The Effect of Race on Treatment Response to Terlipressin in Patients With Hepatorenal Syndrome: A Pooled Analysis of 3 Phase III Clinical Studies

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Introduction

- Hepatorenal syndrome (HRS) is a potentially reversible form of acute kidney injury observed in patients with cirrhosis and ascites[1]
- Without treatment, mortality associated with HRS is approximately 80% within 3 months, and the median survival time is 2–4 weeks[1]
  - The only potential cure for HRS is liver transplantation to treat the underlying cause of cirrhosis and portal hypertension[2]
- Terlipressin is the first and only US Food and Drug Administration (FDA)-approved therapy for the treatment of HRS and is recommended by the American Association for the Study of Liver Diseases (AALSD) in combination with albumin as a first-line therapy for adult patients with HRS; and by the American College of Gastroenterology (ACG) guidelines in hospitalized patients with cirrhosis and HRS with acute kidney injury without a high acute-on-chronic liver failure (ACLF) grade[3-5]
  - Terlipressin is associated with HRS reversal, defined as any serum creatinine (SCr) ≤1.5 mg/dL while on treatment up to 24 hours after the final study drug dose, within 14 days or discharge[6]
- The efficacy and safety of terlipressin treatment in patients with HRS has been examined in 3 placebo-controlled North American Phase III clinical studies: OT-0401 (NCT00089570)[7], REVERSE (NCT01143246)[1], and CONFIRM (NCT02770716)[6]
  - Notably, across these clinical studies, most patients were White
- This study used a pooled dataset of patients with HRS from OT-0401, REVERSE, and CONFIRM to examine if there was any impact of race (White vs non-White) on the treatment response to terlipressin

Methods

- The pooled intent-to-treat (ITT) dataset included data from 3 clinical studies (ie, OT-0401, REVERSE, and CONFIRM) that examined terlipressin treatment in adult patients with HRS, defined as a rapidly progressive worsening in kidney function to SCr ≥2.25 mg/dL (CONFIRM) or ≥2.5 mg/dL (OT-0401 and REVERSE)
- HRS reversal, defined as the proportion of patients achieving a SCr value of ≤1.5 mg/dL while on treatment, including up to 24 hours after the last dose of study drug, was examined by race (ie, White vs non-White)
- Race was assessed for the potential to predict treatment response (ie, HRS reversal) by univariate logistic regression analysis
- A pooled post hoc analysis was performed to evaluate certain subgroups (ie, White vs non-White)
- Safety was also assessed
- Statistical analyses were performed using analysis of variance (ANOVA) and Kruskal-Wallis tests for numerical data or a Fisher's exact test or a Chi-square test for categorical data

Results

Baseline Patient Demographics and Clinical Characteristics

- The OT-0401, REVERSE, and CONFIRM Phase III clinical studies were conducted at large tertiary centers in the US and Canada and enrolled a total of 608 patients (**Table 1**)

Table 1. Patients by Race Across the Individual Phase III Studies and in the Pooled ITT Population[a]

Parameter	OT-0401[5]		REVERSE[1]		CONFIRM[6]		Pooled Population	
	Terlipressin (n = 56)	Placebo (n = 56)	Terlipressin (n = 97)	Placebo (n = 99)	Terlipressin (n = 199)	Placebo (n = 101)	Terlipressin (n = 352)	Placebo (n = 256)
Race, n (%)								
American Indian or Alaskan Native	0	3 (5.4)	1 (1.0)	1 (1.0)	2 (1.0)	0	3 (0.9)	4 (1.6)
Asian	0	0	3 (3.1)	0	5 (2.5)	1 (1.0)	8 (2.3)	1 (0.4)
Black or African American	5 (8.9)	3 (5.4)	7 (7.2)	6 (6.1)	12 (6.0)	5 (5.0)	24 (6.8)	14 (5.5)
Native Hawaiian or Other Pacific Islander	0	1 (1.8)	0	0	0	0	0	1 (0.4)
White	51 (91.1)	49 (87.5)	85 (87.6)	92 (92.9)	177 (88.9)	94 (93.1)	313 (88.9)	235 (91.8)

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

- Most patients who were evaluable for a race group (n = 603) were White (terlipressin, 89.9% [313/348]; placebo, 92.2% [235/255]; **Table 2**)

Table 2. Baseline Demographics and Clinical Characteristics by Race Group (White vs Non-White) and Treatment Arm, Pooled ITT Population[a]

