Treatment of Hepatorenal Syndrome Type 1 With Terlipressin Reduces the Need for Renal Replacement Therapy Post–Liver Transplantation

Juan Carlos Q. Velez[1]; Seth Sclair[2]; Antonio Sanchez[3]; Stephen Caldwell[4]; Samuel Sigal[5]; Paul J. Thuluvath[6]; Rohit Satoskar[7]; S. Chris Pappas[8]; Khurram Jamil[9]

[1]Department of Nephrology, Ochsner Health System, New Orleans, LA, USA; [2]University Hospitals Cleveland Medical Center, Cleveland, OH, USA; [3]University of Iowa Hospitals & Clinics, Iowa City, IA, USA; [4]University of Virginia, Charlottesville, VA, USA; [5]Montefiore Medical Center, New York, NY, USA; [6]Mercy Medical Center & University of Maryland School of Medicine, Baltimore, MD, USA; [7]MedStar Georgetown University Hospital, Washington, DC, USA; [8]Orphan Therapeutics, Annandale, NJ, USA; [9]Mallinckrodt Pharmaceuticals, Bedminster, NJ, USA

DISCLOSURES: Juan Carlos Q. Velez: Consulting (Retrophin), Scientific Advisor or Membership (Mallinckrodt Pharmaceuticals), Speakers Bureau (Otsuka Pharmaceuticals). Seth Sclair: Nothing to disclose. Antonio Sanchez: Research funding as principal investigator of clinical trials (Enanta Pharmaceuticals, Merck, Valeant Pharmaceuticals). Stephen Caldwell: Research funding (Mallinckrodt Pharmaceuticals). Samuel Sigal: Consulting (Mallinckrodt Pharmaceuticals), research funding (Mallinckrodt Pharmaceuticals, Gilead, Lilly, Intercept, Genfit). Paul J. Thuluvath: Clinical research grant and Advisory board (Mallinckrodt Pharmaceuticals). Rohit Satoskar: Research funding (Mallinckrodt Pharmaceuticals), Grant funding (Gilead), Consulting (Salix). S. Chris Pappas: Consulting (Orphan Therapeutics LLC, Mallinckrodt Pharmaceuticals, Durect). Khurram Jamil: Employee and shareholder (Mallinckrodt Pharmaceuticals).

Introduction

- Hepatorenal syndrome type 1 (HRS-1) is a serious, but potentially reversible form of acute kidney injury that can occur as a complication of advanced chronic liver disease associated with cirrhosis[1,2]
- Liver transplantation is the best treatment option for HRS-1[3]
  - Preexisting renal dysfunction and the need for renal replacement therapy (RRT) have been associated with negative outcomes after liver transplantation, including reduced survival, increased costs, longer intensive care unit (ICU) stays, sepsis, and posttransplant RRT[4-7]
- Poor kidney function/RRT pretransplant and posttransplant is associated with poor graft function and graft survival[6,8]
- The recently completed randomized, placebo-controlled CONFIRM trial (NCT02770716) demonstrated the efficacy of terlipressin, a synthetic vasopressin analog that acts as a systemic vasoconstrictor, for inducing reversal of HRS-1 and reducing the cumulative need for RRT
- Improving renal function prior to liver transplant may be associated with better posttransplant outcomes[9,10]
- The objective of the current analysis was to assess the efficacy of terlipressin in improving RRT outcomes, including in patients listed for liver transplantation and those who received a liver transplant

Methods

- CONFIRM was a North American trial (N=300) that compared the efficacy and safety of terlipressin 1 mg given intravenously every 6 hours (n=199) versus placebo (n=101) in patients with HRS-1 receiving standard-of-care albumin therapy[11]
  - Study drug was administered every 6 hours and continued until either 24 hours after achieving 2 consecutive serum creatinine (SCr) values of ≤1.5 mg/dL or until Day 14
  - If SCr was at or above baseline value after a minimum of 10 doses, study drug was discontinued. Study drug was also discontinued if a patient was to undergo RRT, liver transplant, transjugular intrahepatic portosystemic shunt placement, or receive vasopressor therapy
  - An overview of key design features for OT-0401, REVERSE, and CONFIRM is presented in **Table 1**
- The 90-day overall survival rate in patients who received a liver transplant and rate of RRT post–liver transplant by intention-to-treat analysis through 90 days of follow-up were assessed
- A pooled analysis of the 3 randomized controlled trials of terlipressin in patients with HRS-1 (OT-0401 [NCT00089570],[12] REVERSE [NCT01143246],[13] and CONFIRM) examined 90-day overall survival rates in the patients who received a liver transplant. A pooled analysis of data from REVERSE and CONFIRM was also performed to assess the RRT-free survival rate in transplant-listed patients

Table 1. Key Study Design Features of the 3 Randomized Controlled Trials of Terlipressin in Patients With HRS-1

