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The Effect of Obesity on the Clinical Response to Terlipressin in Patients with Hepatorenal Syndrome: Retrospective Assessment from a Pooled Patient Cohort

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INTRODUCTION

- Hepatorenal syndrome-acute kidney injury (HRS-AKI) is a potentially reversible, life-threatening deterioration in kidney function occurring in patients with advanced liver cirrhosis and ascites[1]
  - Ascites is a key feature of HRS-AKI[2]
- Per guidelines from the American Association for the Study of Liver Diseases (AASLD), ascites, in patients with cirrhosis, can be graded for severity (from grade 1 to 3) according to the amount of fluid accumulated in the abdominal cavity[3]
- Patients with HRS-AKI may present in different weight categories ranging from underweight to obese owing to the severity of ascites[2]
- Body mass index (BMI) is often used to identify weight category; however, in patients with HRS-AKI, BMI estimates should be corrected for the presence of ascites[2]
- Terlipressin, the only US Food and Drug Administration-approved therapy for adult patients with HRS and a rapid deterioration in kidney function, can reverse HRS[4]
- Pharmacokinetic and pharmacodynamic simulations indicated that body weight has no clinically meaningful effect on the exposure of the active terlipressin metabolite, lysine-vasopressin; consequently, no weight-based dose adjustment for terlipressin is needed[5]
  - However, the direct impact of BMI on HRS reversal rates in patients with HRS-AKI who are treated with terlipressin has not been previously studied

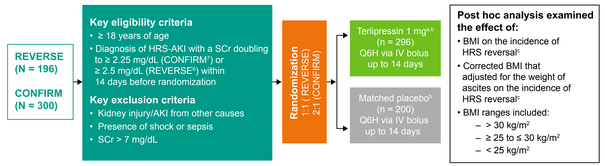
AIM OF THE STUDY

- To assess the potential impact of BMI and corrected BMI (cBMI) for the presence of ascites on the incidence of HRS reversal in patients with HRS-AKI

METHODS

- Using data pooled from 2 Phase III, placebo-controlled, clinical studies of terlipressin in patients with HRS-AKI (REVERSE[6] [NCT03439254] and CONFIRM[7] [NCT02770716]), the effects of baseline BMI and cBMI on the incidence of HRS reversal were examined (**Figure 1**)

Figure 1. Study design



[a]**Concomitant albumin was strongly recommended** at a dose of 20–40 g/day in REVERSE; and 1 g/kg body weight to a maximum of 100 g on Day 1 and 20–40 g/day thereafter in CONFIRM.
[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.
[c]Defined as a ≥ 1 SCr value of ≤ 1.5 mg/dL while on treatment (≤ 24 hours after the last dose of study drug).
AKI, acute kidney injury; BMI, body mass index; HRS-AKI, hepatorenal syndrome-acute kidney injury; IV, intravenous; Q6H, every 6 hours; SCr, serum creatinine.

- HRS reversal was defined as ≥ 1 serum creatinine value of ≤ 1.5 mg/dL while on treatment (≤ 24 h after the last dose of the study drug)
- Based on an ultrasound and computerized tomography examination of 60 patients with alcohol-associated hepatitis[8], the mean volume of ascitic fluid was estimated as follows: grade 1 = 796 mL; grade 2 = 3498 mL; and grade 3 = 7648 mL (**Table 1**)
- Further, based on previously published data[9], the density of ascitic fluid was estimated as 1 g/mL
- Consequently, based on the estimates of mean volume and density, the weight of ascites grades 1, 2, and 3, were estimated to be **0.8 kg, 3.5 kg, and 7.7 kg**, respectively (**Table 1**)
- A cBMI for individual patients was calculated as follows:
  - (body weight [kg] − weight of ascites [kg])/height [m²]
- Screened *P* values for HRS incidence comparisons were derived from a Chi-square test or a Fisher's Exact test

Table 1. Ascites grade and weight estimates

Ascites	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Large)
Detection	Only detected by ultrasound	Moderate symmetric distension of the abdomen	Marked distension of the abdomen
Estimated mean volume	796 mL	3498 mL	7648 mL
Estimated mean weight	0.8 kg	3.5 kg	7.7 kg

RESULTS

- Baseline patient demographic and clinical characteristics in the pooled intent-to-treat study population (N = 496; terlipressin, n = 296; placebo, n = 200) were consistent with the presence of advanced cirrhosis and HRS-AKI (**Table 2**)

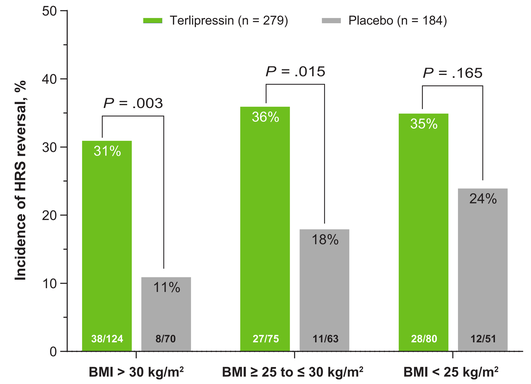
Table 2. Demographic and baseline characteristics, pooled CONFIRM and REVERSE ITT population

