ACG 2022
October 21–26, Charlotte, NC

Treatment Response to Terlipressin Plus Albumin Varies by Precipitating Factor in Patients with Hepatorenal Syndrome Type 1

R. Todd Frederick[1], Nicholas Lim[2], Mohammed Khan[3], Zunaria Zafar[4], Khurram Jamil[5]

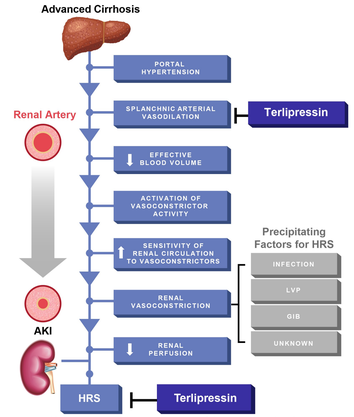
[1]Department of Transplant, California Pacific Medical Center, San Francisco, CA, USA; [2]Division of Gastroenterology, Hepatology and Nutrition, University of Minnesota, Minneapolis, MN, USA; [3]Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA, USA; [4]St. Mary Medical Center, Langhorne, PA, USA; [5]Mallinckrodt Pharmaceuticals, Hampton, NJ, USA.

D0499

Introduction

- Hepatorenal syndrome type 1 (HRS; formerly HRS-1, now known as HRS-acute kidney injury [HRS-AKI]) is a severe, but potentially reversible type of AKI that occurs in patients with portal hypertension, most commonly in the setting of decompensated cirrhosis[1]
- HRS is, in part, the consequence of severe portal hypertension, systemic and splanchnic arterial vasodilation, effective hypovolemia, and compensatory renal artery vasoconstriction that together impair renal function that ultimately leads to the development of AKI[2] (**Figure 1**)

Figure 1. Development of HRS[a], associated precipitating factors[b], and the role of terlipressin in HRS reversal[c]



[a] Worsening portal hypertension—a key consequence of decompensated cirrhosis—progressively worsens vasodilation of the splanchnic vasculature, leading to a reduction in effective blood volume and organ hypoperfusion[2]. Compensatory mechanisms in the form of renin-angiotensin-aldosterone release and upregulation of the sympathetic nervous system results in profound renal vasoconstriction, impaired renal perfusion, and the development of HRS[2].
[b] Many cases of HRS arise from a precipitating event that accelerates impairments in renal function[2].
[c] Terlipressin, a vasopressin analogue, counteracts the hemodynamic dysfunction characteristic of HRS and leads to HRS reversal—defined as at least 1 serum creatinine value of ≤1.5 mg/dL while on treatment—in approximately 20% to 40% of patients[4–6].
AKI, acute kidney injury; GIB, gastrointestinal bleeding; HRS, hepatorenal syndrome; LVP, large volume paracentesis.

- HRS is often triggered by a precipitating event that further impairs renal function, such as infection, large volume paracentesis (LVP) with consequent circulatory dysfunction syndrome, an excessive response to diuretics, or gastrointestinal bleeding (GIB)[2] (**Figure 1**). However, sometimes a specific precipitating event cannot be identified (**Figure 1**)
- Terlipressin, a vasopressin analogue, exerts vasoconstrictive effects on the splanchnic circulation, improves renal perfusion, and, when combined with albumin, reverses HRS in 20% to 40% of patients, as demonstrated by 3 Phase III, randomized, placebo-controlled studies[4–6]
- Further, terlipressin was recently approved by the United States Food and Drug Administration to improve kidney function in adult patients with HRS[7]
- However, few studies have evaluated whether the clinical response to terlipressin therapy varies based on the type of precipitating event that triggers HRS[8,9]

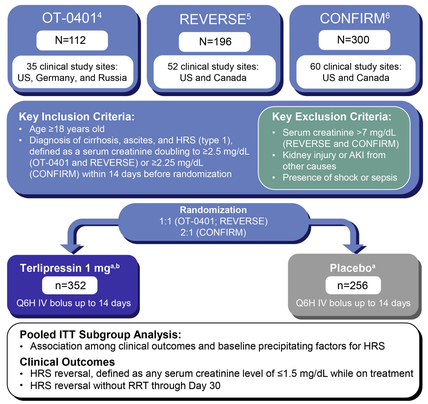
Study Aims

- To assess the impact of common baseline precipitants of HRS on the clinical response to terlipressin in patients with HRS in the pooled population from 3 Phase III, randomized, placebo-controlled studies (OT-0401[4], REVERSE[5], and CONFIRM[6])
- To determine whether the clinical response to terlipressin therapy varies between patients who present with an identifiable—and therefore treatable—precipitant at baseline versus an unknown precipitant at baseline

