Terlipressin Therapy in Patients with HRS and Comorbidities: The North American Experience

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Background

- Hepatorenal syndrome (HRS) is a rapid kidney failure that occurs in patients with decompensated cirrhosis and ascites[1]
  - The development of HRS is associated with a decrease in mean arterial pressure (MAP)[2]
- Systemic inflammation plays a key role in the pathogenesis of acute kidney injury (AKI) in patients with cirrhosis[3,4]
  - Certain systemic inflammation processes are caused by bacterial translocation, which is a characteristic of advanced liver disease[3,4]
  - Irrespective of bacterial infection, systemic inflammation may also be associated with alcohol-related hepatitis (AH) and systemic inflammatory response syndrome (SIRS)[3,4]
- The American Association for the Study of Liver Diseases (AASLD) and the American College of Gastroenterology (ACG) guidelines recommend use of the vasopressin analogue, terlipressin, as a first-line treatment for patients with HRS-AKI[5,6]
- 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[7], and has demonstrated efficiency in improving renal function in a subgroup of patients with HRS and SIRS[8], and in those with HRS and AH[9]
- It was hypothesized that terlipressin is especially effective in patients with pronounced inflammation due to its possible direct and indirect anti-inflammatory effects[8]

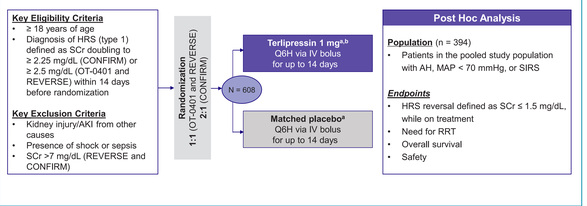
Aim of the Study

- This study was conducted to assess the effect of terlipressin on HRS reversal, the need for renal replacement therapy (RRT), and overall survival (OS) in the subpopulation of patients with HRS and other comorbidities (ie, those with SIRS, AH, and low MAP—defined as < 70 mmHg)

Methods

- Data from 3 prospective, randomized, placebo-controlled, Phase III studies of terlipressin in patients with HRS (OT-0401 [NCT00089570][10], REVERSE [NCT01143246][11], and CONFIRM [NCT02770716][12]) were pooled in the largest-to-date database (N = 608) **(Figure 1)**
- Patients from the pooled database with AH (based on investigator assessment), low MAP, or SIRS were identified as the *subpopulation with comorbidities* and were included in the analysis
- Study outcomes included the incidence of HRS reversal, the need for RRT, and OS
  - HRS reversal was defined as at least 1 serum creatinine (SCr) value ≤ 1.5 mg/dL while on treatment (up to 24 hours after the last dose of study medication). Any SCr values obtained posttransplant or after RRT were excluded
- A Chi-square test was used to calculate *P* values for categorical outcomes
- Survival estimates were compared using a 2-sample log-rank test

Figure 1. Study design



[a] **Concomitant albumin was strongly recommended** at a dose of 100 g on Day 1 and then 25 g/d until 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] If after day 3 SCr had decreased, but by less than 30%, then the terlipressin dose could be increased to 2 mg Q6H.
AH, alcohol-related hepatitis; AKI, acute kidney injury; HRS, hepatorenal syndrome; IV, intravenous; MAP, mean arterial pressure; Q6H, every 6 hours; RRT, renal replacement therapy; SCr, serum creatinine; SIRS, systemic inflammatory response syndrome.

Results

Demographics and baseline characteristics

- In the pooled population, 64.8% (394/608) of patients were identified as having comorbidities, and 35.2% (214/608) of patients did not have a comorbidity
- Demographic and baseline clinical characteristics among the subpopulation of patients with comorbidities were comparable between treatment groups and consistent with advanced liver disease and kidney damage (**Table 1**):
  - Mean Model for End-stage Liver Disease (MELD) scores were 33.0 in the terlipressin group, and 33.1 in the placebo group
  - Mean SCr was 3.6 mg/dL in both treatment groups
  - AH was diagnosed in 51.9% (121/233) and 52.2% (84/161) of patients in the terlipressin and placebo groups, respectively

Table 1. Demographics and baseline characteristics for patients with alcohol-related hepatitis, SIRS, or baseline MAP < 70 mmHg; pooled ITT population[a,b].

