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Terlipressin Treatment Is Associated With Significantly Increased Survival in Patients With Hepatorenal Syndrome Type 1 (HRS-1) and Low Baseline Mean Arterial Pressure (MAP), Independent of HRS Reversal

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BACKGROUND

- Hepatorenal syndrome Type 1 (HRS-1) in patients with decompensated cirrhosis or acute liver failure can progress rapidly and is associated with very short survival if not treated[1,2]
- The vasopressin analog terlipressin administered concomitantly with albumin improved renal function in patients with cirrhosis and HRS-1 when compared with placebo and albumin in the **R**andomized, plac**E**bo-controlled, double-blind study to confirm the re**VERS**al of hepatorenal syndrom**E** Type 1 with terlipressin (REVERSE; NCT01143246)[3] and in the OT-0401 clinical study (NCT00089570)[4]
- Low mean arterial pressure (MAP) is common in patients with decompensated cirrhosis and HRS-1 in the absence of overt shock[5,6]
- A pooled analysis[7] of data from the REVERSE and OT-0401 studies showed that lower baseline MAP unexpectedly predicted improved overall survival (OS) and transplant-free survival (TFS) in cirrhotic patients with HRS-1 treated with terlipressin compared with placebo

AIM

- To characterize the relationship between low baseline MAP and improved survival in patients with HRS-1 treated with terlipressin in the REVERSE and OT-0401 studies

MATERIALS & METHODS

- Data from 2 phase 3, randomized, double-blind, placebo-controlled studies that compared the efficacy of terlipressin and albumin with that of placebo and albumin in patients with HRS-1 (REVERSE and OT-0401) were pooled and analyzed
  - In both studies, patients received terlipressin or placebo and albumin intravenously (IV) every 6 hours for up to 14 days
- In the current analysis, baseline MAP was used to dichotomize 307 patients with HRS-1 into 2 groups stratified according to baseline MAP: <65 mm Hg and ≥65 mm Hg
- Demographics and the following outcomes of interest were compared between terlipressin and placebo within each MAP group:
  - OS
  - TFS
  - HRS reversal (defined as ≥1 SCr value <133 μmol/L on treatment, up to 24 hours after the last dose of study medication)
  - Change in SCr from baseline through end of treatment (EOT)
- Between-group comparisons for HRS reversal were conducted within each MAP group using the Fisher exact test; *P* values comparing survival estimates were calculated using a two-sample log-rank test (randomization was stratified by SCr, <3.6 mg/dL or ≥3.6 mg/dL) and alcoholic hepatitis (present or not).

RESULTS

- Baseline patient and disease characteristics were similar between patients treated with terlipressin and placebo in both the MAP <65 mm Hg and ≥65 mm Hg groups (**Table 1**)

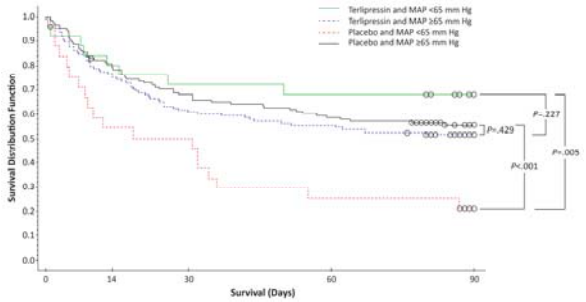
Table 1. Baseline Patient Demographics and Disease Characteristics

	Baseline MAP <65 mm Hg		Baseline MAP ≥65 mm Hg	
	Terlipressin n=25	Placebo n=25	Terlipressin n=128	Placebo n=129
Age, mean (SD), y	52.8 (12.1)	52.6 (10.9)	54.2 (9.0)	54.6 (9.2)
Female, n (%)	13 (52.0)	13 (52.0)	47 (36.7)	36 (27.9)
Race, n (%)				
White	21 (84.0)	24 (96.0)	115 (89.8)	116 (89.9)
Black	3 (12.0)	0	9 (7.0)	9 (7.0)
Other	1 (4.0)	1 (4.0)	3 (2.3)	4 (3.1)
Missing	0	0	1 (0.8)	0
SCr, mean (SD), mg/dL	4.1 (1.93)	3.9 (1.33)	3.6 (1.49)	3.7 (1.10)
Total bilirubin, mean (SD), mg/dL	9.9 (8.16)	16.5 (14.89)	13.2 (12.50)	12.9 (13.52)
MAP, mean (SD), mm Hg	58.2 (5.05)	59.9 (3.34)	79.0 (9.24)	79.2 (10.05)
MELD score, mean (SD)	34.0 (5.64)	34.2 (6.16)	33.3 (6.23)	32.7 (5.74)
Child-Pugh score, n (%)				
Class A (5-6)	0 (0)	0 (0)	2 (1.6)	1 (0.8)
Class B (7-9)	5 (20.0)	2 (8.0)	27 (21.1)	37 (28.7)
Class C (10-15)	19 (76.0)	22 (88.0)	90 (70.3)	84 (65.1)
Missing	1 (4.0)	1 (4.0)	9 (7.0)	7 (5.4)
Alcoholic hepatitis present, n (%)	4 (16.0)	7 (28.0)	36 (28.1)	37 (28.7)

MAP, mean arterial pressure; MELD, model for end-stage liver disease; SCr, serum creatinine; SD, standard deviation.

