The Effect of Terlipressin on Blood Pressure, Mean Arterial Pressure, and Heart Rate in Patients With Hepatorenal Syndrome: A Post Hoc Analysis of the CONFIRM Study

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Introduction

- Hepatorenal syndrome (HRS) is a rapidly progressive renal failure that occurs in patients with decompensated cirrhosis and ascites, and is associated with hemodynamic abnormalities in arterial circulation[1,2]
- Terlipressin is the first and only drug approved by the US Food and Drug Administration (FDA) for the treatment of 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) and American College of Gastroenterology (ACG) guidelines as a first-line treatment for patients with HRS-acute kidney injury[4,5]
- Terlipressin, a synthetic, systemic vasoconstrictor, is a prodrug of lysine [Lys8]-vasopressin (LVP), which is a full agonist of the vascular vasopressin V_1 receptor[6]
  - The concentration of LVP peaks in plasma 1–2 hours after terlipressin administration[7]
- Terlipressin improves renal function in patients with HRS by reducing portal hypertension and increasing effective arterial volume and mean arterial pressure (MAP)—a marker of the hemodynamic response to treatment[8]
  - The pharmacological mechanism of action of terlipressin is associated with a decrease in heart rate, with a possibility of bradycardia as an expected adverse event[9]

Aim of the study

- This study was designed to attain more nuanced information on the changes in MAP, systolic and diastolic blood pressure (SBP and DBP, respectively), and heart rate during terlipressin treatment versus placebo

Methods

- Data from CONFIRM (NCT02770716)—the largest, prospective, placebo-controlled clinical study in patients with HRS who were randomly assigned to receive terlipressin (n = 199) or placebo (n = 101)—both with albumin—were retrospectively analyzed
- Maximum change and time to maximum change in MAP, SBP, DBP, and heart rate were evaluated from predose on Day 1, dose 1, and on the last day, last dose of treatment
- Analysis of variance (ANOVA) or a Kruskal-Wallis test were used to compare numerical outcomes after testing for normality of data distribution

Results

Baseline Patient Demographics and Clinical Characteristics

- In CONFIRM, baseline characteristics were consistent with decompensated liver disease and were similar across treatment groups[2] (**Table 1**)

Table 1. Baseline demographics, clinical characteristics, and vital signs; ITT population[a]

Parameter at baseline	Terlipressin (n = 199)	Placebo (n = 101)
Age, years	54.0 ± 11.3	53.6 ± 11.8
Male sex, n (%)	120 (60)	59 (58)
Cause of liver cirrhosis, n (%)		
Alcohol use	134 (67)	67 (66)
Nonalcoholic steatohepatitis	42 (21)	24 (24)
Viral hepatitis	35 (18)	8 (8)
Autoimmune hepatitis	10 (5)	5 (5)
Primary biliary cirrhosis	5 (3)	3 (3)
Other causes or cryptogenic liver disease	15 (8)	8 (8)
Alcoholic hepatitis, n (%)	81 (41)	39 (39)
SIRS, n (%)	84 (42)	48 (48)
MAP, mm Hg	78.7 ± 12.1	77.5 ± 9.4
SBP, mm Hg; safety population	111.7 ± 17.6	110.5 ± 13.9
DBP, mm Hg; safety population	62.1 ± 11.7	61.3 ± 9.0
Heart rate, beats/min; safety population	79.2 ± 15.7	83.6 ± 14.9
Serum Na, mmol/L	133.1 ± 5.6	133.3 ± 5.5
SCr, mg/dL	3.5 ± 1.0	3.5 ± 1.1
Total bilirubin, mg/dL	13.1 ± 13.5	15.0 ± 15.6
Albumin, g/dL	3.7 ± 0.7	4.0 ± 2.6
Child-Pugh score	10.0 ± 1.9	10.2 ± 1.9
MELD score	32.7 ± 6.6	33.1 ± 6.2