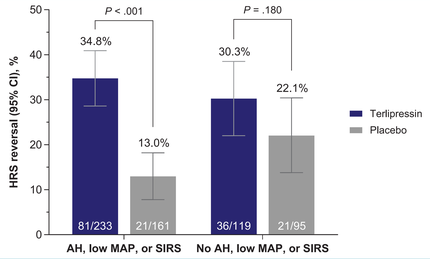
Parameter at baseline	Terlipressin (n = 233)	Placebo (n = 161)
Age, years	53.6 ± 10.8	51.8 ± 10.8
Male sex, n (%)	140 (60.1)	99 (61.5)
Alcohol-related hepatitis, n (%)	121 (51.9)	84 (52.2)
MAP, mmHg	75.3 ± 12.5	74.4 ± 11.6
Heart rate, beats/min	81.1 ± 15.5	83.8 ± 13.9
SCr, mg/dL	3.6 ± 1.3	3.6 ± 1.1
Total bilirubin, mg/dL	14.2 ± 13.4	15.7 ± 15.6
Prior albumin use, n (%)	219 (94.0)	153 (95.0)
Prior albumin amount, g	320.9 ± 170.8	310.2 ± 244.0
Child-Pugh Turcotte score, n (%)		
Class A [5–6]	5 (2.1)	2 (1.2)
Class B [7–9]	61 (26.2)	44 (27.3)
Class C [10–15]	157 (67.4)	104 (64.6)
Missing	10 (4.3)	11 (6.8)
MELD score	33.0 ± 6.4	33.1 ± 5.9

Data are presented as the mean ± SD unless otherwise noted.
[a] Criteria to define the SIRS subgroup were not collected for OT-0401; patients with SIRS are identified from the REVERSE and CONFIRM studies only.
[b] Population was pooled from the OT-0401, REVERSE, and CONFIRM studies.
ITT, intent-to-treat; MAP, mean arterial pressure; MELD, Model for End-stage Liver Disease; SCr, serum creatinine; SD, standard deviation; SIRS, systemic inflammatory response syndrome.

Clinical outcomes

- Significantly more patients with comorbidities achieved HRS reversal in the terlipressin group versus the placebo group (*P* < .001, **Figure 2**)
  - In the subgroup of patients without comorbidities, the difference between treatment groups was not significant (**Figure 2**)

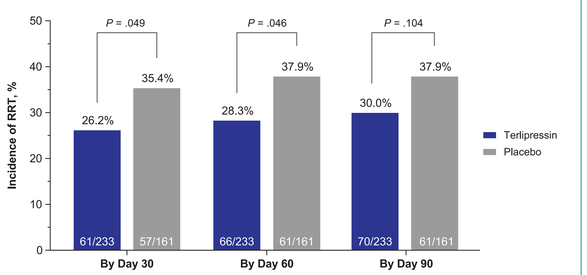
Figure 2. HRS reversal among patients with and without comorbidities by treatment; pooled ITT population.



AH, alcohol-related hepatitis; CI, confidence interval; HRS, hepatorenal syndrome; ITT, intent-to-treat; MAP, mean arterial pressure; SIRS, systemic inflammatory response syndrome.

- Among patients with comorbidities, fewer patients in the terlipressin group (vs the placebo group) needed RRT by Day 30 (*P* = .049), Day 60 (*P* = .046), and Day 90 (*P* = .104) (**Figure 3**)

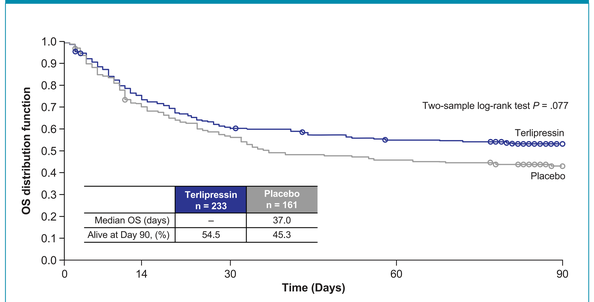
Figure 3. Need for RRT among patients with HRS and AH, SIRS, or low MAP; pooled ITT population.