Parameter	Terlipressin (n = 296)	Placebo (n = 200)
Age, years, mean ± SD	55 ± 10	54 ± 10
Sex, male	172 (58)	126 (63)
Race		
American Indian or Alaska Native	3 (1)	1 (1)
Asian	8 (3)	1 (1)
Black or African American	19 (6)	11 (6)
White	262 (89)	186 (93)
Alcohol-associated hepatitis	101 (34)	64 (32)
Baseline serum creatinine (mg/dL), mean ± SD	3.5 ± 1.0	3.6 ± 1.1
SIRS subgroup	112 (38)	78 (39)
MELD score (n)	261	174
mean ± SD	32.9 ± 6.5	32.9 ± 5.8
Child-Pugh score		
Class A [5–6]	5 (2)	2 (1)
Class B [7–9]	91 (31)	61 (31)
Class C [10–15]	189 (64)	124 (62)
Missing	11 (4)	13 (7)
MAP, mm Hg (n)	296	199
mean ± SD	78 ± 12	77 ± 10
MAP < 65 mm Hg	42 (14)	23 (12)
Hepatocellular carcinoma	20 (7)	18 (9)
Etiology of cirrhosis		
Alcohol-associated	183 (62)	121 (61)
Autoimmune hepatitis	11 (4)	6 (3)
MASLD	50 (17)	31 (16)
Viral hepatitis B	7 (2)	4 (2)
Viral hepatitis C	68 (23)	49 (25)
Primary biliary cirrhosis	9 (3)	6 (3)
Ascites grade (yes)	291 (98)	192 (96)
1	79 (27)	41 (21)
2	112 (38)	62 (31)
3	100 (34)	89 (45)

Data are presented as the n (%) unless otherwise noted.
ITT, intent-to-treat; MAP, mean arterial pressure; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, Model for End-Stage Liver Disease; SD, standard deviation; SIRS, systemic inflammatory response syndrome.

- In the terlipressin group, out of the 291 patients with a recorded ascites grade, 79/291 had ascites grade 1, 112/291 had ascites grade 2, and 100/291 had ascites grade 3, respectively
- In the placebo group, out of the 192 patients with a recorded ascites grade, 41/192 had ascites grade 1, 62/192 had ascites grade 2, and 89/192 had ascites grade 3, respectively
- Among patients evaluable for BMI (n = 463), HRS reversal was significantly higher among patients in the terlipressin group versus the placebo group in the BMI categories > 30 kg/m² (31% vs 11%, *P* = .003) and ≥ 25 to ≤ 30 kg/m² (36% vs 18%, *P* = .015); in the BMI category < 25 kg/m², the difference did not reach statistical significance (35% vs 24%, *P* = .165) (**Figure 2**)

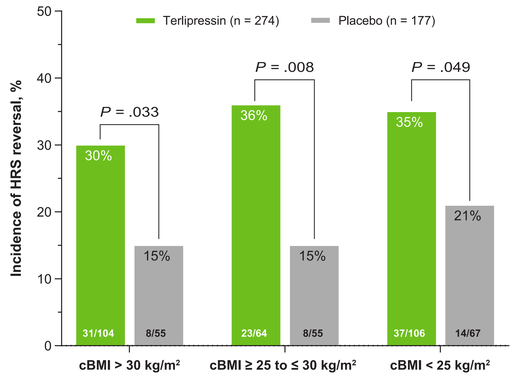
Figure 2. HRS reversal by treatment group and BMI category



BMI, body mass index; HRS, hepatorenal syndrome.

- Among patients evaluable for cBMI (n = 451), HRS reversal was significantly higher in the terlipressin group versus the placebo group in all 3 cBMI categories (ie, > 30 kg/m² [30% vs 15%, *P* = .033], ≥ 25 to ≤ 30 kg/m² [36% vs 15%, *P* = .008], and < 25 kg/m² [35% vs 21% *P* = .049]) (**Figure 3**)
- Notably, within each treatment group (ie, terlipressin or placebo), there were no significant differences in the incidence of HRS reversal between the BMI and cBMI subgroups > 30 kg/m², ≥ 25 to ≤ 30 kg/m², and < 25 kg/m² (all *P* > .05)

Figure 3. HRS reversal by treatment group and cBMI category



cBMI, corrected body mass index; HRS, hepatorenal syndrome..

CONCLUSIONS

- **Patients with HRS-AKI and obesity (cBMI > 30 kg/m²) who were treated with terlipressin had a significantly higher incidence of HRS reversal versus placebo, similar to patients with a cBMI ≥ 25 to ≤ 30 kg/m², and cBMI < 25 kg/m²**
- **Terlipressin treatment provides clinical benefit to patients with HRS-AKI, regardless of their BMI category**

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