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

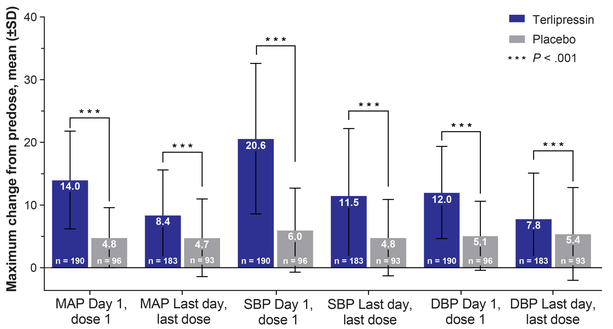
[a] Unless noted as the safety population (terlipressin, n = 200; placebo, n = 99).

DBP, diastolic blood pressure; ITT, intent-to-treat; MAP, mean arterial pressure; MELD, Model for End-stage Liver Disease; Na, sodium; SBP, systolic blood pressure; SCr, serum creatinine; SD, standard deviation; SIRS, systemic inflammatory response syndrome.

Changes in blood pressure during treatment

- There was a significantly higher increase in MAP, SBP, and DBP from predose in patients in the terlipressin group compared with the placebo group, both on Day 1, dose 1, and on the last day, last dose (all $P < .001$) (**Figure 1**)
  - On average, MAP increased by 14.0 mm Hg in the terlipressin group versus 4.8 mm Hg in the placebo group on Day 1, dose 1
  - On the last day, last dose, the average MAP increase was 8.4 mm Hg in the terlipressin group versus 4.7 mm Hg in the placebo group
  - Similar trends were observed for changes in SBP and DBP (**Figure 1**)

Figure 1. Maximum change in MAP, SBP, and DBP from predose on Day 1, dose 1, and on the last day, last dose; ITT population



DBP, diastolic blood pressure; ITT, intent-to-treat; MAP, mean arterial pressure; SBP, systolic blood pressure; SD, standard deviation.

- Median times to maximum change in SBP, DBP, and MAP on Day 1, dose 1, and on the last day, last dose were similar between treatment groups ($P > .20$ in all instances) (**Tables 2** and **3**)

Table 2. Time to maximum change in MAP, SBP, and DBP from predose on Day 1, dose 1; ITT population

Time (hours)	MAP		SBP		DBP	
	Terlipressin (n = 190)	Placebo (n = 96)	Terlipressin (n = 190)	Placebo (n = 96)	Terlipressin (n = 190)	Placebo (n = 96)
Mean ± SD	1.3 ± 1.61	1.3 ± 1.83	1.4 ± 1.60	1.3 ± 1.83	1.3 ± 1.68	1.2 ± 1.84
Median (Q1, Q3)	0.1 (0.1, 2.0)	0.1 (0.1, 2.0)	2.0 (0.1, 2.0)	0.1 (0.1, 2.0)	0.1 (0.1, 2.0)	0.1 (0.1, 2.0)
Min, max	0.08, 6.0	0.08, 6.0	0.08, 6.0	0.08, 6.0	0.08, 6.0	0.08, 6.0
***P* value[a]**	.415		.212		.236	

[a] *P* values comparing terlipressin and placebo groups were calculated from a Kruskal-Wallis test.

DBP, diastolic blood pressure; ITT, intent-to-treat; MAP, mean arterial pressure; max, maximum; min, minimum; Q1, 25% quartile; Q3, 75% quartile; SBP, systolic blood pressure; SD, standard deviation.

