (1–3)	2 (2–3)	2 (1–3)	
Change	0 (0–1)	0	0 (0–0.5)	
p: within-treatment-arm change	0.56	1.00	0.40	

EOT = end of treatment, Q1–Q3 = 25th–75th percentile.
[a]χ^2 or Fisher exact tests were used to generate *p* values.
[b]Kruskal-Wallis test was used to generate *p* values.

Table 2). There were no significant differences in goals of care between patients in the ICU: 17 of 31 patients (55%) in the terlipressin arm versus four of 14 (29%) in the placebo arm were listed for do-not-resuscitate (DNR)/do-not-intubate (DNI) order/comfort care during the study period ($p = 0.10$).

Compared with baseline, the ICU patients in the terlipressin arm had a significantly greater improvement in renal function at the EOT compared with placebo (least square mean of change, –0.7 vs +0.2 mg/dL; $p = 0.001$), including when accounting for the interaction between treatment and day of patient admission to the ICU (least square mean of change, –0.7 vs +0.9 mg/dL; $p < 0.001$; **Fig. 2**). Although not statistically significant, more patients who survived without RRT or LT within 30 days were in the terlipressin arm versus the placebo arm, respectively (i.e., at day 14: 9/31 [29%] vs 1/14 [7%], $p = 0.14$; at day 30: 4/31 [13%] vs 0/14, $p = 0.29$, respectively; Table 2).

With illness severity measured by the Chronic Liver Failure-Sequential Organ Failure Assessment (CLIF-SOFA) score (16) and ACLF grade (2), there were no significant differences between CLIF-SOFA scores or ACLF grade from baseline to the EOT in either the terlipressin arm ($p > 0.39$ for both) or the placebo arm ($p > 0.2$ for both; Table 3).

Among patients who were alive at the end of the ICU stay, those randomly assigned to terlipressin had

TABLE 4.
Renal Replacement Therapy by ICU Admission and Treatment in CONFIRM, Intent-to-Treat Population

Time Point	Parameter	Admitted to ICU			Not Admitted to ICU		
		Terlipressin (*n* = 31)	Placebo (*n* = 14)	*p*[b]	Terlipressin (*n* = 168)	Placebo (*n* = 87)	*p*[c]
Active study period	Patients starting RRT, *n* (%)	2 (7)	1 (7)	1.00	2 (1)	0	0.55
	Continuous RRT[a]	2 (7)	1 (7)	N/E	2 (1)	0	N/E
	Intermittent RRT[a]	0	0	N/E	0	0	N/E
10 d after verified HRS reversal[b]	Within 10 d of verified HRS reversal, *n* (%)	1 (3)	0	1.00	4 (2)	1 (1)	0.66
Posttreatment	Patients starting RRT, *n* (%)	9 (29)	7 (50)	0.17	32 (19)	27 (31)	0.03
	Continuous RRT[a]	6 (19)	5 (36)	0.24	11 (7)	9 (10)	0.29
	Intermittent RRT[a]	3 (10)	4 (29)	0.18	24 (14)	23 (26)	0.02
	Cumulative duration of RRT through posttreatment (d)			0.73			0.29
	n	10	7		33	27	
	Median (Q1–Q3, 25th–75th percentile)	3 (1–7)	6 (1–7)		1 (1–4)	3 (1–6)	
30-d follow-up	Patients receiving RRT since the previous assessment, *n* (%)	2 (7)	4 (29)	0.07	20 (12)	19 (22)	0.04
	Continuous RRT[a]	0	2 (14)	0.09	5 (3)	6 (7)	0.14
	Intermittent RRT[a]	2 (7)	3 (21)	0.17	17 (10)	15 (17)	0.10
	Cumulative number of patients since the active study period, *n* (%)	10 (32)	8 (57)	0.12	41 (24)	30 (35)	0.09
	Continuous RRT[a]	7 (23)	6 (43)	0.17	16 (10)	11 (13)	0.44
	Intermittent RRT[a]	5 (16)	5 (36)	0.14	30 (18)	25 (29)	0.05
60-d follow-up	Patients receiving RRT since the previous assessment	1 (3)	1 (7)	0.53	18 (11)	15 (17)	0.14
	Continuous RRT[a]	0	0	N/E	0	2 (2)	0.12
	Intermittent RRT[a]	1 (3)	1 (7)	0.53	18 (11)	14 (16)	0.22
	Cumulative number of patients since the active study period, *n* (%)	10 (32)	8 (57)	0.12	46 (27)	30 (35)	0.24
90-d follow-up	Patients receiving RRT since the previous assessment, *n* (%)	0	1 (7)	0.31	12 (7)	11 (13)	0.15
	Continuous RRT[a]	0	0	N/E	1 (1)	2 (2)	0.27
	Intermittent RRT[a]	0	1 (7)	0.31	11 (7)	9 (10)	0.29
	Cumulative number of patients since the active study period, *n* (%)	10 (32)	8 (57)	0.12	48 (29)	31 (36)	0.25
	Continuous RRT[a]	7 (23)	6 (43)	0.17	17 (10)	13 (15)	0.26
	Intermittent RRT[a]	5 (16)	5 (36)	0.14	36 (21)	27 (31)	0.09

