Understanding the Relationship Between Mean Arterial Pressure and Terlipressin in Hepatorenal Syndrome-Acute Kidney Injury Reversal: A Post Hoc Analysis of the CONFIRM, REVERSE, and OT-0401 Trials

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Introduction

- Hepatorenal syndrome–acute kidney injury (HRS-AKI) is a deadly but potentially reversible rapid progressive renal failure that occurs in patients with decompensated cirrhosis and ascites, and is characterized by hemodynamic abnormalities and extreme renal vasoconstriction[1]
- The improvement in renal blood flow in patients with HRS-AKI with terlipressin is mediated via arteriolar vasoconstriction, leading to reduced portal hypertension and effective arterial blood volume redistribution[2,3]
  - It is hypothesized that terlipressin reverses HRS-AKI by increasing mean arterial pressure (MAP), leading to improved renal perfusion[3]
- Moreover, terlipressin is recommended as a first-line treatment for patients with HRS-AKI per the American Association for the Study of Liver Diseases (AASLD) guidelines[4]
  - Terlipressin is the only medication approved by the US Food and Drug Administration (FDA) for the treatment of adult patients with HRS and a rapid reduction in kidney function[5]

Aim of the study

- This study evaluated the effect of terlipressin treatment on MAP, as an indicator of the hemodynamic response to treatment, utilizing data from 3 large Phase III studies

Methods

- Data from 3 prospective, randomized, placebo-controlled Phase III studies in patients with HRS and a rapid deterioration in kidney function who were treated with terlipressin (plus albumin) (OT-0401 [NCT00089570], REVERSE [NCT01143246], and CONFIRM [NCT02770716]) were pooled for this analysis
- To determine the impact of terlipressin on MAP:
  - Daily median MAP was compared between treatment and placebo groups using a Wilcoxon rank sum exact test
  - A linear mixed-effects model was completed with fixed effects for treatment and time and a random intercept for each patient
- To determine the impact of MAP on HRS-AKI reversal:
  - Time-dependent Cox models were completed
  - Target MAP cut-offs were determined by comparing log-rank statistics
- To determine the impact of the relationship between MAP and terlipressin on HRS-AKI reversal:
  - The interaction was tested between MAP and terlipressin in Cox models for HRS-AKI reversal
  - A mediation analysis was completed between terlipressin and time-weighted MAP on full HRS-AKI reversal
- HRS-AKI reversal was defined as at least 1 serum creatinine (SCr) value ≤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 were excluded

Results

- A total of 477 patients were included in the analysis: 293 (61%) patients in the terlipressin group and 184 (39%) patients in the placebo group

Impact of terlipressin on MAP

- At baseline, MAP was similar in the terlipressin and placebo groups (median: 77 mmHg vs 76 mmHg, *P* = 0.4); however, after randomization, MAP was significantly higher in the terlipressin group versus the placebo group up to Day 11 (**Table 1**)

Table 1. Average MAP by treatment group and date.

Characteristic	Placebo (n = 184)	Terlipressin (n = 293)	*P* value[a]
Baseline	76 (69, 83)	77 (70, 85)	0.400
Day 1	75 (70, 81)	85 (78, 93)	<0.001
Day 2	75 (70, 81)	79 (75, 86)	<0.001
Day 3	76 (71, 82)	81 (75, 87)	<0.001
Day 4	77 (70, 83)	81 (76, 89)	<0.001
Day 5	77 (71, 84)	82 (76, 89)	<0.001
Day 6	77 (70, 83)	83 (77, 90)	<0.001
Day 7	79 (73, 84)	82 (77, 91)	0.002
Day 8	77 (73, 84)	83 (78, 94)	<0.001
Day 9	77 (73, 84)	82 (77, 93)	0.006
Day 10	77 (72, 85)	84 (77, 93)	0.007
Day 11	76 (72, 83)	82 (79, 92)	0.010
Day 12	78 (76, 82)	82 (78, 88)	0.140
Day 13	78 (75, 84)	84 (78, 90)	0.066
Day 14	79 (72, 85)	84 (78, 92)	0.089
30-Day follow-up	81 (73, 93)	81 (72, 94)	0.900

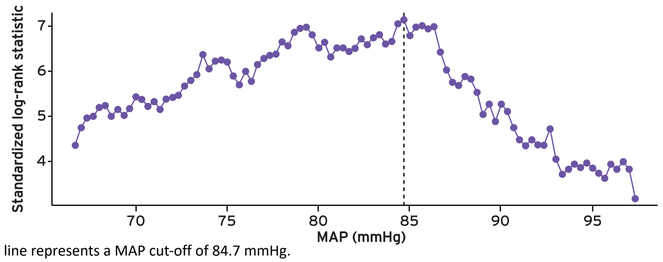
Data are presented as the median (IQR).
[a]The *P* value was generated using a Wilcoxon rank sum exact test.
IQR, interquartile range; MAP, mean arterial pressure.