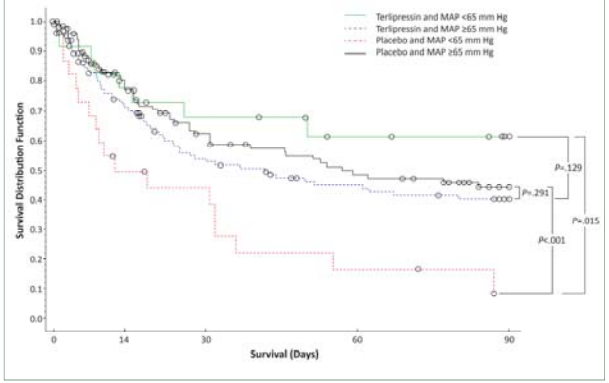
- Duration of exposure
  - In the MAP <65 mm Hg group, mean (SD) duration of exposure to study treatment was 4.7 (3.54) days with terlipressin versus 4.5 (2.77) days with placebo
  - In the MAP ≥65 mm Hg group, the respective mean (SD) duration of exposure was 6.0 (4.27) versus 6.3 (3.99)
- Overall survival
  - At 90 days, OS in the MAP <65 mm Hg group was significantly higher among patients receiving terlipressin (17/25 [68.0%]) than among those receiving placebo (6/25 [24.0%]): OS estimate: 0.680 versus 0.209, respectively; *P*=.005 (**Figure 1**)
  - No difference in OS at 90 days was observed between terlipressin (66/128 [51.6%]) and placebo (72/129 [55.8%]) in the MAP ≥65 mm Hg group: OS estimate: 0.515 versus 0.554, respectively; *P*=.429 (**Figure 1**)

Figure 1. Overall Survival by Baseline MAP



- Transplant-free survival
  - In the MAP <65 mm Hg group, TFS at 90 days was significantly higher among patients receiving terlipressin (17/25 [68.0%]) than among those receiving placebo (7/25 [28.0%]): TFS estimate: 0.618 versus 0.083, respectively; *P*=.015 (**Figure 2**)
  - In the MAP ≥65 mm Hg group, no difference in TFS at 90 days was observed between terlipressin (67/128 [52.3%]) and placebo (76/129 [58.9%]): TFS estimate: 0.404 versus 0.444, respectively; *P*=.291 (**Figure 2**)

Figure 2. Transplant-Free Survival by Baseline MAP



- HRS reversal
  - Rates of HRS reversal among patients receiving terlipressin were similar between the MAP <65 mm Hg and ≥65 mm Hg groups; the proportion of patients with HRS reversal in the MAP ≥65 mm Hg group was significantly higher among patients receiving terlipressin than among those receiving placebo (**Table 2**)
  - Improvement in SCr from baseline to end of treatment was significantly greater with terlipressin than with placebo in both MAP groups; however, the degree of improvement was lower in the MAP ≥65 mm Hg group (**Table 2**)

Table 2. HRS Reversal and Change in SCr, Change in MAP (Baseline to EOT)

	Baseline MAP <65 mm Hg			Baseline MAP ≥65 mm Hg		
	Terlipressin n=25	Placebo n=25	*P* Value	Terlipressin n=128	Placebo n=129	*P* Value
HRS reversal, n (%)	6 (24.0)	2 (8.0)	.247	36 (28.1)	20 (15.5)	.016
LS mean (SE) change in SCr, baseline to EOT, mg/dL*	−0.8 (0.20)	0.2 (0.19)	.0001	−0.9 (0.11)	−0.6 (0.10)	.042
LS mean (SE) change in MAP, baseline to EOT, mmHg*	14.4 (1.54)	3.4 (1.44)	<.001	2.0 (0.81)	−2.4 (0.81)	<.001

*From an analysis of variance for repeated measures as implemented in the SAS PROC MIXED procedure, with factors of treatment, alcoholic hepatitis, and day. LS, least squares.

CONCLUSIONS

- Treatment with terlipressin was associated with a considerable improvement in OS and TFS in patients with HRS-1 and a baseline MAP <65 mm Hg
  - This effect appears to be independent of HRS reversal and may be related to a marked improvement in SCr from baseline to EOT in this group
  - Patients in this group who received terlipressin also experienced a significant improvement in MAP from baseline to EOT compared with patients who received placebo
- Overall, findings from the current analysis suggest that treatment with terlipressin is particularly beneficial for patients with HRS-1 and low MAP

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DISCLOSURES

KJ and SE: Employees of Mallinckrodt Pharmaceuticals.
SCP: Consultant for Orphan Therapeutics, LLC, Mallinckrodt Pharmaceuticals, and Roche.
PT: Consultant for Mallinckrodt Pharmaceuticals; President Orphan Therapeutics, LLC.
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Terlipressin is not FDA-approved for use in the United States.

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