HRS = hepatorenal syndrome, N/E = not estimable, RRT = renal replacement therapy.

[a]Continuous RRT includes continuous venovenous hemofiltration, continuous venovenous hemodialysis, continuous venovenous hemodiafiltration; intermittent RRT includes intermittent dialysis; patients could have received both continuous RRT and intermittent RRT.

[b]Only patients with a verified HRS reversal completed the case report form page.

[c]For continuous data, analysis of variance or Kruskal-Wallis tests were used after testing for normality. For categorical data, χ^2 or Fisher exact tests were used.

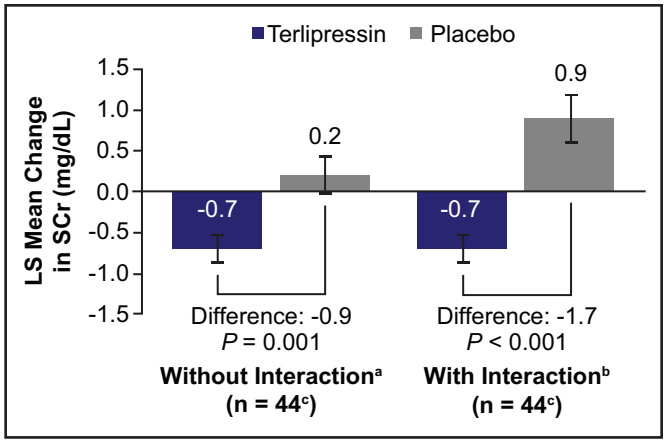

Figure 2. Change in renal function among patients admitted to the ICU. Data are presented as least squares (LS) mean ± SE. Serum creatinine (SCr) values after renal replacement therapy, transjugular intrahepatic portosystemic shunt placement, liver transplant, or open-label vasopressors were excluded. [a]From repeated measures analysis of covariance as implemented in Proc Mixed with factors of "study," "treatment," and "day." [b]From repeated measures analysis of covariance as implemented in Proc Mixed with factors of "study," "treatment," "day," and the "treatment-by-day interaction." [c]One patient in the terlipressin arm did not have an end-of-treatment SCr value and, therefore, was not included in the analysis.

a significantly shorter median length of ICU stay than the placebo arm (4 vs 11 d; $p < 0.001$; Table 2). Serious adverse events (SAEs) of respiratory failure in patients who were admitted to the ICU were more frequent in the terlipressin arm compared with the placebo arm (16/31 [52%] vs 2/14 [14%]; $p = 0.02$).

