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The Impact of Terlipressin Treatment on Liver Transplantation Rates in Patients with Hepatorenal Syndrome-Acute Kidney Injury (HRS-AKI) in the Context of Changing MELD Score Definitions

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Pierre M. Gholam[1], Stuart C. Gordon[2], Arun B. Jesudian[3], Satheesh Nair[4], Mark W. Russo[5], Rachel Black[6], Sanaz Cardoza[6]

[1]University Hospitals Cleveland Medical Center, Cleveland, OH, USA; [2]Henry Ford Health, Detroit, MI, USA; [3]Weill Cornell Medicine, New York, NY, USA; [4]Methodist Transplant Institute, Memphis, TN, USA; [5]Atrium Health-Wake Forest, Charlotte, NC, USA; [6]Mallinckrodt Pharmaceuticals, Bridgewater, NJ, USA

INTRODUCTION

- Hepatorenal syndrome-acute kidney injury (HRS-AKI) is a lethal, rapidly progressive, renal failure that occurs in patients with decompensated cirrhosis and ascites.[1] Liver transplantation (LT) is the only curative option for patients with HRS-AKI[1]
- In the US, organ priority allocation is based on the Model for End-Stage Liver Disease (MELD) score. The MELD-sodium (MELD-Na) score has been used since 2016, and in 2023, MELD 3.0 (which also includes albumin and sex) replaced MELD-Na[2,3]
- CONFIRM, a large (N = 300), Phase III, placebo-controlled study (NCT02770716), demonstrated that terlipressin can improve renal function in patients with HRS-AKI[4]
  - Terlipressin is the first US Food and Drug Administration (FDA)-approved drug for the treatment of adult patients with HRS with a rapid reduction in kidney function[5]
- A reduction in MELD score, secondary to an improvement in serum creatinine (SCr) levels due to HRS reversal, may impact liver transplant prioritization if the MELD score is not locked (ie, the MELD score that is measured prior to terlipressin treatment initiation is used for transplant eligibility/prioritization)[6]
- The FDA prescribing information for terlipressin contains the following limitations / warnings regarding terlipressin use[5]:
  - Patients with SCr > 5 mg/dL are unlikely to experience a clinical benefit
  - Patients with volume overload or acute-on-chronic liver failure (ACLF) grade 3 are at an increased risk of respiratory failure
  - For patients with a high prioritization for LT (ie, MELD ≥ 35), the benefits of terlipressin may not outweigh its risks because adverse events (AEs; ie, respiratory failure, ischemia) may make a patient ineligible for LT, if transplant listed
- Patients who would be eligible for treatment per the terlipressin FDA label (ie, MELD score < 35 if transplant listed, SCr < 5 mg/dL, and ACLF grade 0–2) are characterized by a reduced risk of respiratory failure AEs, as well as overall and pre-transplant mortality
  - Patients in the population conforming to the FDA label are expected to experience the most differential benefit from terlipressin treatment versus placebo
  - Henceforth this population of patients with HRS-AKI will be referred to as the 'label-specific population'

AIM OF THE STUDY

To assess clinical outcomes (ie, the incidence of HRS reversal and LT) and changes in MELD scores in patients who would be eligible for treatment per the terlipressin FDA label (ie, the label-specific population)

METHODS

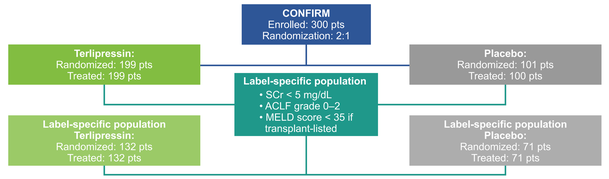
- The label-specific population from the CONFIRM study[4] was retrospectively assessed for the rate of LT up to the end of the study observation period (ie, 90 days)
- The incidence of HRS reversal was defined as the percentage of patients with a SCr value ≤ 1.5 mg/dL while on treatment (defined as up to 24 hours after the final dose of the study drug) by Day 14 or discharge. SCr values obtained after renal replacement therapy, transjugular intrahepatic portosystemic shunt, LT, or open-label vasopressor use were excluded
- Changes from baseline to the end of treatment in MELD, MELD-Na, and MELD 3.0 scores were retrospectively evaluated
- The following standard formulas to calculate MELD scores were used[3]
  - **MELD = 9.57 × $\log_e$(SCr) + 3.78 × $\log_e$(bilirubin) + 11.20 × $\log_e$(INR) + 6.43**, where SCr (mg/dL), bilirubin (mg/dL), and international normalized ratio (INR) values < 1.0 were set to 1.0, and SCr values to 4.0 mg/dL, if SCr was ≥ 4 mg/dL, or the patient received 2 or more dialysis treatments within the prior week. The resulting score was rounded to the nearest whole number to yield the MELD score
  - **MELD-Na = MELD + 1.32*(137 – Na) – (0.033*MELD*[137 – Na])**, where the serum sodium (Na) concentration is bound between 125 mmol/L and 137 mmol/L. The resulting score was rounded to the nearest whole number to yield the MELD-Na score
  - **MELD 3.0 = 1.33 (if female) + 4.56*$\log_e$(bilirubin) + 0.82*(137 – Na) – 0.24*(137 – Na)*$\log_e$(bilirubin) + 9.09*$\log_e$(INR) + 11.14*$\log_e$ (SCr) + 1.85*(3.5 – albumin) – 1.83*(3.5 – albumin)*$\log_e$ (SCr) + 6**, which is rounded to the nearest whole number