Methods

- A subgroup analysis was performed using data from 3 large Phase III randomized, placebo-controlled clinical studies in which patients with HRS were treated with terlipressin 4–8 mg/day (1–2 mg every 6 hours) plus albumin or placebo plus albumin (**Figure 2**)
- The subgroup analysis compared the efficacy of terlipressin versus placebo in 4 subgroups of patients in the pooled intent-to-treat (ITT) population who presented with either infection, LVP and/or diuretic use, GIB, or an unknown precipitant at baseline, as determined by the principal investigators
  - The precipitant subgroups were not mutually exclusive (ie, a proportion of patients presented with >1 precipitant at baseline)

Figure 2. Study design for the subgroup analysis



[a] **Concomitant albumin was recommended** at a dose of 100 g on Day 1 and then 25 g daily until the EOT in OT-0401; 20–40 g/day in REVERSE; and 1 g/kg to a maximum of 100 g on Day 1 and 20–40 g/day thereafter in CONFIRM.
[b] Each study utilized the same starting dose of terlipressin (1 mg Q6H) and allowed an increase in dose (to 2 mg Q6H) if serum creatinine had decreased by less than 30% from baseline—after 3 days of treatment.
AKI, acute kidney injury; EOT, end of treatment; HRS, hepatorenal syndrome; ITT, intent-to-treat; IV, intravenous; Q6H, every 6 hours; RRT, renal replacement therapy; US, United States.

- Efficacy outcomes included the proportion of patients who achieved HRS reversal and HRS reversal without renal replacement therapy (RRT) by Day 30 in the pooled ITT population
  - HRS reversal was defined as the percentage of patients with at least 1 serum creatinine measurement of ≤1.5 mg/dL while on treatment
  - RRT was defined as any procedure to replace non-endocrine kidney function
- Safety data are presented for the proportion of patients with an adverse event (AE) or a serious adverse event (SAE) by treatment group in the pooled safety population
- Data were analyzed using Chi-square or Fisher's exact tests

Results

Baseline patient demographics and clinical characteristics

- Baseline demographics and clinical characteristics of patients in the pooled ITT population were generally similar between treatment groups (**Table 1**)

Table 1. Baseline demographics and clinical characteristics, pooled ITT population[a]

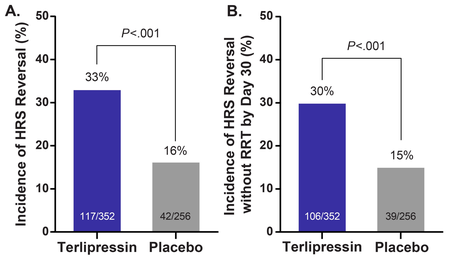
Parameter	Terlipressin (n=352)	Placebo (n=256)
Age (year), median (min, max)	55 (23, 78)	56 (25, 82)
Sex		
Male	213 (61)	165 (65)
Female	139 (40)	91 (36)
Race		
American Indian or Alaskan Native	3 (1)	4 (2)
Asian	8 (2)	1 (0.4)
Black or African American	24 (7)	14 (6)
Native Hawaiian or Other Pacific Islander	0	1 (0.4)
White	313 (89)	235 (92)
Etiology of cirrhosis		
Alcohol use	212 (60)	150 (59)
Hepatitis C	90 (26)	68 (27)
Nonalcoholic steatohepatitis	52 (15)	36 (14)
Autoimmune hepatitis	13 (4)	9 (4)
Hepatitis B	11 (3)	5 (2)
Primary biliary cirrhosis	11 (3)	7 (3)
Alcoholic hepatitis	121 (34)	84 (33)
SIRS subgroup[b]	112 (38)	78 (39)
Hepatocellular carcinoma	24 (7)	24 (9)
Esophageal varices	187 (53)	141 (55)
Ascites	347 (99)	247 (97)
MAP (mm Hg), n	352	255
Mean ± SD	77.3 ± 12.0	76.6 ± 10.9
Serum creatinine (mg/dL), mean ± SD	3.6 ± 1.3	3.7 ± 1.1
Total bilirubin (mg/dL), n	338	249
Mean ± SD	12.8 ± 12.7	14.1 ± 14.6
Child-Pugh class, n	337	242
Class A (5–6)	5 (1)	3 (1)
Class B (7–9)	100 (28)	71 (28)
Class C (10–15)	232 (66)	168 (66)
MELD score, n	312	221
Mean ± SD	33.0 ± 6.4	33.1 ± 5.9
Prior albumin[c] (g), n	312	220
Mean ± SD	328.4 ± 187.7	313.3 ± 236.8
Concomitant albumin (g), n	299	228
Mean ± SD	217.7 ± 195.8	242.0 ± 183.7

