Improvement in Serum Creatinine Was Associated With Favorable Clinical Outcomes in Patients With Hepatorenal Syndrome: A Post Hoc Analysis of the CONFIRM Study

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Background

- Hepatorenal syndrome (HRS) is a life-threatening but potentially reversible form of acute kidney injury (AKI) that occurs in people with liver cirrhosis and ascites[1]
- Within the context of liver disease, kidney dysfunction has been characterized by a serum creatinine (SCr) value of ≥ 1.5 mg/dL, and HRS-AKI is associated with a rapid doubling in SCr levels[2]
- Terlipressin is the first and only US Food and Drug Administration (FDA)-approved treatment for adult patients with HRS and a rapid reduction in kidney function[3], and is recommended by the American Association for the Study of Liver Diseases (AASLD)[4] and the American College of Gastroenterology (ACG) as a first-line therapy once a diagnosis of HRS-AKI has been made[5]
  - Terlipressin dosing is adjusted on Day 4 based on the patient's SCr level relative to treatment initiation: patients with a > 30% improvement in SCr should continue to receive 1 mg every 6 hours; and a dose increase to 2 mg every 6 hours is recommended for patients with an improvement in SCr of ≤ 30% from baseline[3]
- In the Phase III CONFIRM study, patients treated with terlipressin achieved more verified reversal of HRS—defined as 2 consecutive SCr measurements of ≤ 1.5 mg/dL obtained at least 2 hours apart while receiving treatment up to Day 14 or discharge, and alive without renal replacement therapy (RRT) for at least an additional 10 days—compared with placebo (terlipressin, 31.7% [63/199]; placebo, 16.8% [17/101]; $P = .006$)[6]

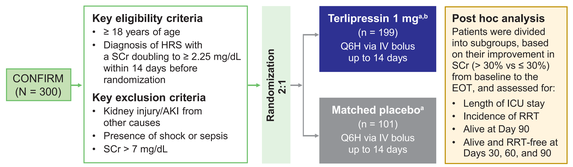
Aim of the Study

- This post hoc analysis assessed patient data from the CONFIRM study to determine if an improvement in SCr of > 30% from baseline to the end of treatment (EOT) was associated with improved clinical outcomes, including length of intensive care unit (ICU) stay, incidence of RRT, and long-term patient survival (the number of patients alive at Day 90, and the number of patients alive and RRT-free at Days 30, 60, and 90)

Methods:

- The Phase III CONFIRM study enrolled adult patients with cirrhosis, ascites, HRS, and a SCr value of ≥ 2.25 mg/dL with a projected doubling of SCr within 2 weeks
- Patients were treated intravenously with terlipressin 1 mg every 6 hours or matched placebo (plus albumin in each case)
- Patients from the CONFIRM intent-to-treat (ITT) population were analyzed by their improvement in SCr (ie, > 30% vs ≤ 30%) from baseline (ie, Day 0; or a prestudy value, if the Day 0 value was missing) to the EOT for the following outcomes: length of ICU stay, the incidence of RRT at Days 30, 60, and 90, the number of patients alive at Day 90, and the number of patients alive and RRT-free at Days 30, 60, and 90 (**Figure 1**)
- Statistical analyses were performed using analysis of variance (ANOVA) or a Kruskal-Wallis test for continuous variables after testing for normality, or a Chi-square or Fisher's exact test was used for categorical variables

Figure 1. Study Design



[a] **Concomitant albumin was strongly recommended** at a dose of 1 g/kg to a maximum of 100 g on Day 1 and 20–40 g/day thereafter.

[b] If, after Day 3, SCr levels had decreased—but by less than 30%—then the terlipressin dose could be increased to 2 mg Q6H.

AKI, acute kidney injury; EOT, end of treatment; HRS, hepatorenal syndrome; ICU, intensive care unit; IV, intravenous; Q6H, every 6 hours; RRT, renal replacement therapy; SCr, serum creatinine.

Results

Baseline demographics

- The CONFIRM study included a total of 300 patients (terlipressin, n = 199; placebo, n = 101)[6]; of these, 109 patients had a > 30% improvement in SCr, and 191 patients had a ≤ 30% improvement in SCr from baseline to the EOT (**Table 1**)
- Baseline demographics were comparable across both SCr improvement status subgroups, irrespective of treatment (**Table 1**)

Table 1. Baseline Demographics and Clinical Characteristics by Status of Improvement in Serum Creatinine From Baseline to EOT, and Treatment Group, CONFIRM ITT Population

