Utility of Concurrent Administration of Albumin with Terlipressin for the Treatment of Hepatorenal Syndrome-Acute Kidney Injury: A Pooled Analysis of Two Randomized Controlled Trials

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Introduction

- Hepatorenal syndrome-acute kidney injury (HRS-AKI) is a serious complication of decompensated cirrhosis[1]
- Terlipressin is a systemic vasoconstrictor recommended as a first-line treatment for patients with HRS-AKI[2,3]
  - Terlipressin is the only drug approved by the US Food and Drug Administration (FDA) for the treatment of adult patients with HRS and a rapid decline in kidney function[4]
- Guidelines from the American Association for the Study of Liver Diseases (AASLD) recommend co-administration of albumin with vasoconstrictors for the treatment of HRS-AKI[3]
- Although terlipressin efficacy has been proven in several Phase III studies[5-7], data on the effect of concurrent albumin use are limited[8]

Aim of the study

- This study evaluated clinical outcomes in patients who received terlipressin with albumin compared to those patients who received terlipressin only

Methods

- This is a post hoc analysis of pooled data from 2 Phase III randomized placebo-controlled trials (RCTs; REVERSE, NCT01143246[5] and CONFIRM, NCT02770716[7]) which studied terlipressin use in patients with HRS-AKI
- In patients who were treated with terlipressin, co-administration of albumin was recommended as per standard medical practice; however, its use and dosage were at the discretion of the investigator
  - All patients received an albumin challenge prior to terlipressin treatment
- Efficacy and safety outcomes were compared among patients who received terlipressin with albumin versus those who received terlipressin only
  - The primary endpoint was HRS-AKI reversal defined as at least 1 serum creatinine value ≤ 1.5 mg/dL while on treatment (up to 24 hours after the last dose of study medication)
  - Incidence of respiratory adverse events (AEs) was a secondary endpoint
    - Respiratory events included respiratory failure, acute respiratory failure, pleural effusion, pulmonary edema, hypoxia, and dyspnea
- *P* values were generated by ANOVA or a Kruskal-Wallis test following testing for normality for continuous variables, and by a Fisher's exact or Chi-square test for categorical variables, based on the minimum counts
- Potential predictors of outcomes were analyzed using a univariable logistic regression analysis; *P* values were derived from a 2-sample log-rank test
  - All significant univariable results were added to the model and step-wise selection was used to obtain the final model in the multivariable analysis

Results

- Of the 296 patients in REVERSE and CONFIRM who were randomly assigned to terlipressin, 172 (58.1%) were men, median age was 54 years, and mean MELD score was 33; 46 (15.5%) patients received terlipressin alone
- Demographics and clinical characteristics considered as potential predictors of HRS reversal were compared between the terlipressin plus albumin group and the terlipressin only group (**Table 1**)
  - There were no significant differences in baseline demographics, MELD score, and Child-Pugh score between the 2 groups (**Table 1**)
  - Albumin use prior to terlipressin initiation in both groups was similar (*P* = 0.798; **Table 1**)

Table 1. Baseline demographics and clinical characteristics in the terlipressin plus albumin group versus the terlipressin only group in the CONFIRM and REVERSE studies, ITT population.