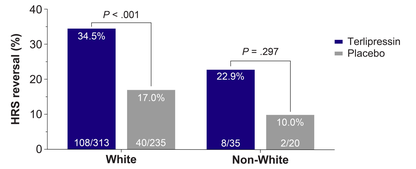
Parameter	White			Non-White		
	Terlipressin (n = 313)	Placebo (n = 235)	*P* value	Terlipressin (n = 35)	Placebo (n = 20)	*P* value
Age, years	54.3 ± 10.54	53.9 ± 10.59	.535	52.2 ± 10.55	55.1 ± 9.71	.319
Male sex, n (%)	190 (60.7)	155 (66.0)	.212	20 (57.1)	10 (50.0)	.779
Etiology of cirrhosis, n (%)						
Alcohol	120 (38.3)	64 (27.2)	.008	13 (37.1)	2 (10.0)	.057
Hepatitis B	3 (1.0)	1 (0.4)	.639	1 (2.9)	0	1.000
Hepatitis C	24 (7.7)	6 (2.6)	.012	7 (20.0)	1 (5.0)	.234
Non-alcoholic steatohepatitis	40 (12.8)	22 (9.4)	.223	1 (2.9)	2 (10.0)	.546
Autoimmune hepatitis	8 (2.6)	4 (1.7)	.568	2 (5.7)	1 (5.0)	1.000
Primary biliary cirrhosis	3 (1.0)	3 (1.3)	1.000	2 (5.7)	0	.529
Cryptogenic	6 (1.9)	2 (0.9)	.476	0	1 (5.0)	.364
Alcoholic hepatitis, n (%)	108 (34.5)	77 (32.8)	.715	12 (34.3)	6 (30.0)	1.000
SCr, mg/dL	3.5 ± 1.25	3.6 ± 1.10	.130	3.9 ± 1.64	4.0 ± 1.22	.446
SIRS subgroup, n/N (%)[b]	104/262 (39.7)	72/186 (38.7)	.845	8/30 (26.7)	5/13 (38.5)	.485
MELD score	32.8 ± 6.41	33.2 ± 5.71	.679	35.1 ± 5.68	32.8 ± 7.05	.266
Child-Pugh score	10.4 ± 1.93	10.5 ± 1.84	.354	10.8 ± 1.84	10.4 ± 1.89	.522
Bilirubin, mg/dL	12.7 ± 12.72	14.2 ± 14.8	.376	13.3 ± 12.35	13.4 ± 12.20	.847
INR	2.3 ± 0.81	2.3 ± 1.72	.892	2.5 ± 0.77	2.4 ± 1.63	.157
MAP, mm Hg, n (%)	77.1 (11.85)	76.2 (10.77)	.306	78.5 (13.40)	80.7 (11.22)	.542
MAP <70 mm Hg, n (%)	79 (25.2)	68 (28.9)	.381	9 (25.7)	2 (10.0)	.293
BUN, mmol/L	65.9 ± 26.77	69.9 ± 32.57	.303	58.6 ± 24.61	61.1 ± 21.87	.434
HCO_3 or CO_2, mmol/L	19.2 ± 4.13	18.8 ± 3.94	.257	19.5 ± 4.00	19.0 ± 3.26	.656
Received prior albumin, n (%)	295 (94.2)	224 (95.3)	.701	31 (88.6)	19 (95.0)	.643
Amount of prior albumin, g	331.2 ± 187.97	317.1 ± 242.27	.098	292.5 ± 194.41	277.2 ± 163.30	.927
ACLF grade, n (%)			.607			.825
1	145 (46.3)	104 (44.3)		15 (42.9)	9 (45.0)	
2	105 (33.5)	88 (37.4)		10 (28.6)	4 (20.0)	
3	61 (19.5)	42 (17.9)		10 (28.6)	7 (35.0)	
Missing	2 (0.6)	0		0	0	
CLIF-SOFA score	10.1 ± 2.39	10.1 ± 2.31	.873	10.6 ± 2.04	10.2 ± 2.33	.622
Alcoholic hepatitis, baseline MAP <70 mm Hg or SIRS, n (%)	211 (67.4)	151 (64.3)	.466	21 (60.0)	9 (45.0)	.399

Data are presented as the mean ± SD unless otherwise noted.
P values were generated using ANOVA and Kruskal-Wallis tests for numerical data or a Fisher's exact test for categorical data.
[a] Pooled data were collated from the following Phase III studies: OT-0401, REVERSE, and CONFIRM.
[b] SIRS subgroup data were available for the CONFIRM and REVERSE studies only.
ACLF, acute-on-chronic liver failure; ANOVA, analysis of variance; BUN, blood urea nitrogen; CLIF-SOFA, chronic liver failure-sepsis organ failure assessment; CO_2, carbon dioxide; HCO_3, bicarbonate; INR, international normalized ratio; 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 Race on Treatment Response