- In the mixed-effects model, terlipressin was associated with a 6.1 mmHg increase in MAP (97.5% confidence interval [CI] 4.4–7.8)
  - The effect was observed immediately, and was constant
  - There was no significant interaction between treatment and MAP (*P* = 0.3)

Impact of MAP on HRS-AKI reversal

- In a time-dependent Cox model, each 5 mmHg increase in MAP was associated with a decreased risk of HRS-AKI nonreversal, with a hazard ratio (HR) of 0.86 (95% CI 0.8–0.9, *P* < 0.001)
- A MAP cut-off of 84.7 mmHg demonstrated the strongest association with HRS-AKI nonreversal (**Figure 1**)

Figure 1. MAP cut-off identification.

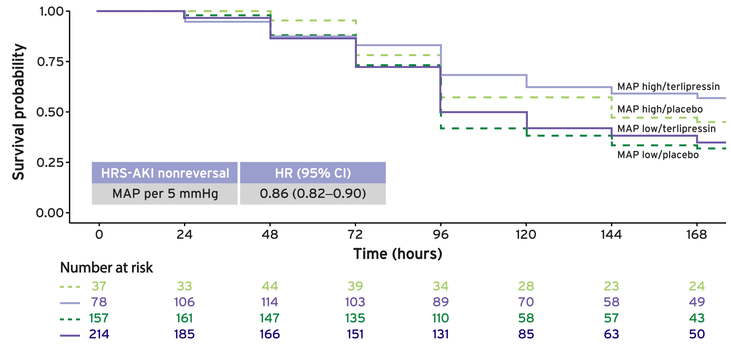


The dashed line represents a MAP cut-off of 84.7 mmHg.
MAP, mean arterial pressure.

Impact of the relationship between MAP and terlipressin on HRS-AKI reversal

- Patients in the terlipressin group had a lower risk of HRS-AKI nonreversal compared with patients in the placebo group, with an HR of 0.81 (95% CI 0.66–1.00, *P* = 0.047)
- Patients in the terlipressin group with MAP ≥ 84.7 mmHg had numerically lower HRS-AKI nonreversal compared with patients with high MAP in the placebo group, and with all patients with low MAP (**Figure 2**)
  - However, there was no significant interaction between MAP and terlipressin (HR: 1.01, 95% CI 0.99–1.03)

Figure 2. HRS-AKI nonreversal by MAP category and treatment group.



CI, confidence interval, HR, hazard ratio; HRS-AKI, hepatorenal syndrome-acute kidney injury; MAP, mean arterial pressure.

- In the mediation analysis, MAP was a significant mediator of the impact of terlipressin on HRS-AKI reversal (average causal mediation effect: 35%, 95% CI 21%–50%)

Conclusions

- In this analysis, terlipressin led to an immediate, sustained increase in MAP
- A cut-off of 84.7 mmHg was identified as a key pharmacodynamic target for HRS-AKI reversal
- These findings support the notion that MAP is a significant mediator of the impact of terlipressin on HRS-AKI reversal

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Disclosure information

Giuseppe Cullaro is a consultant for Ocelot Bio.
Kavish R. Patidar has no financial relationships to report.
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References

1. Angeli P, et al. *J Hepatol*. 2019;71(4):811–822.
2. Bera C, Wong F. *Therap Adv Gastroenterol*. 2022;15:17562848221102679.
3. Narahara Y, et al. *J Gastroenterol Hepatol*. 2009;24(11):1791–1797.
4. Biggins SW, et al. *Hepatology*. 2021;74(2):1014–1048.
5. TERLIVAZ® (Terlipressin). Full Prescribing Information. Bedminster, NJ. Mallinckrodt Pharmaceuticals; 2022.

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