Long-Term Outcomes

Long-term outcomes are shown in Figure 1 and Table 2. At day 90 at the end of the follow-up period in CONFIRM, six of 31 patients (19%) in the terlipressin arm were alive, of whom three had received an LT and three had not. Of the original 31 patients, 10 (32%) received some form of RRT and 5 (16%) received IRRT. In the placebo arm, at day 90 at the end of follow-up, five of 14 patients (36%) were alive, of which four had undergone a transplant, and one had not. Among all patients who were transferred to the ICU, the cumulative incidence of RRT through day 90 was 32% (10/31) in the terlipressin arm versus 57% (8/14) in the placebo arm ($p = 0.12$). Among patients admitted to the ICU, 13 patients received an LT. Of those, five of eight patients (63%) in the terlipressin arm and five of five patients (100%) in the placebo arm needed RRT through day 90; three of eight (38%) and four of five (80%) patients in the terlipressin and placebo arms, respectively, were alive by day 90 (**eTable 1**, http://links.lww.com/CCX/B164).

DISCUSSION

Key Findings

In this subanalysis of the CONFIRM study, 15% of enrolled patients (45/300) with HRS-AKI were managed in the ICU. Patients treated in the ICU in the terlipressin arm achieved a significant improvement in renal function (based on SCr) at the end of the study, whereas those in the placebo arm did not, even after adjustment for interaction. In addition, patients with HRS-AKI who were managed in the ICU, received terlipressin versus placebo, and survived, had significantly shorter lengths of stay in the ICU. Irrespective of whether patients with HRS-AKI were randomly assigned to terlipressin or placebo, the clinical outcomes of patients treated in the ICU were similar to the outcomes of patients treated on the ward. Further, SAEs of respiratory failure were observed more frequently in the terlipressin arm versus the placebo arm.

Comparison With the Literature

There is a growing body of literature demonstrating that terlipressin is more effective in treating HRS-AKI outside of the ICU (i.e., on the ward) than other available therapies (e.g., midodrine, octreotide, albumin) (8, 17, 18). Improvement in renal function/HRS may facilitate ongoing management of patients with decompensated cirrhosis/ACLF on the ward, with the potential benefits of preventing ICU admission and the requirement for RRT. Terlipressin may be given as an infusion or bolus via peripheral IV administration; in Europe, it is often given on general hospital wards. Its use eliminates the need for central venous catheter placement and the significant costs and logistical challenges involved in transferring a patient who otherwise may not require ICU admission (19). Beyond this, terlipressin may reduce mortality compared with placebo (18) and may potentially bridge a patient to a safer LT with preserved renal function (13).

In this analysis, we have demonstrated that there are potential benefits associated with the use of terlipressin for patients with HRS-AKI in the ICU as well.

Specifically, patients admitted to the ICU who were randomized to terlipressin therapy and survived had significantly shorter lengths of stay in the ICU and were more likely to have improvement in renal function. These results are in keeping with other studies that evaluated the use of terlipressin in the ICU setting. Although in North America, norepinephrine is commonly used in the ICU to treat patients with HRS-AKI, the recent largest randomized trial comparing terlipressin and norepinephrine in 120 patients with ACLF demonstrated a significantly higher rate of HRS reversal with terlipressin versus norepinephrine (40% vs 16.7%, respectively; $p = 0.004$) (20). This trial also reported significantly higher 28-day survival (48.3% vs 20%, respectively; $p = 0.001$).

These clinical studies may reflect the potential pharmacological benefits of terlipressin over norepinephrine and vasopressin in patients with HRS-AKI in the ICU setting. Terlipressin is delivered as a prodrug, whereby metabolism results in a sustained release of pharmacological activity (21). Compared with vasopressin (half-life < 20 min), the stepwise release of terlipressin results in a prolonged duration of action, even when given in bolus form. The active metabolite of terlipressin, lysine-vasopressin (LyVP), has an activity peak at 60–120 minutes and remains metabolically active for 240–360 minutes (9, 21). LyVP has been demonstrated to have twice the affinity for V_1 receptors (primarily located in vascular smooth muscle) and six times greater affinity for V_2 receptors (primarily located in the distal nephron) than vasopressin (9, 21, 22). In patients with HRS-AKI, terlipressin administration results in splanchnic vasoconstriction, shunting blood to the systemic circulation, reducing activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system, and blunting the release of arginine vasopressin, ultimately enhancing renal perfusion (21). The potential clinical benefits of terlipressin may reflect beneficial effects on renal perfusion beyond the increase in systemic vascular resistance produced by other vasoconstricting agents (22).