- More White (n = 548) patients achieved HRS reversal with terlipressin than with placebo (34.5% [108/313] vs 17.0% [40/235], respectively; *P* < .001; **Figure 1**)
- More non-White (n = 55) patients achieved HRS reversal with terlipressin (22.9% [8/35]) than with placebo (10.0% [2/20]); however, the difference was not statistically significant (*P* = .297; **Figure 1**)
- Moreover, more patients who received terlipressin were twice as likely to achieve HRS reversal compared with patients who received placebo, irrespective of race (**Figure 1**)

Figure 1. Incidence of HRS Reversal by Race, Pooled ITT Population[a]

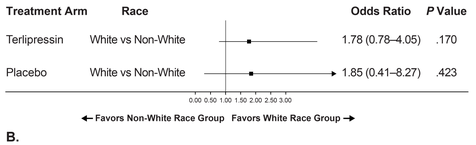


[a] Pooled data were collated from the following Phase III studies: OT-0401, REVERSE, and CONFIRM.
HRS reversal was defined as at least 1 SCr ≤1.5 mg/dL while on treatment (up to 24 hours after the last dose of study drug). Any SCr values obtained after transplant or RRT were excluded.
P values were determined using a Chi-square or Fisher's exact test.
ITT, intent-to-treat; HRS, hepatorenal syndrome; RRT, renal replacement therapy; SCr, serum creatinine.

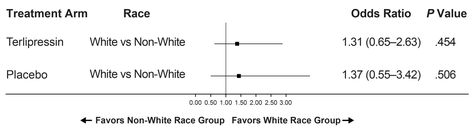
- Race (White vs non-White) was not significantly associated with a greater odds of achieving HRS reversal, in either treatment arm (odds ratio [95% CI]: terlipressin, 1.778 [0.781–4.048], *P* = .170; placebo, 1.846 [0.412–8.273], *P* = .423; **Figure 2A**), or with overall survival rates (odds ratio [95% CI]: terlipressin, 1.307 [0.648–2.634], *P* = .454; placebo, 1.365 [0.545–3.417], *P* = .506; **Figure 2B**)

Figure 2. Univariate Logistic Regression of Race Group (White vs Non-White) by Treatment for **A.** HRS Reversal, and **B.** Overall Survival, ITT Population[a]

A.



B.



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

- Overall, the incidence of adverse events (AEs) was comparable across race groups (White vs non-White) and treatment arms (**Table 3**)
- More terlipressin-treated patients in the White race group had a permanent withdrawal of study drug compared with placebo-treated patients (*P* = .003). In contrast, there were no statistically significant differences related to permanent study drug withdrawal observed between treatment arms in the non-White race group (**Table 3**)
- There were some differences in the incidence of serious AEs (SAEs) reported in >5% of patients in the White versus non-White race groups by treatment (**Table 3**)
  - Of note, respiratory failure occurred more frequently in terlipressin-treated patients compared with placebo-treated patients in the White race group (9.0% [28/310] vs 2.2% [5/228], respectively; *P* = .001). There were no significant differences observed between treatment arms in the non-White race group (5.7% [2/35] vs 5.0% [1/20], respectively; *P* = 1.000) (**Table 3**)

Table 3. Adverse Events by Race Group and Treatment Arm, Pooled Safety Population[a]

