The Impact of MELD Score and ACLF Grade on Outcomes of Hepatorenal Syndrome Following Treatment With Terlipressin and Albumin in Patients With Alcohol-associated Hepatitis

Ethan M. Weinberg[1], Khurram Jamil[2], Richard Deng[3], and K. Rajender Reddy[1]

[1]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [2]Mallinckrodt Pharmaceuticals, Bridgewater, NJ, USA; [3]Tech Data Corporation, Fairfax, VA, USA

3046-A

Background

- Hepatorenal syndrome-acute kidney injury (HRS-AKI) is a devastating complication of end-stage liver disease (ESLD), resulting from circulatory dysfunction and systemic inflammation[1,2]
- Liver transplantation (LT) is the best treatment for ESLD for patients who experience HRS-AKI; however, most patients with HRS-AKI are not candidates for LT, including many patients with acute alcohol-associated hepatitis (AAH)[1,3]
- AAH is an acute condition with a potentially reversible component, and thus may facilitate avoidance of LT or death, if HRS-AKI is effectively treated[4]
  - Reversal of HRS—defined as a reduction in serum creatinine (SCr) to ≤ 1.5 mg/dL—in patients with AAH is imperative to allow them to clinically recover, and subsequently, seek treatment for alcohol use disorder, or to achieve LT eligibility[3,4]
- Terlipressin is the only US Food and Drug Administration (FDA)-approved therapy for the treatment of patients with HRS and a rapid reduction in kidney function[5]
- It was hypothesized that terlipressin might serve as a bridge for recovery between HRS-AKI and a potentially reversible acute liver disease such as AAH

Aim of the Study

- The study aimed to evaluate the interplay between baseline renal and hepatic characteristics and HRS reversal and survival among patients with AAH and HRS-AKI who were enrolled in 3 large, randomized, Phase III, placebo-controlled studies

Methods

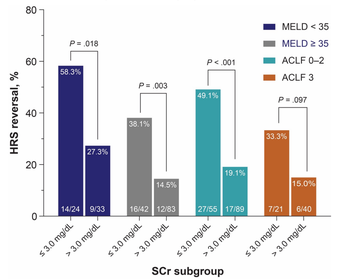
- Patients with a diagnosis of HRS and AAH (based on investigator assessment) from 3 Phase III double-blind, placebo-controlled studies of terlipressin plus albumin for the treatment of HRS-AKI (formerly, HRS type 1; OT-0401 [NCT00089570][6], REVERSE [NCT01143246][7], and CONFIRM [NCT02770716][8]) were pooled for the analysis
  - Patients were divided into 2 groups based on SCr at baseline: SCr ≤ 3.0 mg/dL or SCr > 3.0 mg/dL
  - Each group was then further divided based on baseline Model for End-stage Liver Disease (MELD) scores (ie, < 35 or ≥ 35) and acute-on-chronic liver failure (ACLF) grade (0–2 or 3)
- Treatment efficacy was evaluated for HRS reversal and 90-day survival
  - HRS reversal was defined as at least 1 SCr value of ≤ 1.5 mg/dL while on treatment (up to 24 hours after the last dose of study medication). Any SCr values obtained posttransplant or after renal replacement therapy (RRT) were excluded
- *P* values for numerical comparisons of categorical variables were calculated from a Chi-square test

Results

Outcomes in the overall population

- Across the 3 Phase III studies, 205 patients had AAH at baseline; of those, 76 patients had a SCr ≤ 3.0 mg/dL and 129 patients had a SCr > 3.0 mg/dL
- In the overall population, the rate of HRS reversal was more than 2 times as likely among patients with baseline SCr ≤ 3.0 mg/dL (vs patients with SCr > 3.0 mg/dL) in all MELD and ACLF subgroups (**Figure 1**)
  - This effect was statistically significant between SCr groups in subgroups of patients with MELD < 35, MELD > 35, and ACLF 0–2 (*P* < .05 each) (**Figure 1**)

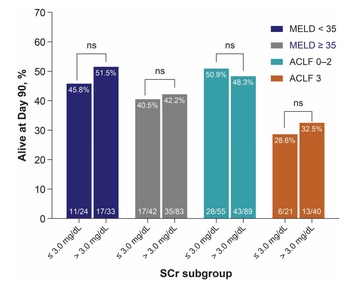
Figure 1. Incidence of HRS reversal in the overall population of patients with AAH; pooled ITT population.