RESULTS

Label-specific population

- The label-specific population from CONFIRM included 132 patients in the terlipressin arm and 71 patients in the placebo arm (**Figure 1**)

Figure 1. The ITT and label-specific populations from the CONFIRM study



ACLF, acute-on-chronic liver failure; ITT, intent-to-treat; MELD, Model for End-Stage Liver Disease; pts, patients; SCr, serum creatinine.

- Baseline patient demographics and clinical characteristics in the label-specific population were similar in both the terlipressin and placebo treatment arms (**Table 1**)

Table 1. Baseline patient demographics and clinical characteristics in the CONFIRM label-specific population

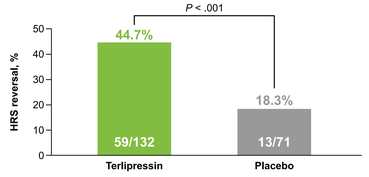
Baseline parameter	Terlipressin (n = 132)	Placebo (n = 71)
Age (years), mean ± SD	55.6 ± 10.8	54.1 ± 12.1
Sex, male, n (%)	78 (59.1)	41 (57.7)
Race, n (%)		
American Indian or Alaska Native	1 (0.8)	0
Asian	2 (1.5)	0
Black or African American	6 (4.5)	3 (4.2)
White	120 (90.9)	67 (94.4)
Alcohol-associated hepatitis, n (%)	46 (34.8)	23 (32.4)
Baseline serum creatinine (mg/dL), mean ± SD	3.2 ± 0.7	3.3 ± 0.8
SIRS subgroup, n (%)	51 (38.6)	30 (42.3)
MELD score, n	111	58
mean ± SD	30.1 ± 6.1	31.1 ± 5.8
Child-Pugh score, n (%)		
Class A [5–6]	3 (2.3)	2 (2.8)
Class B [7–9]	55 (41.7)	27 (38.0)
Class C [10–15]	71 (53.8)	39 (54.9)
Missing	3 (2.3)	3 (4.2)
Prior albumin, n (%)	131 (99.2)	70 (98.6)
Amount of prior albumin (g), mean ± SD	329.8 ± 170.5	348.6 ± 299.3

MELD, Model for End-Stage Liver Disease; SD, standard deviation; SIRS, systemic inflammatory response syndrome.

Clinical outcomes: HRS reversal and LT

- In the label-specific population, the incidence of HRS reversal was 44.7% (59/132) versus 18.3% (13/71) in the terlipressin and placebo arms, respectively (*P* < .001) (**Figure 2**)

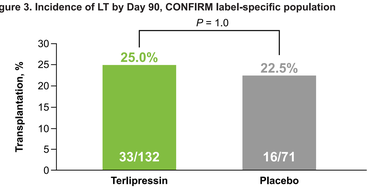
Figure 2. Incidence of HRS reversal, CONFIRM label-specific population



Screened *P* values to compare the incidence of HRS reversal were generated using a Cochran-Mantel-Haenszel test stratified by qualifying SCr (< 3.4 mg/dL vs ≥ 3.4 mg/dL) and prior large volume paracentesis within 14 days of randomization (at least one single event of ≥ 4 L vs < 4 L).
HRS, hepatorenal syndrome; SCr, serum creatinine.

