ACG 2022
October 21–26, Charlotte, NC

Impact of Terlipressin on Serum Sodium Levels in Patients With Hepatorenal Syndrome Type 1 (HRS-1) in the CONFIRM Study

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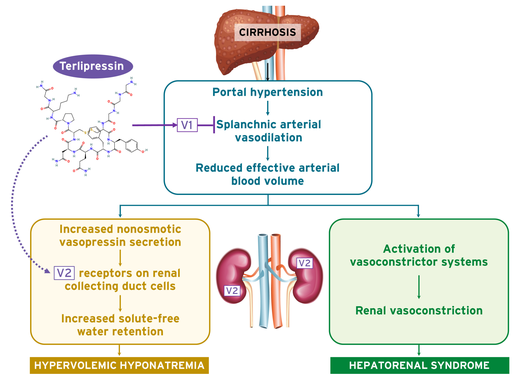
Background

- Hyponatremia—defined as a serum sodium (Na) concentration of ≤135 mmol/L—is a complication observed in 49% of patients with decompensated advanced liver disease and is associated with a poor prognosis (**Figure 1**)[1–3]
- Decompensated cirrhosis with ascites may also lead to a potentially fatal hepatorenal syndrome-acute kidney injury (HRS-AKI), formerly known as hepatorenal syndrome type 1 (HRS-1) (**Figure 1**)[4]
- Terlipressin is a vasopressin analogue that can successfully reverse HRS and improve kidney function in eligible patients diagnosed with HRS-1[5,6]
  - The mechanism of action of terlipressin is based on its agonistic interaction with vasopressin receptor type 1 (V1) leading to vasoconstriction of the splanchnic circulation, a reduction in renal arterial resistance, and an increase in renal perfusion pressure (**Figure 1**)[4,7]
- It was noted that terlipressin can also worsen hyponatremia in patients with acute portal-hypertensive bleeding, possibly via activation of renal vasopressin receptor type 2 (V2) located on the basolateral membrane of the distal tubule and collecting ducts in the kidney, which results in an antidiuretic effect (**Figure 1**)[8]
  - However, worsening of hyponatremia was rarely observed when patients were treated with terlipressin for HRS[8]

Figure 1. Pathogenesis of hepatorenal syndrome and hyponatremia in cirrhosis and the effect of terlipressin[a].



[a]Based on reference [8].
A possible mechanism underlying the development of hyponatremia is related to the circulatory dysfunction caused by decompensated cirrhosis. Reduced blood flow leads to increased vasopressin secretion, which activates V2 receptors, resulting in the impairment of renal solute-free secretion and, consequently, the development of hypervolemic hyponatremia.
Terlipressin acts as a splanchnic and systemic vasoconstrictor with selective activity for V1 receptors, resulting in reduced renal arterial resistance and increased renal perfusion pressure in patients with hepatorenal syndrome. At the same time, terlipressin activates V2 receptors in the renal collecting duct cells, exerting an antidiuretic effect that can worsen hyponatremia.
V1, vasopressin receptor type 1; V2, vasopressin receptor type 2.

Aim of the study

- This study was designed to evaluate the effect of terlipressin on serum Na levels, using data from the CONFIRM study—the largest-to-date, prospective, randomized, placebo-controlled, Phase III study of terlipressin in patients with HRS-1[5]

Methods

- Data from the CONFIRM study (N=300, clinicaltrials.gov NCT02770716), in which patients with HRS-1 were treated with terlipressin (1–2 mg every 6 hours) plus concomitant albumin or placebo plus concomitant albumin, were retrospectively analyzed
  - Presently, terlipressin is an investigational product in the United States (US) and is not labeled for the usage discussed in this poster. The use of terlipressin for the treatment of patients with HRS is pending approval by the US Food and Drug Administration (FDA)
- Overall changes and treatment response-dependent changes in serum Na levels were evaluated from baseline to the end of treatment (EOT)
- A complete response (CR=HRS reversal) was defined as at least 1 serum creatinine (SCr) value of ≤1.5 mg/dL while on treatment; a partial response (PR) was defined as a ≥30% improvement in SCr but not achieving HRS reversal; and no response (NR) was defined as no change or worsening in SCr
- EOT was defined as the last date/time of treatment plus 24 hours
- Numerical values were compared using analysis of variance (ANOVA) or Kruskal-Wallis tests following testing for normality

Results

Baseline characteristics

- Baseline characteristics were consistent with decompensated liver disease and were similar across treatment groups (**Table 1**)
  - In the terlipressin and placebo groups, mean Model for End-Stage Liver Disease (MELD) scores (mean ± standard deviation [SD]) were 32.7 ± 6.6 and 33.1 ± 6.2, respectively
  - On average, hyponatremia was moderate; serum Na levels (mean ± SD) were almost identical in the 2 treatment groups: 133.1 ± 5.6 mmol/L and 133.3 ± 5.5 mmol/L, respectively

Results (continued)

Table 1. Baseline demographics and clinical characteristics, ITT population.

