Terlipressin Treatment and Time to Clinical Response: Characterization of Hepatorenal Syndrome Reversal Using a Pooled Database of 3 Placebo-controlled Phase III Clinical Studies

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Introduction

- Hepatorenal syndrome (HRS) is a potentially reversible form of acute kidney injury, manifesting as a late complication of cirrhosis with ascites[1,2]
  - With a median survival of < 2 weeks if left untreated, HRS is associated with significant morbidity and mortality[3]
- Terlipressin is the first and only US Food and Drug Administration (FDA)-approved therapy for adult patients with HRS and rapidly worsening kidney function[4]
  - The American Association for the Study of Liver Diseases (AASLD) recommends terlipressin in combination with albumin for the treatment of patients with HRS[1]
  - Terlipressin, a synthetic vasopressin analogue, acts as a splanchnic and systemic vasoconstrictor and improves renal perfusion. As demonstrated in 3 Phase III, randomized, placebo-controlled studies, terlipressin in combination with albumin reversed HRS in 20% to 40% of patients[5–7]
- It was recently shown that lower baseline serum creatinine (SCr) is positively associated with HRS reversal in patients who were randomized to terlipressin (odds ratio [95% CI]: 0.483 [0.361–0.645], *P* < .001)[2]

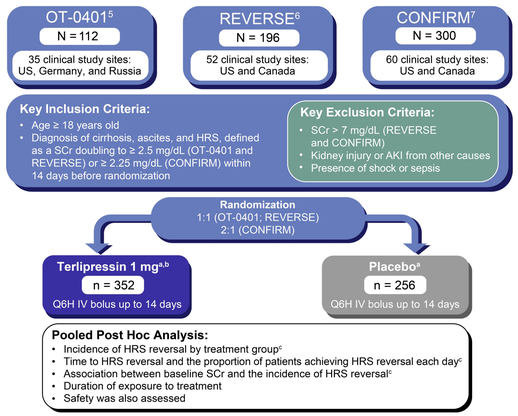
Aim of the study

- This study assessed the timing of HRS reversal using a pooled dataset from 3 North American-centric placebo-controlled Phase III clinical studies

Methods

- This post hoc analysis of pooled data from 3 Phase III clinical studies (N = 608; OT-0401[5] [NCT00089570], REVERSE[6] [NCT01143246], and CONFIRM[7] [NCT02770716]) evaluated terlipressin treatment in patients with HRS by assessing the time to HRS reversal and the proportion of patients who achieved HRS reversal (numerically and cumulatively) each day
- HRS reversal was defined as a SCr of ≤ 1.5 mg/dL while on treatment (ie, up to 24 hours after the last dose of study drug, by Day 14, or at discharge)
- Baseline renal function was assessed using SCr levels as a predictor of clinical response (ie, HRS reversal) by multivariate logistic regression analysis
- The incidence of adverse events (AEs), serious AEs (SAEs), and death were also assessed

Figure 1. Study Design for the Pooled Analysis



[a] **Concomitant albumin was recommended** at a dose of 100 g on Day 1 and then 25 g daily until the end of treatment 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 used the same starting dose of terlipressin (1 mg Q6H) and allowed an increase in dose (to 2 mg Q6H) if SCr had decreased by less than 30% from baseline after 3 days of treatment.
[c] HRS reversal was defined as a SCr value of ≤ 1.5 mg/dL while on treatment up to 24 hours after the last dose of study drug, by Day 14, or at discharge.
AKI, acute kidney injury; HRS, hepatorenal syndrome; IV, intravenous; Q6H, every 6 hours; SCr, serum creatinine; US, United States.