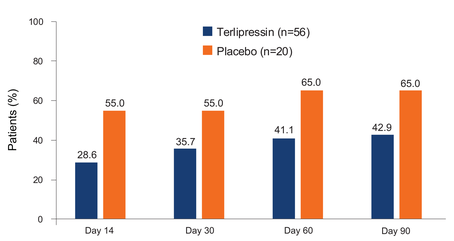
	OT-0401[12]	REVERSE[13]	CONFIRM
Design	All 3 were phase 3, randomized, double-blind, placebo-controlled, multicenter trials		
Randomization rate	1:1	1:1	2:1
Number of patients/study sites	112/35	196/52	300/60
Stratification	Stratified by presence or absence of alcoholic hepatitis	SCr (<3.6 mg/dL or ≥3.6 mg/dL) and alcoholic hepatitis (present or not)	SCr (<3.4 mg/dL or ≥3.4 mg/dL) and pre-enrollment LVP (at least 1 single event of at least 4 L or <4 L within 3 to 14 days prior to randomization)
Treatment	In all 3 trials, patients received terlipressin: 4–8 mg/day (IV q6h) or placebo. All patients in both treatment groups received standard-of-care albumin therapy		

IV, intravenous; LVP, large-volume paracentesis; q6h, every 6 hours; SCr, serum creatinine.

Results

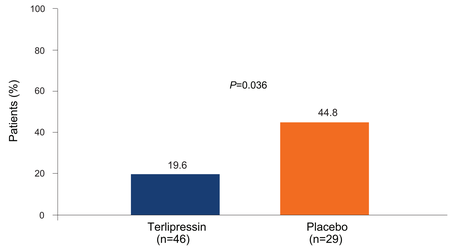
- In the CONFIRM trial, 28.1% of patients (56/199) in the terlipressin group and 19.8% (20/101) in the placebo group were listed for a liver transplant at baseline; of these, 42.9% (24/56) and 65.0% (13/20), respectively, required RRT Day 90 (**Figure 1**)

Figure 1. CONFIRM: Summary of Renal Replacement Therapy Status Among Patients Listed for Liver Transplantation at Baseline



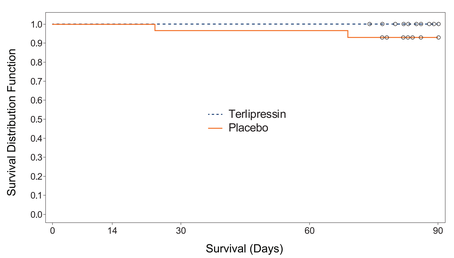
- Among patients listed for a liver transplant at baseline in CONFIRM, 35.7% (20/56) of those in the terlipressin group versus 10.0% (2/20) in the placebo group experienced HRS reversal
  - Least squares (LS) mean (standard error [SE]) change from baseline through end of treatment in SCr was -1.1 (0.11; *P*<0.001) mg/dL in the terlipressin group and -0.4 (0.17; *P*=0.016) mg/dL in the placebo group, with an LS mean (SE) between-group difference of -0.7 (0.21) mg/dL in favor of terlipressin (*P*=0.001)
- In CONFIRM, 23.1% of patients (46/199) in the terlipressin group and 28.7% of patients (29/101) in the placebo group underwent a liver transplant
  - In patients who received a liver transplant, LS mean (SE) change from baseline through end of treatment in SCr was -1.1 (0.11; *P*<0.001) mg/dL in the terlipressin group and -0.5 (0.14; *P*=0.002) mg/dL in the placebo group, with an LS mean (SE) between-group difference of -0.7 (0.18) mg/dL in favor of terlipressin (*P*<0.001)
  - Following liver transplant, the rate of posttransplant RRT in patients who received terlipressin was significantly lower than in those who received placebo (**Figure 2**)

Figure 2. CONFIRM: Patients Requiring Renal Replacement Therapy After Liver Transplantation



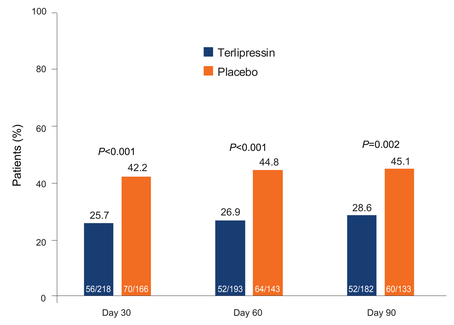
  - The overall 90-day survival rate for patients transplanted in the terlipressin group was 100% (46/46) compared with 93.1% (27/29) in the placebo group (**Figure 3**)

Figure 3. CONFIRM: Overall Survival up to 90 Days for Patients Who Received a Liver Transplant



- In the pooled analysis of OT-0401, REVERSE, and CONFIRM survivors, need for RRT through Day 90 was significantly lower in the terlipressin group versus placebo (**Figure 4**)

Figure 4. Pooled Data From OT-0401, REVERSE, and CONFIRM: Summary of Renal Replacement Therapy Status Among Survivors