Parameter at Baseline	> 30% Improvement in SCr From Baseline to the EOT (n = 109)			≤ 30% Improvement in SCr From Baseline to the EOT (n = 191)		
	Terlipressin (n = 87)	Placebo (n = 22)	*P* value	Terlipressin (n = 112)	Placebo (n = 79)	*P* value
Age, years	54.3 ± 10.46	52.6 ± 13.63	.506	53.7 ± 12.03	53.9 ± 11.37	.891
Male sex, n (%)	55 (63.2)	15 (68.2)	.664	65 (58.0)	44 (55.7)	.748
Race, n (%)			.637			.525
American Indian or Alaska Native	0	0		2 (1.8)	0	
Asian	2 (2.3)	1 (4.5)		3 (2.7)	0	
Black or African American	6 (6.9)	2 (9.1)		6 (5.4)	3 (3.8)	
White	78 (89.7)	19 (86.4)		99 (88.4)	75 (94.9)	
Missing	1 (1.1)	0		2 (1.8)	1 (1.3)	
Alcoholic hepatitis, n (%)	36 (41.4)	8 (36.4)	.668	45 (40.2)	31 (39.2)	.896
SIRS subgroup, n (%)	33 (37.9)	7 (31.8)	.595	51 (45.5)	41 (51.9)	.386
SCr, mg/dL	3.3 ± 0.78	3.0 ± 0.76	.068	3.6 ± 1.14	3.7 ± 1.08	.662
LVP randomization strata, n (%)			.657			.585
LVP < 4L	52 (59.8)	12 (54.4)		71 (63.4)	47 (59.5)	
LVP ≥ 4L	35 (40.2)	10 (45.5)		41 (36.6)	32 (40.5)	
Bilirubin, mg/dL	(n = 83) 11.2 ± 11.77	(n = 22) 17.2 ± 21.42	.378	(n = 105) 14.3 ± 14.39	(n = 77) 14.6 ± 13.86	.626
Received prior albumin, n (%)	86 (98.9)	22 (100.0)	.352	111 (99.1)	78 (98.7)	.528
Amount of prior albumin, g	(n = 86) 317.9 ± 185.27	(n = 22) 344.9 ± 158.10	.306	(n = 111) 348.2 ± 155.32	(n = 78) 377.9 ± 300.31	.919
BUN, mg/dL	(n = 83) 63.1 ± 25.51	(n = 21) 52.8 ± 16.71	.083	(n = 105) 61.9 ± 27.31	(n = 75) 64.3 ± 28.41	.530
HCO_3 or CO_2, mmol/L	(n = 85) 18.9 ± 4.40	(n = 22) 19.9 ± 3.78	.362	(n = 108) 19.2 ± 4.16	(n = 77) 18.7 ± 3.69	.424
MAP, mm Hg, n (%)	78.2 ± 10.31	82.3 ± 10.13	.094	79.0 ± 13.34	76.1 ± 8.73	.093
Child-Pugh score, n (%)			.882			.124
Class A [5–6]	3 (3.4)	0		0	2 (2.5)	
Class B [7–9]	29 (33.3)	9 (40.9)		39 (34.8)	23 (29.1)	
Class C [10–15]	53 (60.9)	13 (59.1)		70 (62.5)	48 (60.8)	
Missing	2 (2.3)	0		3 (2.7)	6 (7.6)	
MELD score	(n = 74) 32.2 ± 6.52	(n = 21) 32.4 ± 7.08	.832	(n = 103) 33.0 ± 6.71	(n = 67) 33.3 ± 5.88	.977
ACLF grade, n (%)			.310			.130
Grade 1	50 (57.5)	9 (40.9)		49 (43.8)	32 (40.5)	
Grade 2	26 (29.9)	8 (36.4)		34 (30.4)	34 (43.0)	
Grade 3	11 (12.6)	5 (22.7)		29 (25.9)	13 (16.5)	
CLIF-SOFA score	(n = 47) 10.1 ± 2.41	(n = 150) 10.1 ± 2.29	.527	(n = 60) 10.7 ± 2.41	(n = 43) 11.1 ± 2.52	.402

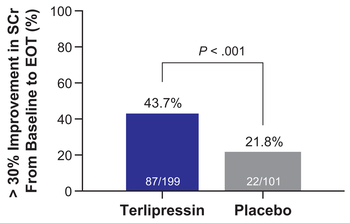
Data are presented as the mean ± SD unless otherwise noted.

For continuous variables, *P* values were generated using ANOVA or a Kruskal-Wallis test following testing for normality; for categorical variables, *P* values were generated using a Chi-square test or a Fisher's exact test.

ANOVA, analysis of variance; ACLF, acute-on-chronic-liver failure; BUN, blood urea nitrogen; CLIF-SOFA, chronic liver failure-sepsis organ failure assessment; CO_2, carbon dioxide; EOT, end of treatment; HCO_3, bicarbonate; ITT, intent-to-treat; LVP, large volume paracentesis; MAP, mean arterial pressure; MELD, Model for End-Stage Liver Disease; SCr, serum creatinine; SD, standard deviation; SIRS, systemic inflammatory response syndrome.