Data are presented as n (%), unless otherwise noted.
[a] Pooled data were collated from the following Phase III studies: OT-0401[4], REVERSE[5], and CONFIRM[6].
[b] Criteria to define the SIRS subgroup were not collected for OT-0401. Percentages are based on the number of patients in each treatment group, excluding OT-0401.
[c] Prior albumin use occurred during the 14 days prior to randomization. In OT-0401, sodium chloride and/or albumin was considered acceptable for fluid challenge. Mean ± SD are based on patients in REVERSE and CONFIRM, excluding OT-0401.
ITT, intent-to-treat; MAP, mean arterial pressure; max, maximum; MELD, Model for End-Stage Liver Disease; min, minimum; SD, standard deviation; SIRS, systemic inflammatory response syndrome.

HRS reversal and HRS reversal without RRT by Day 30

- The incidence of HRS reversal was higher in the terlipressin group compared with the placebo group (33% versus 16%, respectively, *P*<.001; **Figure 3A**)
- Durability of HRS reversal—defined as the percentage of patients with HRS reversal without RRT by Day 30—was achieved by significantly more terlipressin-treated patients than placebo-treated patients (30% versus 15%, respectively, *P*<.001; **Figure 3B**)

Figure 3. (**A**) HRS reversal, and (**B**) HRS reversal without RRT by Day 30, pooled ITT population[a]

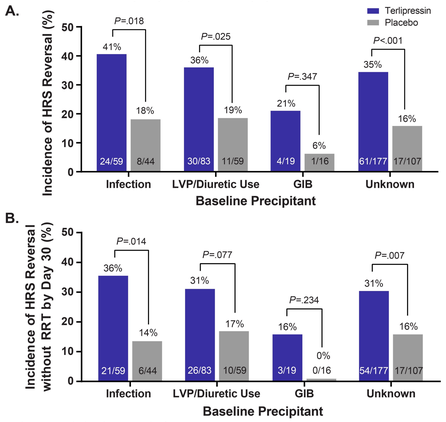


P values were calculated using Chi-square tests.
[a] Pooled data were collated from the following Phase III studies: OT-0401[4], REVERSE[5], and CONFIRM[6].
HRS, hepatorenal syndrome; ITT, intent-to-treat; RRT, renal replacement therapy.

Impact of precipitating factors for HRS on clinical outcomes

- Among patients with HRS who presented with an infection at baseline, HRS reversal was achieved by 41% versus 18% of patients in the terlipressin and placebo groups, respectively (*P*=.018; **Figure 4A**)
  - HRS reversal without RRT by Day 30 in patients with a baseline infection was achieved by 36% of patients in the terlipressin group versus 14% of patients in the placebo group (*P*=.014; **Figure 4B**)
- Among patients who presented with LVP and/or excessive diuretic use at baseline, HRS reversal was achieved by 36% of patients in the terlipressin group compared with 19% of patients in the placebo group (*P*=.025, **Figure 4A**)
  - Numerically, there was a higher incidence of HRS reversal without RRT by Day 30 observed in terlipressin-treated patients who presented with LVP and/or diuretic use at baseline versus placebo-treated patients (terlipressin: 31%; placebo: 17%; *P*=.077; **Figure 4B**)
- HRS reversal and HRS reversal without RRT by Day 30 were not statistically different between treatment groups in patients who presented with GIB at baseline (**Figure 4A** and **Figure 4B**, respectively)
- Finally, the incidence of HRS reversal and HRS reversal without RRT by Day 30 among patients who were classified as having an unknown precipitant at baseline were both significantly higher in the terlipressin group compared with the placebo group (HRS reversal: 35% versus 16%, *P*<.001; HRS reversal without RRT: 31% versus 16%; *P*=.007) (**Figure 4A** and **Figure 4B**, respectively)