AH, alcohol-related hepatitis; HRS, hepatorenal syndrome; ITT, intent-to-treat; MAP, mean arterial pressure; RRT, renal replacement therapy; SIRS, systemic inflammatory response syndrome.

- Overall survival up to 90 days demonstrated a positive trend among patients with comorbidities in the terlipressin group versus the placebo group (*P* = .077; **Figure 4**)

Figure 4. Overall survival among patients with HRS and AH, SIRS, or MAP < 70 mmHg, pooled ITT population.



AH, alcohol-related hepatitis; HRS, hepatorenal syndrome; ITT, intent-to-treat; MAP, mean arterial pressure; OS, overall survival; SIRS, systemic inflammatory response syndrome.

Safety

- The overall incidence of adverse events (AEs), serious adverse events (SAEs), and death were similar in both treatment groups (**Table 2**)
- However, more patients in the terlipressin group versus the placebo group had respiratory failure (terlipressin: 8.7% [20/231], placebo: 2.6% [4/156]; *P* = .017) and septic shock (terlipressin: 3.0% [7/231], placebo: 0%; *P* = .045) (**Table 2**)
- Significantly more patients who received terlipressin versus placebo had permanent study drug withdrawal (terlipressin: 13% [30/231], placebo: 6.4% [10/156]; *P* = .037)

Table 2. Summary of adverse events among patients with HRS and AH, SIRS, or MAP < 70 mmHg; pooled safety population.

Event	Terlipressin (n = 231)	Placebo (n = 156)	*P* value[a]
Any AE	214 (92.6)	141 (90.4)	.429
Permanent withdrawals due to AEs	30 (13.0)	10 (6.4)	.037
Death	105 (45.5)	80 (51.3)	.260
SAEs reported in ≥ 3% of patients within a treatment group by SOC and PT			
Any	109 (47.2)	67 (42.9)	.412
Gastrointestinal disorders	24 (10.4)	8 (5.1)	.065
Gastrointestinal hemorrhage	7 (3.0)	1 (0.6)	.151
General disorders and administration site conditions	11 (4.8)	7 (4.5)	.900
Multiple organ dysfunction syndrome	11 (4.8)	5 (3.2)	.451
Hepatobiliary disorders	29 (12.6)	27 (17.3)	.192
Chronic hepatic failure	6 (2.6)	5 (3.2)	.724
Hepatic failure	10 (4.3)	11 (7.1)	.246
Hepatorenal syndrome	3 (1.3)	6 (3.8)	.166
Infections and infestations	21 (9.1)	6 (3.8)	.047
Septic shock	7 (3.0)	0 (0.0)	.045
Respiratory, thoracic, and mediastinal disorders	39 (16.9)	16 (10.3)	.067
Acute respiratory failure	8 (3.5)	3 (1.9)	.536
Respiratory failure	20 (8.7)	4 (2.6)	.017

Data are presented as n (%).
[a] *P* values are calculated from a Chi-square or Fisher's exact test.
AE, adverse event; AH, alcohol-related hepatitis; MAP, mean arterial pressure; PT, preferred term; SAE, serious adverse event; SIRS, systemic inflammatory response syndrome; SOC, system organ class.

Conclusions

- Patients with HRS and comorbidities (ie, those who had AH, SIRS, or low MAP) had a significantly higher rate of HRS reversal and a lower rate of RRT at Days 30 and 60
- Patients with HRS and comorbidities demonstrated a trend for better OS when randomized to terlipressin versus placebo
- The presence of AH, SIRS, or low MAP in patients with HRS does not negatively impact the efficacy of terlipressin as a treatment for these patients
- Among patients with comorbidities, AEs were similar to those in the overall population of patients with HRS-AKI in the largest randomized controlled CONFIRM study[12]
- Careful patient selection and observation for respiratory distress is recommended to minimize the risk of AEs in patients with HRS-AKI[13]

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