- Overall, a higher number of patients in the terlipressin group had a > 30% improvement in SCr from baseline to the EOT versus the placebo group (terlipressin, 43.7% [87/199] vs placebo, 21.8% [22/101]; $P < .001$) (**Figure 2**)

Figure 2. Proportion of Patients Who Achieved a > 30% Improvement in SCr From Baseline to EOT, by Treatment Group, CONFIRM ITT Population



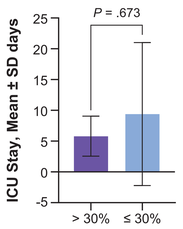
P value was determined using a Chi-square or Fisher's exact test.

EOT, end of treatment; ITT, intent-to-treat; SCr, serum creatinine

Effect of Improved SCr on Clinical Outcomes

- **ICU stay:** Among patients who were admitted to the ICU, the mean (± standard deviation [SD]) length of stay was numerically shorter among those who had a > 30% versus ≤ 30% improvement in SCr from baseline to EOT (5.8 ± 3.25 days vs 9.4 ± 11.62 days, respectively; $P = .673$), but it did not reach statistical significance (**Figure 3**)
- **RRT:** Significantly fewer patients in the > 30% (vs ≤ 30%) improvement in SCr from baseline to EOT subgroup required RRT at Days 30, 60, and 90 ($P < .001$ in each case; **Figure 4**)

Figure 3. Length of ICU Stay in Patients Who Achieved a > 30% or ≤ 30% Improvement in SCr From Baseline to EOT, CONFIRM ITT Population

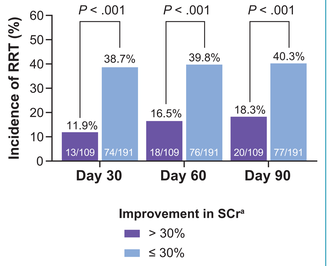


P values were determined using a Kruskal-Wallis test for normality.

[a] Improvement in SCr from baseline to EOT.

EOT, end of treatment; ICU, intensive care unit; ITT, intent-to-treat; SCr, serum creatinine; SD, standard deviation.

Figure 4. Incidence of RRT by Improvement in SCr Status From Baseline to EOT, CONFIRM ITT Population



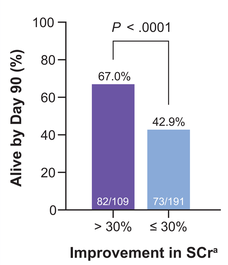
P values were determined using a Chi-square or Fisher's exact test.

[a] Improvement in SCr from baseline to EOT.

EOT, end of treatment; ITT, intent-to-treat; RRT, renal replacement therapy; SCr, serum creatinine.

- **Alive at Day 90:** Overall, a higher proportion of patients who achieved a > 30% improvement in SCr (vs ≤ 30% improvement) were alive by Day 90 (67.0% vs 42.9%, $P < .0001$; **Figure 5**)
- Further, more patients in the > 30% improvement in SCr subgroup were alive and RRT-free by Day 90 compared with those in the ≤ 30% improvement in SCr subgroup (55.0% vs 20.4%, respectively, $P < .001$) (**Figure 6**)

Figure 5. Patients Alive by Day 90 by Improvement in SCr From Baseline to EOT, CONFIRM ITT Population

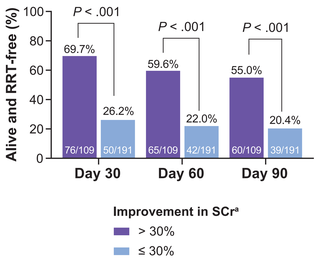


P values were determined using a Chi-square test.

[a] Improvement in SCr from randomization to EOT.

EOT, end of treatment; ITT, intent-to-treat; SCr, serum creatinine.

Figure 6. Patients Alive and RRT-Free by Improvement in SCr From Baseline to EOT, CONFIRM ITT Population



P values were determined using a Chi-square or Fisher's exact test.

[a] Improvement in SCr from baseline to EOT.

EOT, end of treatment; ITT, intent-to-treat; RRT, renal replacement therapy; SCr, serum creatinine.

Conclusions

- Significantly more patients in the terlipressin arm achieved a > 30% improvement in SCr versus placebo
- Patients with a > 30% improvement in SCr had significant improvements in clinical outcomes through Day 90, including a lower incidence of RRT, a greater number of patients alive at Day 90, and a greater number of patients alive and RRT-free at Day 90
- The length of ICU stay was not statistically different between the subgroups of patients with a > 30% improvement versus a ≤ 30% improvement in SCr, although the number of days was numerically shorter for patients who had a > 30% improvement in SCr
- Collectively, the results of this post hoc analysis suggest that the reduction in SCr levels associated with terlipressin treatment improves multiple clinical outcomes among patients with HRS

Acknowledgments

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