Patients With Hepatorenal Syndrome and Lower Baseline Mean Arterial Pressure Derive Significant Survival Benefit From Treatment With Terlipressin

SAT-076

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Background

- Patients with decompensated liver disease may develop hepatorenal syndrome (HRS), a rapidly progressive form of acute kidney injury[1]
- The underlying liver disease is strongly associated with a hypotensive state.[2] Thus, patients with HRS may present with a mean arterial pressure (MAP) below the optimal target MAP of 65 mm Hg, used in the management of septic shock[3]
- Terlipressin, a vasopressin analogue, is used to treat adult patients with HRS to improve renal perfusion and kidney function[4,5]
- Treatment of HRS with vasopressors, including terlipressin, is associated with a subsequent increase in MAP[6]
- Notably, an increase in MAP of 5 mm Hg by Day 3 in response to terlipressin is positively correlated with the odds of achieving HRS reversal[6]
- As treatment response appears to be tightly correlated with an increase in MAP, further understanding of the clinical response in patients who present with HRS and low MAP is of particular interest

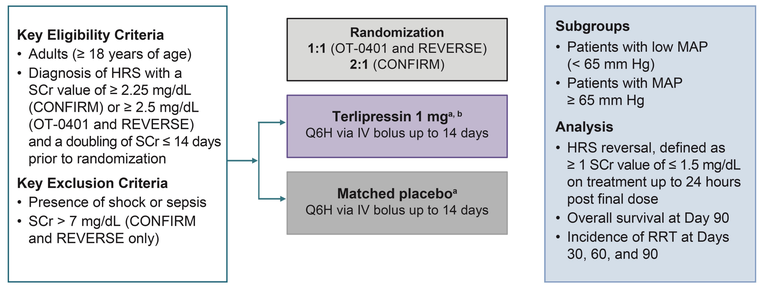
Aims

- This post hoc analysis of the largest database of patients who were treated with terlipressin in 3 prospective Phase III studies aimed to examine patient responses by MAP subgroup (MAP < 65 mm Hg; MAP ≥ 65 mm Hg) to further understand the clinical response to terlipressin in patients with low MAP

Methods

- Patient data were collated from 3 Phase III placebo-controlled studies of terlipressin in patients with HRS and rapidly deteriorating kidney function (defined as a serum creatinine ≥ 2.5 mg/dL [OT-0401[7], REVERSE[8]] or ≥ 2.25 mg/dL [CONFIRM[9]])
- Patients with low baseline MAP (< 65 mm Hg) and baseline MAP ≥ 65 mm Hg were assessed for HRS reversal (defined as ≥1 serum creatinine value of ≤ 1.5 mg/dL on treatment, up to 24 hours after the last dose of study drug) and overall survival (OS) at Day 90
- The proportion of patients with low MAP requiring renal replacement therapy (RRT) at Days 30, 60, and 90 was also assessed (**Figure 1**)

Figure 1. Study design

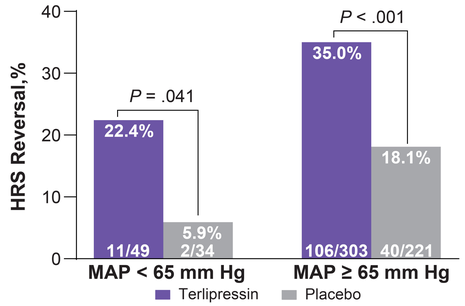


[a] **Concomitant albumin was recommended** at a dose of 1 g/kg body weight up to 100 g on Day 1 followed by 20–40 g/day.
[b] If, after Day 3, serum creatinine levels had decreased—but by less than 30%—then the terlipressin dose could be increased to 2 mg Q6H.
HRS, hepatorenal syndrome; IV, intravenous; MAP, mean arterial pressure; Q6H, every 6 hours; RRT, renal replacement therapy; SCr, serum creatinine.