Data were pooled from the following Phase III studies: OT-0401, REVERSE, and CONFIRM.
AAH, alcohol-associated hepatitis; ACLF, acute-on-chronic liver failure; HRS, hepatorenal syndrome; ITT, intent-to-treat; MELD, Model for End-Stage Liver Disease; SCr, serum creatinine.

- However, survival by Day 90 was similar among patients with SCr ≤ 3.0 mg/dL and SCr > 3.0 mg/dL in subgroups defined by MELD score and ACLF grade (all *P* values > .670) (**Figure 2**)

Figure 2. Incidence of survival by Day 90 in the overall population of patients with AAH; pooled ITT population.

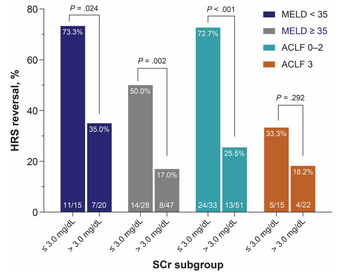


Data were pooled from the following Phase III studies: OT-0401, REVERSE, and CONFIRM.
AAH, alcohol-associated hepatitis; ACLF, acute-on-chronic liver failure; ITT, intent-to-treat; MELD, Model for End-Stage Liver Disease; ns, not significant; SCr, serum creatinine.

Outcomes in the terlipressin group

- In the terlipressin group, HRS reversal was also more frequent among patients with SCr ≤ 3.0 mg/dL (vs patients with SCr > 3.0 mg/dL) in all MELD and ACLF subgroups (**Figure 3**)
  - This effect was statistically significant in the subgroup of patients with MELD < 35, MELD > 35, and ACLF 0–2 (*P* < .05 each), but not in the subgroup of patients with ACLF 3 (*P* = .292), probably due to the small sample size (**Figure 3**)

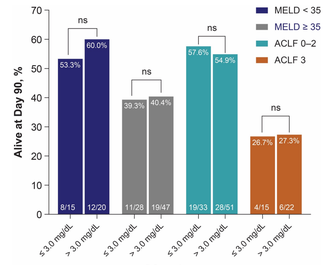
Figure 3. Incidence of HRS reversal in the terlipressin group of patients with AAH; pooled ITT population.



Data were pooled from the following Phase III studies: OT-0401, REVERSE, and CONFIRM.
AAH, alcohol-associated hepatitis; ACLF, acute-on-chronic liver failure; HRS, hepatorenal syndrome; ITT, intent-to-treat; MELD, Model for End-Stage Liver Disease; SCr, serum creatinine.

- Survival by Day 90 was similar among patients with SCr ≤ 3.0 mg/dL and SCr > 3.0 mg/dL in the terlipressin group in all subgroups defined by MELD score and ACLF grade (all *P* values > .690) (**Figure 4**)

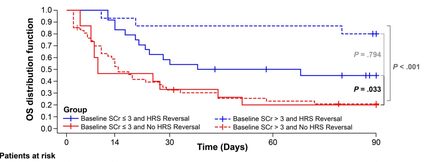
Figure 4 Incidence of survival by Day 90 in the terlipressin group of patients with AAH; pooled ITT population.



Data were pooled from the following Phase III studies: OT-0401, REVERSE, and CONFIRM.
AAH, alcohol-associated hepatitis; ACLF, acute-on-chronic liver failure; ITT, intent-to-treat; MELD, Model for End-Stage Liver Disease; ns, not significant; SCr, serum creatinine.