Characteristics	Terlipressin + albumin (n = 250)	Terlipressin only (n = 46)	*P* value
Age, years	54.8 ± 10.55	53.3 ± 10.16	0.454
Sex (male), n (%)	147 (58.8)	25 (54.3)	0.574
Baseline MELD score	32.9 ± 6.51	33.2 ± 6.53	0.744
Child-Pugh score	10.1 ± 1.83	10.2 ± 1.89	0.521
Pre-terlipressin cumulative albumin dose, g	327.9 ± 180.37	334.1 ± 179.54	0.798
Serum albumin level pre-terlipressin initiation, g/dL	3.6 ± 0.73	3.7 ± 0.72	0.563
Serum albumin difference between EOT and Day 1, g/dL	0.3 ± 0.63	-0.2 ± 0.49	**< 0.001**
Duration of terlipressin from Day 1 to EOT, days	6.6 ± 4.44	4.5 ± 3.05	**0.004**
Daily dose of terlipressin from Day 1 to EOT, mg	3.6 ± 1.43	2.9 ± 1.18	**0.008**
Terlipressin dose at EOT, mg	2.7 ± 1.69	2.4 ± 1.47	0.325
Baseline SpO_2/FiO_2	440 ± 73	411 ± 113	0.852
LVP occurrence pre-terlipressin[a], n (%)	64 (25.6)	12 (26.1)	0.945
Duration of prior midodrine and octreotide, days	3.7 ± 3.08	4.2 ± 2.85	0.088
History of cardiac disease[b], n (%)	18 (7.2)	1 (2.2)	0.327
History of respiratory disease, n (%)	167 (66.8)	29 (63.0)	0.621

[a] Information about LVP was collected only in the CONFIRM study.

[b] History of cardiac disease included angina pectoris, cardiac disorder, cardiac failure, congestive cardiac failure, myocardial infarction, myocardial ischemia, atrial fibrillation, atrial flutter, ventricular arrhythmia.

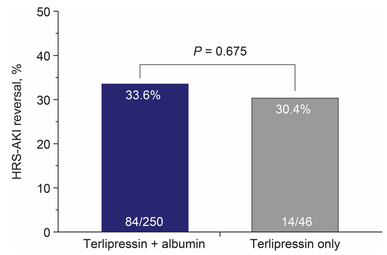
Unless otherwise indicated, the data are presented as the mean ± standard deviation.

EOT, end of treatment; ITT, intent-to-treat; LVP, large volume paracentesis; MELD, Model for End-Stage Liver Disease; SpO_2/FiO_2, oxygen saturation to fraction of inspired oxygen ratio.

HRS-AKI reversal

- Co-administration of albumin with terlipressin was not associated with a greater rate of HRS-AKI reversal compared with terlipressin alone (*P* = 0.675) (**Figure 1**)

Figure 1. HRS-AKI reversal in the terlipressin plus albumin group versus the terlipressin only group in the CONFIRM and REVERSE studies, ITT population.

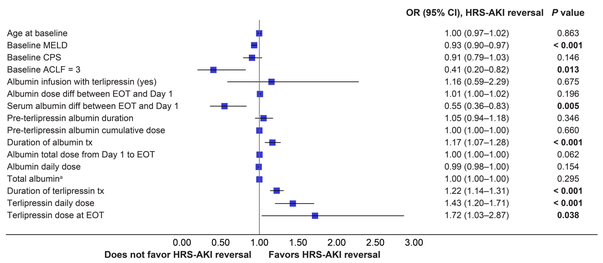


HRS-AKI, hepatorenal syndrome-acute kidney injury; ITT, intent-to-treat.

Factors predicting HRS-AKI reversal

- In the univariable analysis, a higher baseline MELD score and an ACLF score of 3 were associated with lower odds of HRS-AKI reversal (**Figure 2**)
- Total duration of albumin from Day 1 to end of treatment (EOT), duration and daily dose of terlipressin from Day 1 to EOT, and terlipressin dose at EOT were associated with a higher odds of HRS-AKI reversal (**Figure 2**)
- There was no significant association of HRS-AKI reversal with the pre-terlipressin cumulative dose of albumin (*P* = 0.660) or total albumin dose from Day 1 to EOT (*P* = 0.062; **Figure 2**)

Figure 2. Univariable logistic regression analysis for HRS-AKI reversal in patients in the terlipressin group, ITT population.