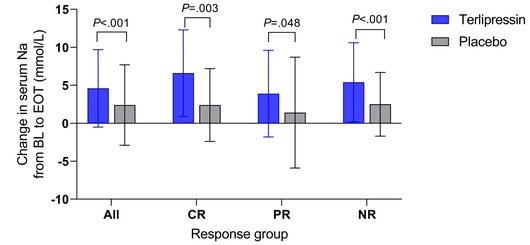
Parameter	Terlipressin (n=199)	Placebo (n=101)
Age (years)	54.0 ± 11.3	53.6 ± 11.8
Male sex, n (%)	120 (60)	59 (58)
Cause of liver cirrhosis, n (%)		
Alcohol use	134 (67)	67 (66)
Nonalcoholic steatohepatitis	42 (21)	24 (24)
Viral hepatitis	35 (18)	8 (8)
Autoimmune hepatitis	10 (5)	5 (5)
Primary biliary cirrhosis	5 (3)	3 (3)
Other cause 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
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 level (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 mean ± SD, unless otherwise noted.
ITT, intent-to-treat; MAP, mean arterial pressure; MELD, Model for End-Stage Liver Disease; Na, sodium; SCr, serum creatinine; SD, standard deviation; SIRS, systemic inflammatory response syndrome.

Treatment effect on hyponatremia

- Changes in serum Na levels are presented in **Figure 2** and **Table 2**
  - By EOT, serum Na levels increased significantly more in the terlipressin group versus the placebo group in the whole population, and in all clinical response categories defined by changes in SCr
  - Within each treatment group, the improvement in serum Na was numerically higher in patients who had a CR versus a PR; however, changes in serum Na were similar in patients who experienced a CR or an NR

Figure 2. Change in serum Na concentrations from baseline to EOT, ITT population.



Data are presented as the mean ± SD.
BL, baseline; CR, complete response; EOT, end of treatment; ITT, intent-to-treat; Na, sodium; NR, no response; PR, partial response; SD, standard deviation.

Table 2. Change from baseline to EOT in serum Na concentrations, ITT population.

Response category		Mean change in serum Na level (mmol/L)		*P* value
		Terlipressin (n=199)	Placebo (n=101)	
All	**n**	194	98	<.001
	Change	4.6 ± 5.1	2.4 ± 5.3	
CR[a]	**n**	71	17	.003
	Change	6.6 ± 5.7	2.4 ± 4.8	
PR[b]	**n**	21	26	.048
	Change	3.9 ± 5.7	1.4 ± 7.3	
NR[c]	**n**	134	50	<.001
	Change	5.4 ± 5.2	2.5 ± 4.2	

The change is presented as the mean ± SD.
[a] CR: HRS reversal; [b] PR: ≥30% improvement in SCr but not achieving HRS reversal; [c] NR: no change or worsening of SCr.
CR, complete response; EOT, end of treatment; HRS, hepatorenal syndrome; ITT, intent-to-treat; Na, sodium; NR, no response; PR, partial response; SCr, serum creatinine; SD, standard deviation.

Conclusions

- The observed increases in serum Na concentrations by EOT indicate an improvement in hyponatremia in both the terlipressin and placebo treatment groups overall, and in all response categories
- In contrast with previous observations[8], serum Na concentrations increased significantly more when patients with HRS-1 were treated with terlipressin versus placebo
- These results suggest that the use of terlipressin does not increase the risk of developing hyponatremia in patients with HRS-1

Contact information

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Acknowledgment

Medical writing and editorial support, conducted in accordance with Good Publication Practice 2022 Update (GPP 2022) and the International Committee of Medical Journal Editors (ICMJE) guidelines, were provided by Julia Grigorieva, PhD, of Oxford PharmaGenesis Inc., Newtown, PA, USA, and funded by Mallinckrodt Pharmaceuticals.

Funding and commercial support: Mallinckrodt Pharmaceuticals.