Mortality as an endpoint is challenging to study in ICU patients hospitalized with ACLF due to high competing risks for death, particularly in the absence of an LT (23). In this study, 45 patients with HRS-AKI who were admitted to the ICU with ACLF had a median ACLF of grade 2 (i.e., two organ failures), which previous studies have shown to be associated with a 90-day mortality of greater than 50% in the absence of a transplant (2). Although no previous randomized trials investigating terlipressin for the treatment of HRS-AKI have been powered to study mortality, two recent meta-analyses demonstrated lower mortality in patients treated for HRS-AKI with terlipressin therapy versus placebo (24, 25).

The challenge of the competing risks of death confounded by LT candidacy is also reflected in this analysis by the significant number of patients in both arms who were admitted to the ICU and had limits on resuscitation/goals of care. Specifically, 55% of ICU patients (17/31) in the terlipressin arm were listed for comfort care and/or no cardiopulmonary resuscitation or endotracheal intubation compared with 29% (4/14) in the placebo arm ($p = 0.10$). While the decision for a patient to have a DNR/DNI order was made by the healthcare provider, this was likely significantly affected by the patients' transplant candidacy. Overall, the number of patients who received a transplant from the ICU in this study was low (13/45 [29%]). As LT is the definitive treatment for ACLF and HRS-AKI, one potential explanation for why a minority of patients in this study went on to receive a transplant, besides having contraindications, could potentially be a preference for transplant-listed patients not to be enrolled in this study because of a perceived potential loss of transplant waitlist priority in the United States due to renal improvement (26).

In the CONFIRM study, respiratory failure (including acute respiratory failure) was reported in 14% of patients treated with terlipressin compared with 5% of patients treated with placebo (14). It was hypothesized that several factors contributed to the higher incidence of these adverse events, including administration of a high, and possibly an excessive, amount of albumin (27). Patients with a high MELD score, a high ACLF grade, and multisystem organ dysfunction—as was the case in the subpopulation of patients admitted to the ICU—are at a higher risk of respiratory failure related to terlipressin therapy; as such, a corresponding warning is included in the FDA label (15). An algorithm for close monitoring using regular pulse oximetry, clinical volume examination and urine output, and regular adjustments of terlipressin and albumin, was proposed to mitigate the safety risks in this patient population (27).

Strengths and Limitations

The results of this subanalysis of the CONFIRM study should be considered within the context of the following strengths and limitations. The data presented herein are especially valuable because information from the placebo-controlled studies of terlipressin in patients with HRS-AKI in the ICU setting—where they are often treated with norepinephrine—is limited. Here, using data from the largest-to-date, randomized, placebo-controlled study of terlipressin in patients with HRS-AKI allowed us to evaluate clinically important information on the effect of terlipressin in this extremely sick patient subgroup. However, limitations of the study include the fact that decisions regarding transfer of patients to the ICU were at the healthcare provider's discretion, which may have introduced potential selection bias. Since LT is a significant competing risk, decisions to list patients for an LT from the ICU were not protocolized and were at the discretion of the treating transplant team, which has introduced some heterogeneity. Furthermore, details regarding limits on life-sustaining therapies (i.e., DNR/DNI orders) were at the discretion of healthcare providers and may have also introduced some variability, as seen in other ICU studies (28). The CONFIRM trial was not powered to assess the between-arm difference in survival. Finally, detailed follow-up beyond 90 days that included an assessment of prespecified outcomes after LT were not performed. Despite these limitations, this study builds on an evolving body of literature that there may be significant benefits to using terlipressin in the ICU setting in patients with HRS-AKI.

CONCLUSIONS

In this subanalysis of the CONFIRM trial, by the end of the treatment period, patients admitted to the ICU with HRS-AKI who received terlipressin were more likely to achieve a significant improvement in renal function based on changes in the SCr level, compared with those patients who were randomly assigned to the placebo arm. Furthermore, surviving patients with HRS-AKI who received terlipressin had significantly shorter lengths of stay in the ICU.

1 Department of Critical Care Medicine and Division of Gastroenterology (Liver Unit), University of Alberta, Edmonton, AB, Canada.