Table 3. Time to maximum change in MAP, SBP, and DBP from predose on the last day, last dose; ITT population

Time (hours)	MAP		SBP		DBP	
	Terlipressin (n = 183)	Placebo (n = 93)	Terlipressin (n = 183)	Placebo (n = 93)	Terlipressin (n = 183)	Placebo (n = 93)
Mean ± SD	0.9 ± 0.96	0.9 ± 0.96	0.9 ± 0.95	0.9 ± 0.96	0.9 ± 0.95	0.9 ± 0.95
Median (Q1, Q3)	0.1 (0.1, 2.0)	0.1 (0.1, 2.0)	0.1 (0.1, 2.0)	0.1 (0.1, 2.0)	0.1 (0.1, 2.0)	0.1 (0.1, 2.0)
Min, max	0.08, 2.0	0.08, 2.0	0.08, 2.0	0.08, 2.0	0.08, 2.0	0.08, 2.0
***P* value[a]**	.909		.688		.747	

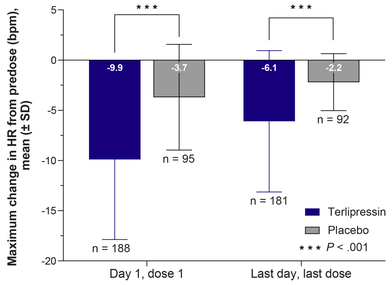
[a] *P* values comparing terlipressin and placebo groups were calculated from a Kruskal-Wallis test.

DBP, diastolic blood pressure; ITT, intent-to-treat; MAP, mean arterial pressure; max, maximum; min, minimum; Q1, 25% quartile; Q3, 75% quartile; SBP, systolic blood pressure; SD, standard deviation.

Changes in heart rate during treatment

- The maximum decrease in heart rate from predose was significantly higher in the terlipressin group versus placebo both on Day 1, dose 1, and on the last day, last dose, $P < .001$ each (**Figure 2**):
  - On Day 1, dose 1, mean change in heart rate was –9.9 beats/min [bpm] in the terlipressin group versus –3.7 bpm in the placebo group
  - On the last day, last dose, the mean decrease in heart rate was larger in the terlipressin group as compared with placebo (terlipressin: –6.1 bpm; placebo:–2.2 bpm; $P < .001$)

Figure 2. Maximum change in heart rate from predose on Day 1, dose 1, and the last day, last dose; ITT population



bpm, beats per minute; ITT, intent-to-treat; HR, heart rate; SD, standard deviation.

- On Day 1, dose 1, median time to maximum change in heart rate from predose in the terlipressin group was 2 hours (compared with 0.1 hours in the placebo group)
- By the last day, last dose, median time to maximum change in heart rate was 0.1 hours in both treatment groups (**Table 4**)

Table 4. Time to maximum change in heart rate from predose; ITT population

Time (hours)	Day 1, dose 1		Last day, last dose	
	Terlipressin (n = 188)	Placebo (n = 95)	Terlipressin (n = 181)	Placebo (n = 92)
Mean ± SD	1.6 ± 1.73	1.4 ± 1.95	1.0 ± 0.96	0.7 ± 0.90
Median (Q1, Q3)	2.0 (0.1, 2.0)	0.1 (0.1, 2.0)	0.1 (0.1, 2.0)	0.1 (0.1, 2.0)
Min, max	0.08, 6.0	0.08, 6.0	0.08, 2.0	0.08, 2.0
***P* value[a]**	.062		.029	

[a] *P* values comparing the terlipressin and placebo groups at each time point were calculated from a Kruskal-Wallis test.

ITT, intent-to-treat; max, maximum; min, minimum; Q1, 25% quartile; Q3, 75% quartile; SD, standard deviation.

Conclusions

- Postadministration, MAP, SBP, and DBP were significantly higher in the terlipressin group versus the placebo group
- There was no significant difference in time to maximum change in MAP, SBP, and DBP between treatment groups
- Heart rate decreased significantly more in the terlipressin group versus placebo
- Time to maximum change in heart rate in the terlipressin group on Day 1 aligns with the known time to peak plasma concentration of LVP—an active metabolite of terlipressin
- These small and predictable changes in heart rate support utilization of terlipressin without the need for cardiac monitoring

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