Figure 4. Impact of baseline precipitant on (**A**) HRS reversal, and (**B**) HRS reversal without RRT by Day 30, pooled ITT population[a]



P values were calculated using a Fisher's exact test.
[a] Pooled data were collated from the following Phase III studies: OT-0401[4], REVERSE[5], and CONFIRM[6].
GIB, gastrointestinal bleeding; HRS, hepatorenal syndrome; ITT, intent-to-treat; LVP, large volume paracentesis; RRT, renal replacement therapy.

Safety

- Overall across the 3 studies, the incidence of AEs and SAEs were similar between treatment groups (terlipressin versus placebo: AEs, 91% versus 90%; SAEs, 65% versus 60%) (**Table 2**)

Table 2. Summary of AEs and SAEs, pooled safety population[a]

Parameter	Terlipressin (n=349)	Placebo (n=249)
AEs of any grade	318 (91)	225 (90)
Withdrawals due to AEs	47 (14)	13 (5)
SAEs[b] of any grade	227 (65)	149 (60)
SAEs by SOC and PT in ≥5% of patients		
Respiratory, thoracic, and mediastinal disorders	**57 (16)**	**26 (10)**
Respiratory failure	29 (8)	6 (2)
General disorders and administration site conditions	**30 (9)**	**14 (6)**
MODS	26 (7)	8 (3)
Hepatobiliary disorders	**74 (21)**	**63 (25)**
Chronic hepatic failure	21 (6)	15 (6)
Hepatic failure	21 (6)	23 (9)
Infections and infestations	**43 (12)**	**19 (8)**
Sepsis	18 (5)	4 (2)

Data are presented as n (%).
[a] Pooled data were collated from the following Phase III studies: OT-0401[4], REVERSE[5], and CONFIRM[6].
[b] Up to 30 days posttreatment.
AE, adverse event; MODS, multiple organ dysfunction syndrome; PT, preferred term; SAE, serious adverse event; SOC, system organ class.

Conclusions

- In this pooled subgroup analysis, a higher proportion of terlipressin-treated patients who presented with infection and LVP/diuretic use at baseline achieved HRS reversal and avoided RRT for up to 30 days compared with patients in the respective placebo groups
- A similar proportion of patients with GIB achieved HRS reversal, regardless of treatment. However, further analysis is needed as the number of patients in the GIB subgroup was comparatively small
- Contrary to an a priori hypothesis, the efficacy of terlipressin therapy in the pooled population was similar in patients who had an unknown precipitant for HRS at the time of treatment compared to patients who presented with an identifiable precipitant
- A limitation of the present study was that the precipitant subgroups were not mutually exclusive. Evaluation of whether the presence of >1 precipitant at baseline influences the efficacy of terlipressin for the treatment of patients with HRS is needed
- In summary, terlipressin plus albumin was more efficacious than placebo plus albumin in facilitating HRS reversal across precipitant subgroups

Contact information

R. Todd Frederick, Todd.Frederick@sutterhealth.org

References

1. Baraldi O et al. *World J Nephrol*. 2015;4(5):511–520.
2. Angeli P et al. *World J Nephrol*. 2019;71(4):811–822.
3. Wong F. *Nat Rev Gastroenterol Hepatol*. 2015;12(12):71–719.
4. Sanyal AJ et al. *Gastroenterology*. 2008;134:1360–1368.
5. Boyer TD et al. Gastroenterology. 2016;150:1579–1589.
6. Wong F et al. *N Engl J Med*. 2021;384:818–828.
7. TERLIVAZ® (terlipressin). Full Prescribing Information. Bedminster, NJ: Mallinckrodt Pharmaceuticals; 2022.
8. Altun R et al. *SpringerPlus*. 2015;4:806.
9. Sanyal AJ et al. *Aliment Pharmacol Ther*. 2017;45(11):1390–1402.

Acknowledgment

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

Funding and commercial support: Mallinckrodt Pharmaceuticals.