- The incidence of LT, including a simultaneous liver-kidney transplant (SLKT), by Day 90 was 25.0% (33/132) and 22.5% (16/71) in the terlipressin and placebo arms, respectively (*P* = 1.0) (**Figure 3**)
  - 2.3% (3/132) of patients in the terlipressin arm and 1.4% (1/71) of patients in the placebo arm received an SLKT
  - The median time to transplantation was 22 days in the terlipressin arm versus 11.5 days in the placebo arm (*P* = .147)

Figure 3. Incidence of LT by Day 90, CONFIRM label-specific population

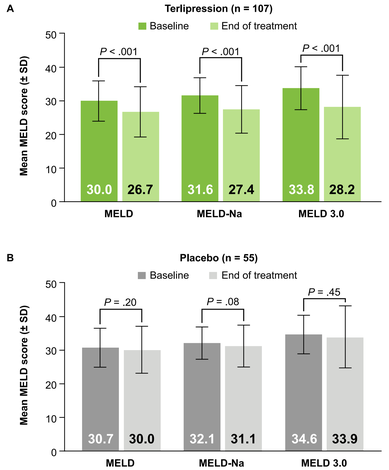


Screened *P* values to compare transplantation incidence were generated from a Fisher's Exact test or a Chi-square test.
LT, liver transplantation.

Changes in MELD scores

- Data to calculate changes in MELD scores were available for 107/132 patients in the terlipressin arm and for 55/71 patients in the placebo arm
- All 3 MELD scores decreased from baseline to the end of treatment in the terlipressin arm (versus a change of 0, all *P* < .001), but not in the placebo arm (**Figure 4**)

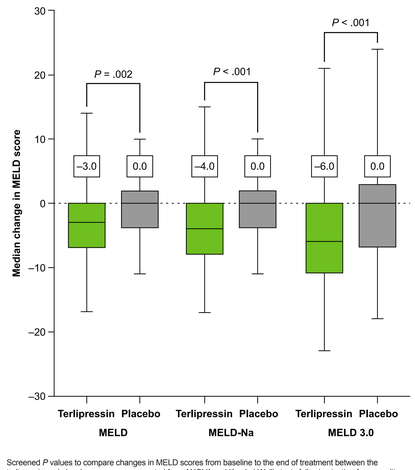
Figure 4. Mean MELD scores at baseline and at the end of treatment in the A) terlipressin and B) placebo arms, CONFIRM label-specific population



Screened *P* values to compare the changes from baseline to the end of treatment with 0 were generated from a *t* test.
MELD, Model for End-Stage Liver Disease; Na, sodium; SD, standard deviation.

- Median score changes were −3.0 for MELD, −4.0 for MELD-Na, and −6.0 for MELD 3.0 in the terlipressin arm, while median score changes for all 3 MELD scores in the placebo arm were 0. The difference in changes in MELD scores between the terlipressin and placebo arms was significant in all cases (all *P* < .01) (**Figure 5**)

Figure 5. Median changes in MELD scores from baseline to the end of treatment, CONFIRM label-specific population



Screened *P* values to compare changes in MELD scores from baseline to the end of treatment between the terlipressin and placebo arms were generated from ANOVA and Kruskal-Wallis tests following testing for normality.
Error bars represent the min, max.
ANOVA, analysis of variance; max, maximum; MELD, Model for End-Stage Liver Disease; min, minimum; Na, sodium.

CONCLUSIONS

- **As expected, in the CONFIRM label-specific population, the incidence of HRS reversal was significantly higher in the terlipressin arm compared with the placebo arm**
- **The incidence of LT in the label-specific population was similar in both treatment arms**
- **Improvement in MELD scores due to terlipressin treatment did not lead to a decrease in transplantation rate, despite a decrease in all 3 MELD score variants for terlipressin versus placebo in the label-specific population from the CONFIRM study**

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DISCLOSURES

Pierre M. Gholam is a consultant for Genetech and has received speaker fees for AbbVie, AstraZeneca, Eisai, Exelixis, Gilead, Intercept, Ipsen, and Madrigal Pharmaceuticals.
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Arun B. Jesudian is a consultant for Dynavax Technologies, Mallinckrodt Pharmaceuticals, and Salix Pharmaceuticals; and has recieved speaker fees for Madrigal Pharmaceuticals, Mallinckrodt Pharmaceuticals, and Salix Pharmaceuticals.
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CONTACT INFORMATION

Pierre M. Gholam
pierre.gholam@uhhospitals.org

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