- Among *transplant-free* patients with AAH in the terlipressin group, overall survival (OS) was significantly longer by Day 90 in patients who achieved HRS reversal (vs non-reversal), in both subgroups of patients with SCr ≤ 3 mg/dL (*P* = .033) and SCr > 3 mg/dL (*P* < .001) (**Figure 5**)
  - There was no significant difference in OS between patients with SCr ≤ 3 mg/dL and > 3 mg/dL, who experienced HRS reversal (*P* = .794) (**Figure 5**)

Figure 5. Overall survival up to 90 days by baseline SCr subgroup (ie, ≤ 3 mg/dL and > 3 mg/dL) and HRS reversal status among transplant-free patients with AAH in the terlipressin group; pooled ITT population



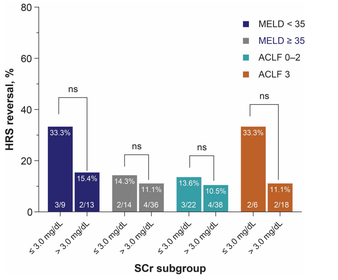
Patients at risk					
Baseline SCr ≤ 3 and HRS Reversal	24	22	14	10	6
Baseline SCr ≤ 3 and No HRS Reversal	15	7	5	3	3
Baseline SCr > 3 and HRS Reversal	15	14	13	13	11
Baseline SCr > 3 and No HRS Reversal	47	27	15	10	8

P values comparing overall survival estimates are from a 2-sample log rank test.
Data were pooled from the following Phase III studies: OT-0401, REVERSE, and CONFIRM.
AAH, alcohol-associated hepatitis; HRS, hepatorenal syndrome; ITT, intent-to-treat; OS, overall survival; SCr, serum creatinine.

Outcomes in the placebo group

- In contrast to the terlipressin group, the rate of HRS reversal in the placebo group was not significantly different between the subgroups of patients with SCr ≤ 3.0 mg/dL and SCr > 3.0 mg/dL in all MELD and ACLF subgroups (all *P* values > .250), although the results could be affected by the small number of events (**Figure 6**)

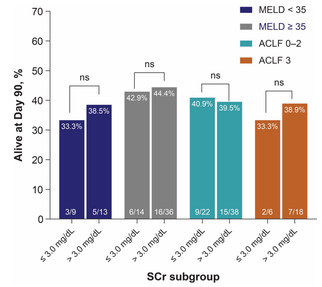
Figure 6 Incidence of HRS reversal in the placebo group of patients with AAH; pooled ITT population.



Data were pooled from the following Phase III studies: OT-0401, REVERSE, and CONFIRM.
AAH, alcohol-associated hepatitis; ACLF, acute-on-chronic liver failure; HRS, hepatorenal syndrome; ITT, intent-to-treat; MELD, Model for End-Stage Liver Disease; ns, not significant; SCr, serum creatinine.

- There were no significant differences in survival by Day 90 in the subgroup of patients with SCr ≤ 3.0 mg/dL and SCr > 3.0 mg/dL in all MELD and ACLF subgroups (**Figure 7**)

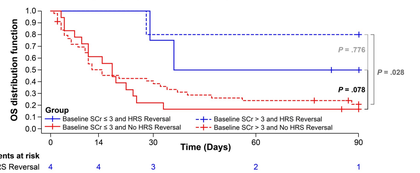
Figure 7. Incidence of survival by Day 90 in the placebo group of patients with AAH; pooled ITT population.



Data were pooled from the following Phase III studies: OT-0401, REVERSE, and CONFIRM.
AAH, alcohol-associated hepatitis; ACLF, acute-on-chronic liver failure; ITT, intent-to-treat; MELD, Model for End-Stage Liver Disease; ns, not significant; SCr, serum creatinine.