2 Departments of Critical Care Medicine and Hepatology, Emory University, Atlanta, GA.

3 Departments of Medicine and Surgery, University of Kansas Medical Center, Kansas City, KS.

4 Mallinckrodt Pharmaceuticals, Hampton, NJ.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccejournal).

Dr. Karvellas designed the study, analyzed and interpreted the data, and drafted the article. Drs. Subramanian and Olson provided critical revision of the article for important intellectual content. Dr. Jamil designed the study, analyzed and interpreted the data, and provided critical revision of the article for important intellectual content. All authors reviewed and approved the final version of the article.

Design of the study, data collection and analysis, and editorial support for the current study were funded by Mallinckrodt Pharmaceuticals. The CONFIRM study was also funded by Mallinckrodt Pharmaceuticals. Editorial support was provided by Oxford PharmaGenesis, Newtown, PA.

Drs. Subramanian and Olson received consultancy fees from Mallinckrodt Pharmaceuticals. Dr. Jamil is an employee of Mallinckrodt Pharmaceuticals. Dr. Karvellas has disclosed that he does not have any potential conflicts of interest.

For information regarding this article, E-mail: dean.karvellas@ualberta.ca

Discussion of statistical endpoints and analysis are included in the article. Summary aggregate (basic) results (including adverse events information) and the study protocol will be available on ClinicalTrials.gov (CONFIRM, NCT02770716;) when required by regulation. Individual de-identified patient data will not be disclosed. Requests for additional information should be directed to the company at medinfo@mnk.com.

ClinicalTrials.gov (NCT02770716); registered May 12, 2016.

REFERENCES

1. Angeli P, Gines P, Wong F, et al; International Club of Ascites: Diagnosis and management of acute kidney injury in patients with cirrhosis: Revised consensus recommendations of the International Club of Ascites. *Gut* 2015; 64:531–537
2. Moreau R, Jalan R, Gines P, et al; CANONIC Study Investigators of the EASL–CLIF Consortium: Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology* 2013; 144:1426–1437, 1437.e1–e9
3. Mendez-Guerrero O, Calle-Rodas DA, Cervantes-Alvarez E, et al: Renal and brain failure predict mortality of patients with acute-on-chronic liver failure admitted to the intensive care unit. *Ann Hepatol* 2021; 22:100270
4. Piano S, Tonon M, Vettore E, et al: Incidence, predictors and outcomes of acute-on-chronic liver failure in outpatients with cirrhosis. *J Hepatol* 2017; 67:1177–1184
5. Cao Z, Liu Y, Cai M, et al: The use of NACSELD and EASL-CLIF classification systems of ACLF in the prediction of prognosis

in hospitalized patients with cirrhosis. *Am J Gastroenterol* 2020; 115:2026–2035