Results

Baseline Patient Demographics and Clinical Characteristics

- Overall, the baseline demographics and clinical characteristics were similar between treatment arms and consistent with advanced liver disease (**Table 1**)
  - In the intent-to-treat (ITT) population, 34.4% (121/352) of patients in the terlipressin group and 32.8% (84/256) of patients in the placebo group had alcoholic hepatitis; Model for End-stage Liver Disease (MELD) scores were 33.0 and 33.1, respectively

Table 1. Baseline Demographics and Clinical Characteristics, Pooled ITT Population[a]

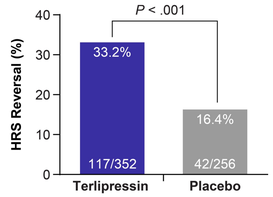
Characteristic	Terlipressin (n = 352)	Placebo (n = 256)
Age, years	54.0 ± 10.6	54.0 ± 10.5
Male sex, n (%)	213 (60.5)	165 (64.5)
Alcoholic hepatitis, n (%)	121 (34.4)	84 (32.8)
SIRS, n (%)[b]	112 (37.8)	78 (39.0)
SCr, mg/dL	3.6 ± 1.29	3.7 ± 1.11
Total bilirubin, mg/dL	12.8 ± 12.7	14.1 ± 14.6
MAP, mm Hg	77.3 ± 12.0	76.6 ± 10.9
Child-Pugh score, n (%)		
Class A (5–6)	5 (1.4)	3 (1.2)
Class B (7–9)	100 (28.4)	71 (27.7)
Class C (10–15)	232 (65.9)	168 (65.6)
Missing	15 (4.3)	14 (5.5)
MELD score	33.0 ± 6.4	33.1 ± 5.9

Data are presented as the mean ± SD unless otherwise noted.
[a] Pooled data were collated from the following Phase III studies: OT-0401, REVERSE, and CONFIRM.
[b] SIRS subgroup data were available from CONFIRM and REVERSE only.
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.

Effect of Treatment on Clinical Response

- HRS reversal was achieved by more patients in the terlipressin group than in the placebo group: 33.2% (117/352) versus 16.4% (42/256), respectively (*P* < .001) (**Figure 2**)

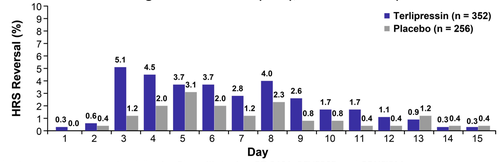
Figure 2. Incidence of HRS Reversal, Pooled ITT Population[a]



[a] Pooled data were collated from the following Phase III studies: OT-0401, REVERSE, and CONFIRM.
The *P* value was determined using a Chi-square test.
HRS, hepatorenal syndrome; ITT, intent-to-treat.

- Among patients who achieved HRS reversal, the mean ± standard deviation (SD) time to HRS reversal was roughly 6 days across treatment groups: terlipressin, 6.3 ± 3.02 days, and placebo, 6.7 ± 3.29 days (**Figure 3**)
- Over 80% of patients who achieved a response did so by Day 10
- The greatest proportion of patients achieved HRS reversal on Day 3 (5.1%) in the terlipressin group and Day 5 (3.1%) in the placebo group

Figure 3. Patients Achieving HRS Reversal by Day, Pooled ITT Population[a]



[a] Pooled data were collated from the following Phase III studies: OT-0401, REVERSE, and CONFIRM.
HRS, hepatorenal syndrome; ITT, intent-to-treat.

- In both treatment groups, lower baseline SCr was an independent predictor of HRS reversal and was positively associated with HRS reversal (odds ratio [95% CI]: terlipressin, 0.498 [0.369–0.674; *P* < .001]; placebo, 0.437 [0.284–0.671; *P* < .001])
- Baseline SCr was also the only baseline characteristic significantly associated with a response of > 30% improvement in SCr on Day 4, in the terlipressin treatment group (**Table 2**)

Table 2. Univariate Logistic Regression Analysis of the Association of Baseline Characteristics With Response in the Terlipressin Group[a], Pooled ITT Population[b]