Results

- In the pooled intent-to-treat dataset (N = 608), most patients had a MAP ≥ 65 mm Hg (terlipressin, 86.1% [303/352]; placebo, 86.7% [221/255])
- The proportion of patients with a low MAP of < 65 mm Hg was 13%–14%, and was similar across treatment arms (terlipressin, 13.9% [49/352]; placebo, 13.3% [34/255])
- While HRS reversal was higher among patients with MAP ≥ 65 mm Hg (compared with MAP < 65 mm Hg) for both terlipressin and placebo, significantly more patients achieved HRS reversal with terlipressin than with placebo in both the low MAP (22.4% [11/49] vs 5.9% [2/34], *P* = .041) and MAP ≥ 65 mm Hg (35.0% [106/303] vs 18.1% [40/221], *P* < .001) subgroups (**Figure 2**)

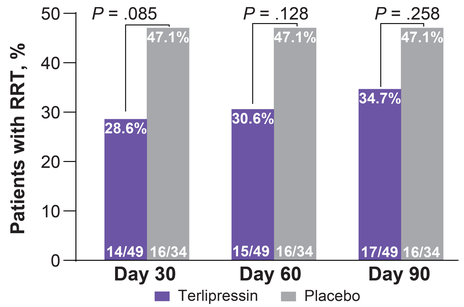
Figure 2. HRS reversal in patients with low MAP (< 65 mm Hg) or a MAP ≥ 65 mm Hg at baseline; Pooled ITT population[a]



[a] The pooled ITT population included patients from the following Phase III studies: OT-0401, REVERSE, and CONFIRM.
ITT, intent-to-treat; HRS, hepatorenal syndrome; MAP, mean arterial pressure.

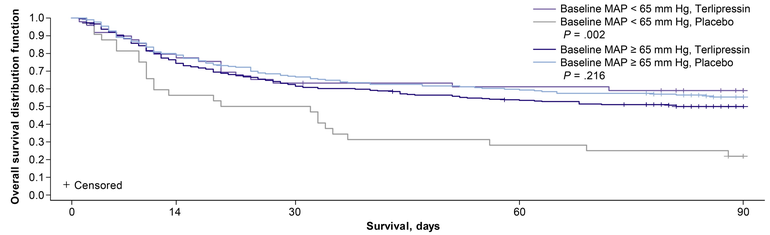
- More than 50% of patients with a baseline MAP ≥ 65 mm Hg were alive at Day 90 (terlipressin, 50.5% [153/303]; placebo, 56.1% [124/221]), with no significant difference in survival estimates between the terlipressin and placebo treatment arms (*P* = .216)
- Notably, patients with low MAP (< 65 mm Hg) had a significant improvement in OS estimates up to 90 days in the terlipressin arm (*P* = .002), with 59.2% of patients alive at Day 90 (vs 26.5% in the placebo arm) (**Figure 3**)
- The proportion of patients with low baseline MAP who received RRT was numerically higher in the placebo arm versus the terlipressin arm, at Days 30, 60, and 90 (terlipressin vs placebo: Day 30, 28.6% [14/49] vs 47.1% [16/34], *P* = .085; Day 60, 30.6% [15/49] vs 47.1% [16/34], *P* =.128; Day 90, 34.7% [17/49] vs 47.1% [16/34], *P* = .258) (**Figure 4**)

Figure 4. Incidence of RRT in patients with low MAP (< 65 mm Hg) at baseline; Pooled ITT population[a]



[a] The pooled ITT population included patients from the following Phase III studies: OT-0401, REVERSE, and CONFIRM.
ITT, intent-to-treat; MAP, mean arterial pressure; RRT, renal replacement therapy.

Figure 3. Overall survival up to 90 Days by baseline MAP subgroups; Pooled ITT population[a]



Patients at risk, n					
Baseline MAP < 65 mm Hg, Terlipressin	49	39	31	29	22
Baseline MAP < 65 mm Hg, Placebo	34	18	16	9	6
Baseline MAP ≥ 65 mm Hg, Terlipressin	303	230	188	160	117
Baseline MAP ≥ 65 mm Hg, Placebo	221	175	146	130	91

[a] The pooled ITT population included patients from the following Phase III studies: OT-0401, REVERSE, and CONFIRM.
[b] The *P* value compares survival estimates via a 2-sample log rank test.
ITT, intent-to-treat; MAP, mean arterial pressure.

Conclusions

- Patients with HRS who presented with either MAP < 65 mm Hg or MAP ≥ 65 mm Hg at baseline derived a significant improvement in renal function (ie, HRS reversal) from terlipressin treatment (compared with placebo)
- Over half of the patients treated with terlipressin were alive at Day 90, regardless of baseline MAP
- Notably, nearly 60% of patients with a low MAP (< 65 mm Hg) were alive at Day 90 in the terlipressin arm compared with 26.5% in placebo; thus, the significant improvements in OS with terlipressin treatment in the low MAP subgroup, is likely due to lower survival in patients with low MAP in the placebo arm
- Taken together, these data suggest that terlipressin treatment improves clinical outcomes in patients with a range of baseline MAP values

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