6. Angeli P, Garcia-Tsao G, Nadim MK, et al: News in pathophysiology, definition and classification of hepatorenal syndrome: A step beyond the International Club of Ascites (ICA) consensus document. *J Hepatol* 2019; 71:811–822
7. Biggins SW, Angeli P, Garcia-Tsao G, et al: Diagnosis, evaluation, and management of ascites, spontaneous bacterial peritonitis and hepatorenal syndrome: 2021 practice guidance by the American Association for the Study of Liver Diseases. *Hepatology* 2021; 74:1014–1048
8. Facciorusso A, Chandar AK, Murad MH, et al: Comparative efficacy of pharmacological strategies for management of type 1 hepatorenal syndrome: A systematic review and network meta-analysis. *Lancet Gastroenterol Hepatol* 2017; 2:94–102
9. Jamil K, Pappas SC, Devarakonda KR: In vitro binding and receptor-mediated activity of terlipressin at vasopressin receptors V1 and V2. *J Exp Pharmacol* 2018; 10:1–7
10. Kiszka-Kanowitz M, Henriksen JH, Hansen EF, et al: Effect of terlipressin on blood volume distribution in patients with cirrhosis. *Scand J Gastroenterol* 2004; 39:486–492
11. Gines P, Sola E, Angeli P, et al: Hepatorenal syndrome. *Nat Rev Dis Primers* 2018; 4:23
12. Sanyal AJ, Boyer T, Garcia-Tsao G, et al; Terlipressin Study Group: A randomized, prospective, double-blind, placebo-controlled trial of terlipressin for type 1 hepatorenal syndrome. *Gastroenterology* 2008; 134:1360–1368
13. Boyer TD, Sanyal AJ, Wong F, et al; REVERSE Study Investigators: Terlipressin plus albumin is more effective than albumin alone in improving renal function in patients with cirrhosis and hepatorenal syndrome type 1. *Gastroenterology* 2016; 150:1579–1589.e2
14. Wong F, Pappas SC, Curry MP, et al; CONFIRM Study Investigators: Terlipressin plus albumin for the treatment of type 1 hepatorenal syndrome. *N Engl J Med* 2021; 384:818–828
15. TERLIVAZ® (Terlipressin): *Full Prescribing Information*. Bedminster, NJ, Mallinckrodt Pharmaceuticals, 2022
16. Jalan R, Saliba F, Pavesi M, et al; CANONIC study investigators of the EASL-CLIF Consortium: Development and validation of a prognostic score to predict mortality in patients with acute-on-chronic liver failure. *J Hepatol* 2014; 61:1038–1047
17. Cavallin M, Kamath PS, Merli M, et al; Italian Association for the Study of the Liver Study Group on Hepatorenal Syndrome: Terlipressin plus albumin versus midodrine and octreotide plus albumin in the treatment of hepatorenal syndrome: A randomized trial. *Hepatology* 2015; 62:567–574
18. Pitre T, Kiflen M, Helmeczi W, et al: The comparative effectiveness of vasoactive treatments for hepatorenal syndrome: A systematic review and network meta-analysis. *Crit Care Med* 2022; 50:1419–1429
19. Mattos AZ, Mattos AA, Ribeiro RA; TERLIPRESSIN VERSUS NORADRENALINE FOR HEPATORENAL SYNDROME: Economic evaluation under the perspective of the Brazilian Public Health System. *Arq Gastroenterol* 2016; 53:123–126
20. Arora V, Maiwall R, Rajan V, et al: Terlipressin is superior to noradrenaline in the management of acute kidney injury in acute on chronic liver failure. *Hepatology* 2020; 71:600–610
21. Kulkarni AV, Arab JP, Premkumar M, et al: Terlipressin has stood the test of time: Clinical overview in 2020 and future perspectives. *Liver Int* 2020; 40:2888–2905
22. Colson PH, Virsolvy A, Gaudard P, et al: Terlipressin, a vasoactive prodrug recommended in hepatorenal syndrome, is an agonist of human V1, V2 and V1B receptors: Implications for its safety profile. *Pharmacol Res* 2016; 113:257–264
23. Belcher JM, Parada XV, Simonetto DA, et al; HRS-HARMONY Study Investigators: Terlipressin and the treatment of hepatorenal syndrome: How the CONFIRM trial moves the story forward. *Am J Kidney Dis* 2022; 79:737–745
24. Wang H, Liu A, Bo W, et al: Terlipressin in the treatment of hepatorenal syndrome: A systematic review and meta-analysis. *Medicine (Baltim)* 2018; 97:e0431
25. Israelsen M, Krag A, Allegretti AS, et al: Terlipressin versus other vasoactive drugs for hepatorenal syndrome. *Cochrane Database Syst Rev* 2017; 9:CD011532
26. O'Leary JG, Levitsky J, Wong F, et al: Protecting the kidney in liver transplant candidates: Practice-based recommendations from the American Society of Transplantation Liver and Intestine Community of Practice. *Am J Transplant* 2016; 16:2516–2531
27. Allegretti AS, Subramanian RM, Francoz C, et al: Respiratory events with terlipressin and albumin in hepatorenal syndrome: A review and clinical guidance. *Liver Int* 2022; 42:2124–2130
28. Hart JL, Harhay MO, Gabler NB, et al: Variability among US intensive care units in managing the care of patients admitted with preexisting limits on life-sustaining therapies. *JAMA Intern Med* 2015; 175:1019–1026