- In the pooled analysis of OT-0401, REVERSE, and CONFIRM, the 90-day survival rates for patients who received a liver transplant were 98.9% (93/94) in the terlipressin group and 91.0% (71/78) with placebo (*P*=0.014; **Figure 5**)
  - Incidence of HRS reversal was 28.7% (27/94) in the terlipressin group versus 12.8% (10/78) in the placebo group (*P*=0.012)
  - Need for RRT through Day 90 was also significantly lower in the terlipressin group versus the placebo group (**Figure 6**)

Figure 5. Pooled Data From OT-0401, REVERSE, and CONFIRM: Overall Survival up to 90 Days for Patients Who Received a Liver Transplant

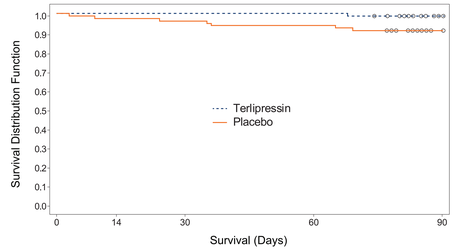
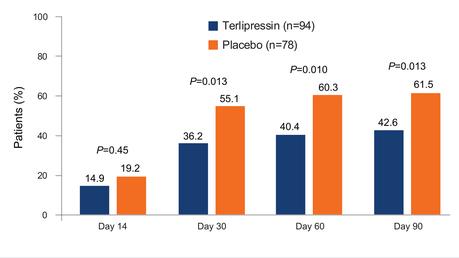


Figure 6. Pooled Data From OT-0401, REVERSE, and CONFIRM: Summary of Renal Replacement Therapy Status Among Patients Who Received a Liver Transplant



- In the pooled analysis of REVERSE and CONFIRM for transplant-listed patients, a significantly higher proportion of patients in the terlipressin group were alive without RRT at Day 90 compared with the placebo group (**Figure 7**)
  - The proportions of patients needing RRT through Day 90 were numerically lower in the terlipressin group versus placebo (**Figure 8**)

Figure 7. Pooled Data From REVERSE and CONFIRM: Renal Replacement-Free Survival up to 90 Days for Liver Transplant-Listed Patients

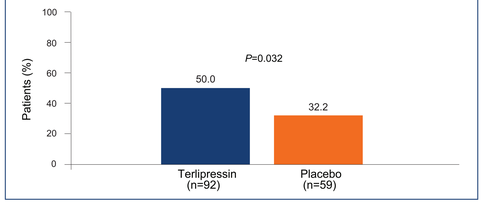
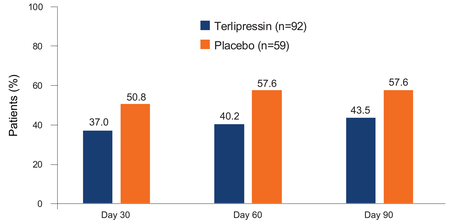


Figure 8. Pooled Data From REVERSE and CONFIRM: Summary of Renal Replacement Therapy Status Among Patients Listed for Liver Transplantation at Baseline



CONCLUSIONS

- Treatment with terlipressin plus albumin is associated with decreased need for RRT following a liver transplant in patients with HRS-1
- Renal dysfunction and the need for RRT before a liver transplant reduces survival, raises costs and increases the length of ICU stays, elevates the risk for sepsis, and increases the need for RRT post–liver transplantation [4-7]
- Treatment with terlipressin plus albumin is associated with improved 90-day survival post–liver transplantation

References

1. Velez JCQ, et al. *Nat Rev Nephrol*. 2020;16(3):137-55.
2. Salerno F, et al. *Gut*. 2007;56(9):1310-8.
3. European Association for the Study of the Liver. *J Hepatol*. 2018;69(2):406-60.
4. Weber ML, et al. *Liver Transpl*. 2012;18(11):1290-301.
5. Zand MS, et al. *Clin Transplant*. 2011;25(2):213-21.
6. Nair S, et al. *Hepatology*. 2002;35(5):1179-85.
7. Weismuller TJ, et al. *Scand J Gastroenterol*. 2008;43(6):736-46.
8. Gonwa TA, et al. *Transplantation*. 1995;59(3):361-5.
9. Piano S, et al. *Hepatology*. 2020.
10. Restuccia T, et al. *J Hepatol*. 2004;40(1):140-6.
11. Wong F, et al. *Hepatology*. 2019;70(6 suppl):1480A-1A.
12. Sanyal AJ, et al. *Gastroenterology*. 2008;134(5):1360-8.
13. Boyer TD, et al. *Gastroenterology*. 2016;150(7):1579-89.

Acknowledgments

We thank the research staff, patients, and families who participated in the phase 3 studies of terlipressin. This study was funded by Mallinckrodt Pharmaceuticals. Medical writing and editorial support was provided by Michael D. Morren, RPh, MBA, of Peloton Advantage, LLC, an OPEN Health company, and funded by Mallinckrodt Pharmaceuticals.

KIDNEY WEEK 2020 REIMAGINED OCTOBER

Presented at the Annual Meeting of the American Society of Nephrology (ASN), October 20–25, 2020 – Virtual Conference