	Terlipressin (n = 352)			
Parameter	N	Odds Ratio	95% Confidence Interval	*P* value
Alcoholic hepatitis	352	1.293	0.791 – 2.113	.305
Serum creatinine	352	0.754	0.595 – 0.956	.020
Age < 65 years	352	1.031	0.532 – 1.995	.929
Male sex	352	0.727	0.450 – 1.175	.193
Race group (White vs Non-white)	348	0.762	0.357 – 1.624	.481
MELD score	312	0.984	0.946 – 1.025	.441
Child-Pugh score	337	1.016	0.897 – 1.151	.804
MAP, mm Hg	352	1.004	0.984 – 1.024	.699
MAP < 65 mm Hg	352	0.780	0.381 – 1.599	.498
ACLF grade (0–2 vs 3)	352	1.628	0.859 – 3.085	.135
Total bilirubin	338	0.992	0.972 – 1.011	.407
Serum sodium	349	0.991	0.953 – 1.030	.644
Diastolic blood pressure	352	1.006	0.986 – 1.027	.557
Systolic blood pressure	352	1.000	0.986 – 1.014	.994
International normalized ratio	325	0.878	0.639 – 1.207	.424

[a] Responders are defined as those with > 30% improvement in serum creatinine on Day 4 compared to baseline, in the terlipressin treatment group.
[b] Pooled data were collated from the following Phase III studies: OT-0401, REVERSE, and CONFIRM.
ACLF, acute-on-chronic liver failure; ITT, intent-to-treat; MAP, mean arterial pressure; MELD, Model for End-stage Liver Disease.
The *P* values were determined using a logistic regression model.
N = number of patients in the baseline characteristic.

Safety

- The most commonly reported AEs in the terlipressin group were abdominal pain, nausea, and diarrhea (**Table 3**)
  - A between-treatment group difference of ≥ 5% in AE incidence was noted for abdominal pain, diarrhea, dyspnea, and bradycardia, all of which were reported at a higher incidence in terlipressin-treated patients
- The most commonly reported treatment-related SAE was intestinal ischemia, which occurred in 1.1% (4/349) of terlipressin-treated patients; other treatment-related SAEs that occurred in > 1 terlipressin-treated patient were abdominal pain, respiratory distress, and vascular skin disorder, all of which occurred in 0.6% (2/349) of patients
- As expected in a patient population with advanced liver disease, the most commonly reported (≥ 5%) AEs leading to death in the terlipressin group within 90 days from the start of treatment were chronic hepatic failure, multiple organ dysfunction syndrome, hepatic failure, and respiratory failure
  - Treatment-related deaths were reported for 4 terlipressin-treated patients and were due to tachypnea, acute respiratory failure, respiratory failure, and subarachnoid hemorrhage/multiorgan failure (n = 1 each)

Table 3. Summary of AEs and SAEs in ≥ 5% of Terlipressin-treated Patients, Pooled Safety Population[a,b]

Parameter	Terlipressin (n = 349)	Placebo (n = 249)
Any AE[c]	318 (91.1)	225 (90.4)
Abdominal pain	75 (21.5)	31 (12.4)
Nausea	53 (15.2)	30 (12.0)
Diarrhea	52 (14.9)	14 (5.6)
Dyspnea	42 (12.0)	15 (6.0)
Hypotension	41 (11.7)	19 (7.6)
Vomiting	36 (10.3)	16 (6.4)
Hypokalemia	32 (9.2)	20 (8.0)
Hepatic encephalopathy	30 (8.6)	28 (11.2)
Pulmonary edema	29 (8.3)	14 (5.6)
Respiratory failure	29 (8.3)	9 (3.6)
Anemia	28 (8.0)	21 (8.4)
Fluid overload	28 (8.0)	9 (3.6)
Bradycardia	22 (6.3)	2 (0.8)
Metabolic acidosis	22 (6.3)	15 (6.0)
MODS	19 (5.4)	8 (3.2)
Pain in extremity	19 (5.4)	2 (0.8)
Pleural effusion	19 (5.4)	5 (2.0)
Pneumonia	18 (5.2)	8 (3.2)
Any treatment-related AE[d,e]	147 (42.1)	60 (24.1)
Abdominal pain	47 (13.5)	14 (5.6)
Nausea	36 (10.3)	12 (4.8)
Diarrhea	33 (9.5)	4 (1.6)
Vomiting	18 (5.2)	4 (1.6)
Any SAE[f]	227 (65.0)	149 (59.8)
Respiratory failure	29 (8.3)	6 (2.4)
MODS	26 (7.4)	8 (3.2)
Chronic hepatic failure	21 (6.0)	15 (6.0)
Hepatic failure	21 (6.0)	23 (9.2)
Sepsis	18 (5.2)	4 (1.6)
Any treatment-related SAE[e,f]	24 (6.9)	5 (2.0)