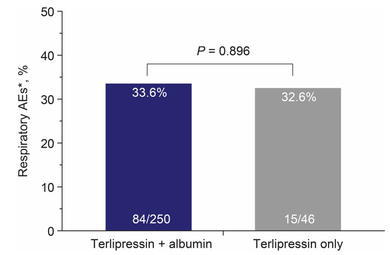
[a] Total albumin includes pretreatment and concomitant amounts.
ACLF, acute-on-chronic liver failure; CI, confidence interval; CPS, Child-Pugh score; diff, difference; EOT, end of treatment; HRS-AKI, hepatorenal syndrome-acute kidney injury; ITT, intent-to-treat; MELD, Model for End-Stage Liver Disease; OR, odds ratio; tx, treatment.

- In the multivariable analysis, the only independent predictors of HRS-AKI reversal were:
  - Duration of terlipressin treatment (predictive of a higher odds of HRS-AKI reversal [OR 1.22, 95% CI 1.13–1.32, *P* < 0.001])
  - Baseline MELD score (predictive of a lower odds of HRS-AKI reversal [OR 0.93, 95% CI 0.90–0.97, *P* < 0.001])

Respiratory adverse events

- There was no difference in the incidence of all respiratory adverse events, irrespective of co-administration with albumin (**Figure 3**)

Figure 3. Respiratory adverse events in the terlipressin plus albumin group versus the terlipressin only group in the CONFIRM and REVERSE studies, ITT population.

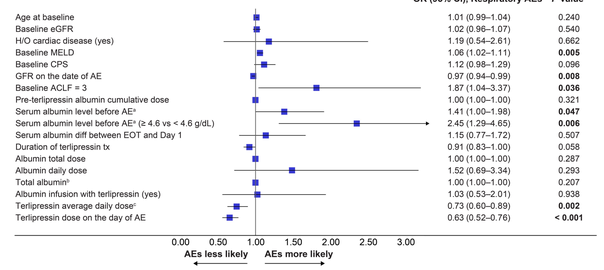


* Respiratory events include respiratory failure, pleural effusion, pulmonary edema, hypoxia, and dyspnea, as adjudicated by the investigators.
AEs, adverse events; ITT, intent-to-treat.

Factors predicting respiratory adverse events

- In the combined treatment group (ie, terlipressin with and without albumin) the univariable analysis shows that respiratory events were associated with baseline MELD score, ACLF grade 3, pre-event glomerular filtration rate (GFR), pre-event or day-of-event albumin level, dose of terlipressin on event date, and average daily dose of terlipressin (**Figure 4**)

Figure 4. Univariable analysis for respiratory adverse events in the combined treatment group, ITT population.



[a] On or before the day of the event; if a patient did not have a respiratory failure; the last albumin value before the EOT was used.
[b] Total albumin included pretreatment and concomitant amounts.
[c] From Day 1 to the EOT or occurrence of the event.
ACLF, acute-on-chronic liver failure; AE, adverse event; CI, confidence interval; CPS, Child-Pugh score; diff, difference; EOT, end of treatment; GFR, glomerular filtration rate; eGFR, estimated glomerular filtration rate; EOT, end of treatment; H/O, history of; ITT, intent-to-treat; MELD, Model for End-Stage Liver Disease; OR, odds ratio; tx, treatment.

- In the multivariable analysis, the independent predictors of respiratory AEs were:
  - Baseline MELD score (associated with a higher odds of respiratory AEs [OR 1.06, 95% CI 1.001–1.11, *P* = 0.027])
  - Terlipressin dose on the event date (associated with a lower odds of respiratory AEs [OR 0.62, 95% CI 0.51–0.75, *P* < 0.001])

Conclusions

- Results from the 2 Phase III RCTs suggest that, in a subgroup of patients, the use of terlipressin without albumin does not compromise clinical efficacy
- Larger RCTs are needed to further support the findings of this analysis
- A comparable rate of all respiratory adverse events—regardless of albumin use—emphasizes the need for careful selection and monitoring of patients, even when using terlipressin without albumin

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