- Among *transplant-free* patients with AAH in the placebo group, OS by Day 90 was numerically longer in the subgroup of patients with HRS reversal and SCr ≤ 3 mg/dL (vs non-reversal and SCr ≤ 3 mg/dL; *P* = .078); and was significantly longer among patients with HRS reversal and SCr > 3 mg/dL (vs SCr > 3 mg/dL and no HRS reversal; *P* = .028) (**Figure 8**)
  - Among patients who experienced HRS reversal, there was no significant difference in OS between patients with SCr ≤ 3 mg/dL and > 3 mg/dL, (*P* = .776) (**Figure 8**)

Figure 8. Overall survival up to 90 days by baseline SCr (ie, ≤ 3 mg/dL and > 3 mg/dL) and HRS reversal status among transplant-free patients with AAH in the placebo group; pooled ITT population.



Patients at risk					
Baseline SCr ≤ 3 and HRS Reversal	4	4	3	2	1
Baseline SCr ≤ 3 and No HRS Reversal	18	11	4	3	2
Baseline SCr > 3 and HRS Reversal	5	5	4	4	4
Baseline SCr > 3 and No HRS Reversal	44	21	17	10	7

Data were pooled from the following Phase III studies: OT-0401, REVERSE, and CONFIRM.
P values comparing OS estimates are from a 2-sample log rank test.
AAH, alcohol-associated hepatitis; HRS, hepatorenal syndrome; ITT, intent-to-treat; OS, overall survival SCr, serum creatinine.

Conclusions

- In the combined treatment population of patients with AAH, lower baseline SCr levels (ie, SCr ≤ 3 mg/dL) were associated with a significantly higher rate of HRS reversal among patients with HRS-AKI, irrespective of their MELD score and among patients with an ACLF grade 0–2
  - However, the effect in the subgroup of patients with an ACLF grade 3 did not reach statistical significance
- In the terlipressin group, baseline SCr ≤ 3.0 mg/dL was associated with a higher rate of HRS reversal, even among patients with a MELD score ≥ 35 or ACLF grade 3
  - Therefore, early treatment with terlipressin (ie, when SCr is ≤ 3.0 mg/dL) may result in better clinical outcomes in patients with HRS-AKI and AAH, regardless of MELD score or ACLF grade
- In the placebo group, the incidence of HRS reversal was not significantly different between patients with SCr ≤ 3 mg/dL and SCr > 3mg/dL at baseline in all MELD and ACLF subgroups
- Incidence of survival by Day 90 was similar between patients with baseline SCr ≤ 3 mg/dL and SCr > 3 mg/dL within all MELD and ACLF subgroups
- In summary, in the absence of a liver transplant, terlipressin is an effective therapy which results in a clinical response (ie, HRS reversal) in patients with AAH and SCr ≤ 3 mg/dL, even among those with a high MELD score and a higher ACLF grade; therefore, these patients should be treated with terlipressin

Contact

Ethan M. Weinberg
Email: Ethan.Weinberg@pennmedicine.upenn.edu

Funding and commercial support

Mallinckrodt Pharmaceuticals

Acknowledgment

Medical writing and editorial support, conducted in accordance with Good Publication Practice 2022 Update (GPP 2022) and the International Committee of Medical Journal Editors (ICMJE) guidelines, were provided by Julia Grigorieva, PhD, of Oxford PharmaGenesis Inc., Newtown, PA; funded by Mallinckrodt Pharmaceuticals.

References

1. Angeli P et al. *J Hepatol*. 2019;71(4):811–822.
2. Bera C et al. *Therap Adv Gastroenterol*. 2022;15: 17562848221102679.
3. Sigal SH et al. *Clin Gastroenterol Hepatol*. 2023. *In Press*; Epub ahead of print.
4. Hosseini N et al. *Alcohol Alcohol*. 2019;54(4):408–416.
5. TERLIVAZ® (Terlipressin). Full Prescribing Information. Mallinckrodt Pharmaceuticals; 2022.
6. Sanyal AJ et al. *Gastroenterology*. 2008;134(5):1360–1368.
7. Boyer TD et al. *Gastroenterology*. 2016;150(7):1579–1589.
8. Wong F et al. *N Engl J Med*. 2021;394(9):818–828.

Presented at the American Association for the Study of Liver Diseases (AASLD) Annual Meeting, November 10–14, 2023, Boston, MA, USA.