Data are presented as n (%).
[a] Pooled data were collated from the following Phase III studies: OT-0401, REVERSE, and CONFIRM.
[b] Patients experiencing multiple episodes of a given AE or multiple AEs were counted once per preferred term or category, respectively.
[c] Up to 7 days after the end of treatment.
[d] From the start of study treatment to 7 days after the end of treatment.
[e] Considered by the study investigators to be possibly or probably causally related to study treatment.
[f] Up to 30 days post treatment.
AE, adverse event; MODS, multiple organ dysfunction syndrome; SAE, serious adverse event.

- In the pooled safety population (terlipressin, n = 349; placebo, n = 249), the mean ± SD duration of exposure to treatment was 6.2 days ± 4.4 days with terlipressin and 6.0 days ± 3.9 days with placebo (**Table 4**)

Table 4. Treatment Exposure, Pooled Safety Population[a]

Parameter	Terlipressin (n = 349)	Placebo (n = 249)	*P* value
Treatment exposure[b,c], days, mean ± SD	6.2 ± 4.4	6.0 ± 3.9	.792
Duration of treatment[b,c]			.682
≤ 3 days	95 (27.2)	67 (26.9)	
> 3 to ≤ 6 days	131 (37.5)	92 (36.9)	
> 6 to ≤ 9 days	54 (15.5)	47 (18.9)	
> 9 to ≤ 12 days	30 (8.6)	15 (6.0)	
> 12 days	39 (11.2)	28 (11.2)	
Total number of doses[b]			.860
≤ 10	99 (28.4)	69 (27.7)	
> 10	250 (71.6)	180 (72.3)	
Dose level[b,d]			.055
Standard	254 (72.8)	163 (65.5)	
High	95 (27.2)	86 (34.5)	

Data are presented as n (%) unless otherwise noted.
For continuous variables, the *P* value was generated by ANOVA or a Kruskal-Wallis test following testing for normality.
[a] Pooled data were collated from the following Phase III studies: OT-0401, REVERSE, and CONFIRM.
[b] For patients receiving initial and retreatment periods, exposure data are combined from both periods.
[c] The number of days the patient received at least 1 dose of study drug is counted. For the combination of initial and retreatment periods, the counts from each period are added together.
[d] Patients in the standard dose level received only 0.5 mg and 1 mg doses. Patients in the high dose level received at least 1 dose > 2 mg.
ANOVA, analysis of variance; SD, standard deviation.

Conclusions

- More patients in the terlipressin group achieved HRS reversal compared with those in the placebo group
- In the terlipressin group, the greatest proportion of patients achieved HRS reversal as early as Day 3, compared with Day 5 in the placebo group
- Most responses were achieved by Day 10 with few additional patients achieving HRS reversal beyond Day 10
- Although lower baseline SCr was a positive predictor of HRS reversal across treatment groups, overall, more patients who were treated with terlipressin achieved HRS reversal than placebo
- Lower baseline SCr was also positively associated with a response of > 30% improvement in SCr at Day 4 in the terlipressin treatment group
- The most commonly reported AEs in the terlipressin group were abdominal pain, nausea, and diarrhea
- This analysis further supports the use of terlipressin therapy for patients with HRS at a lower SCr to expedite the time to clinical response

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