Event	White			Non-White		
	Terlipressin (n = 310)	Placebo (n = 228)	*P* value[a]	Terlipressin (n = 35)	Placebo (n = 20)	*P* value[a]
Any AE	294 (94.8)	219 (96.1)	.509	33 (94.3)	19 (95.0)	1.000
Permanent withdrawal of study drug due to an AE	42 (13.5)	13 (5.7)	**.003**	4 (11.4)	0	.285
SAEs reported by frequency in ≥5% of patients within a treatment arm						
Any	214 (69.0)	143 (62.7)	.126	25 (71.4)	13 (65.0)	.620
Blood and lymphatic system disorders	4 (1.3)	3 (1.3)	1.000	0	1 (5.0)	.364
Coagulopathy	0	1 (0.4)	.424	0	1 (5.0)	.364
Cardiac disorders	19 (6.1)	19 (8.3)	.324	1 (2.9)	2 (10.0)	.546
Acute myocardial infarction	0	0		0	1 (5.0)	.364
Cardiac arrest	4 (1.3)	4 (1.8)	.727	0	1 (5.0)	.364
Gastrointestinal disorders	43 (13.9)	17 (7.5)	**.020**	5 (14.3)	1 (5.0)	.399
Abdominal pain	12 (3.9)	2 (0.9)	.051	3 (8.6)	0	.293
Esophageal varices hemorrhage	6 (1.9)	3 (1.3)	.740	1 (2.9)	1 (5.0)	1.000
General disorders and administration site conditions	24 (7.7)	19 (8.3)	.803	9 (25.7)	0	**.019**
Multiple organ dysfunction syndrome	20 (6.5)	11 (4.8)	.424	8 (22.9)	0	**.041**
Hepatobiliary disorders	77 (24.8)	61 (26.8)	.615	9 (25.7)	8 (40.0)	.270
Chronic hepatic failure	22 (7.1)	16 (7.0)	.972	3 (8.6)	3 (15.0)	.657
Hepatic failure	23 (7.4)	22 (9.6)	.356	3 (8.6)	2 (10.0)	1.000
Hepatorenal syndrome	10 (3.2)	9 (3.9)	.654	1 (2.9)	3 (15.0)	.131
Immune system disorders	2 (0.6)	2 (0.9)	.179	0	1 (5.0)	.364
Liver transplant rejection	0	2 (0.9)	.179	0	1 (5.0)	.364
Infections and infestations	48 (15.5)	18 (7.9)	**.008**	1 (2.9)	1 (5.0)	1.000
Pneumonia	9 (2.9)	7 (3.1)	.910	0	1 (5.0)	.364
Sepsis	18 (5.8)	4 (1.8)	**.026**	1 (2.9)	0	1.000
Septic shock	12 (3.9)	1 (0.4)	**.010**	0	1 (5.0)	.364
Injury, poisoning, and procedural complications	3 (1.0)	9 (3.9)	**.034**	1 (2.9)	1 (5.0)	1.000
Transfusion-related acute lung injury	0	0		0	1 (5.0)	.364
Investigations	3 (1.0)	2 (0.9)	1.000	0	2 (10.0)	.128
Body temperature fluctuation	0	0		0	1 (5.0)	.364
Transaminases increased	0	0		0	1 (5.0)	.364
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	2 (0.6)	1 (0.4)	1.000	0	1 (5.0)	.364
Hepatic neoplasm	0	0		0	1 (5.0)	.364
Nervous system disorders	14 (4.5)	13 (5.7)	.534	3 (8.6)	0	.293
Hepatic encephalopathy	8 (2.6)	8 (3.5)	.531	2 (5.7)	0	.529
Psychiatric disorders	5 (1.6)	1 (0.4)	.409	0	1 (5.0)	.364
Mental status changes	5 (1.6)	1 (0.4)	.409	0	1 (5.0)	.364
Renal and urinary disorders	20 (6.5)	14 (6.1)	.883	4 (11.4)	1 (5.0)	.643
Acute kidney injury	6 (1.9)	4 (1.8)	1.000	2 (5.7)	1 (5.0)	1.000
Respiratory, thoracic, and mediastinal disorders	55 (17.7)	24 (10.5)	**.019**	4 (11.4)	2 (10.0)	1.000
Pleural effusion	0	1 (0.4)	.424	0	1 (5.0)	.364
Respiratory failure	28 (9.0)	5 (2.2)	**.001**	2 (5.7)	1 (5.0)	1.000
Vascular disorders	15 (4.8)	8 (3.5)	.451	0	1 (5.0)	.364
Shock	5 (1.6)	2 (0.9)	.704	0	1 (5.0)	.364

Data are presented as n (%).
If the number of events per cell was <5, then a Fisher's exact test was used to calculate the *P* value; otherwise, a Chi-square test was used. Statistical differences are highlighted in bold.
[a] Pooled data were collated from the following Phase III studies: OT-0401, REVERSE, and CONFIRM.
AE, adverse event; SAE, serious adverse event.

Limitations

- The Phase III studies had limited sample sizes for non-White participants, and <10% of the pooled ITT population were non-White

Conclusions

- Race was not significantly associated with the odds of achieving HRS reversal for patients in the terlipressin arm
- More White patients who received terlipressin achieved HRS reversal compared with placebo (*P* < .001). Although this was also observed in the non-White group, it did not reach statistical significance, likely due to the small sample size
- Patients who were treated with terlipressin were twice as likely to achieve HRS reversal compared with placebo, irrespective of race group
- In summary, race is unlikely to influence the clinical response to terlipressin treatment among patients with HRS

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