Predictors of Response to Terlipressin in Patients with Hepatorenal Syndrome-Acute Kidney Injury (HRS-AKI): A Multicenter Study

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BACKGROUND

- Acute kidney injury (AKI) is a frequent complication of advanced liver disease, occurring in approximately 19% of hospitalized patients with cirrhosis.[1,2]
- Hepatorenal syndrome (HRS) is a functional AKI that results from portal hypertension leading to decreased effective circulating arterial volume, and renal vasoconstriction.[2]
- EASL guidelines recommend terlipressin in combination with albumin as a first-line intervention for HRS-AKI.[3]
- In clinical trials, HRS therapy with terlipressin and albumin have been shown to be significantly more effective in reversing HRS-AKI and are generally effective in ~40% of cases.[4]
- Lower serum creatinine (SCr) at treatment initiation has been linked to higher rates of treatment response in various clinical trials,[4-6] but has not been evaluated for terlipressin in a real-world setting.

OBJECTIVE

- To identify predictors of response to terlipressin and mortality in patients with HRS-AKI in the United Kingdom (UK)

METHODS

Study Design

- This is a *post hoc* analysis of a medical chart review study with data collection by physicians specialized in gastroenterology, nephrology, or critical care at 26 hospitals in the UK.
- Data were collected from hospital admission up to 90 days post-discharge or until death using an electronic case report form (eCRF) hosted on a secured website.
- A decision tool by the UK Health Research Authority (HRA) was used to document that this study did not need approval by a Research Ethics Committee.

Study Patients

- Eligible patients were identified by physicians using International Classification of Disease, 9th revision (ICD-9) code of 572.4 (hepatorenal syndrome) or an ICD-10 code of K76.7 (hepatorenal syndrome) or N17.9 (acute renal failure, unspecified) with K74.6 (Other and unspecified cirrhosis of the liver), or based on chart documentation of HRS diagnosis.

METHODS, CONT.

- To obtain a representative sample of patients, physicians were prompted to select patients based on HRS-AKI diagnosis date and first letter of the patient's last name.
- Inclusion criteria
  - ≥18 years of age at diagnosis
  - HRS-AKI episode between January 1, 2013 and December 31, 2017 with SCr >1.5 mg/dL
  - Treated at participating physician's hospital with a vasopressor therapy
  - Participating physician was able to report on the SCr on the day of diagnosis and on the last day or day 14 of vasopressor treatment (whichever date came first), and at the discharge date.
- Exclusion criteria
  - Dialysis or a transjugular intrahepatic portosystemic shunt (TIPS) within one month prior to hospitalization
  - Died within 24 hours of vasopressor initiation
  - Prior liver transplantation
  - Previous hospitalization for HRS during the previous 6 months

Study Variables

- Data were collected from hospital admission up to 90 days post-discharge
- HRS treatment response was measured by change in SCr from one day prior to vasopressor initiation to last day of vasopressor treatment or day 14 (whichever came first).
- Treatment response was defined as complete response (CR) if SCr decreased to ≤1.5 mg/dL, as partial response (PR) if SCr decreased ≥20% but >1.5 mg/dL, and as no response if SCr decreased <20%.

Statistical Analysis

- Predictors of overall response (CR or PR) and mortality in the subset of patients who received terlipressin (n=203) were evaluated using backwards-selected logistic regression and Cox proportional hazards models, respectively.
- Predictors evaluated in these models included:
  - Age
  - Baseline AKI severity (mild, SCr <2.25 mg/dL; moderate, SCr ≥2.25 mg/dL and <3.5 mg/dL; severe, SCr ≥3.5 mg/dL)
  - Presence of a precipitating event
  - Concomitant use of albumin
  - Presence of encephalopathy
  - Infection during the HRS-AKI hospitalization

RESULTS

Patient Characteristics

- Terlipressin patients had a mean age of 53.9 years and two-thirds were male
- The majority of patients (84%) had ≥1 precipitating event, comorbid encephalopathy was present in 33% of patients, and infection was present in 49%.
- Concomitant albumin was administered to 72% of patients.

Table 1. Baseline and Clinical Characteristics

	Terlipressin (N = 203)
Age (years), mean (SD)	53.9 (11.6)
Male, N (%)	136 (67)
Baseline AKI severity[a]	
Mild	52 (33)
Moderate	52 (36)
Severe	53 (31)
Eligible/listed for transplant, N (%)	45 (22)
Precipitating event(s), N (%)[b,c]	
Treatment with diuretics	79 (39)
Gastrointestinal bleeding	56 (28)
Large-volume paracentesis	43 (21)
Spontaneous bacterial peritonitis	30 (15)
Other infection	29 (14)
Diarrhea	18 (9)
None of the above	32 (16)
Underlying causes, N (%)[c]	
Alcoholic liver disease	140 (69)
Hepatitis C	29 (14)
Non-alcoholic steatohepatitis/ fatty liver disease	36 (18)
Other	22 (11)
Ascites at hospital admission	160 (79)
Encephalopathy at hospital admission	66 (33)

Abbreviations: AKI, acute kidney injury; N, Number; SD, standard deviation.
[a] Mild AKI, SCr <2.25 mg/dL <24 hrs prior to treatment initiation; moderate AKI, SCr ≥2.25 mg/dL and <3.5 mg/dL) <24 hrs prior to treatment initiation; Severe AKI, SCr ≥3.5 mg/dL.
[b] Precipitating events or treatments immediately (within 7 days) prior to the diagnosis of hepatorenal syndrome
[c] Responses are not mutually exclusive.

RESULTS, CONT.

- Overall response rate was 73% and differed between the mild and moderate (79% and 78%) groups compared to the severe group (60%).
- The logistic regression model identified absence of a precipitating event, concomitant use of albumin, and mild or moderate baseline AKI severity as significant predictors of overall response (Table 2).
- Presence of encephalopathy was the only significant predictor of mortality (hazard ratio, 2.77; 95% confidence interval, 1.56 to 4.92).

Table 2. Predictors of Response (Partial or Complete)[a] to Terlipressin in Patients with HRS-AKI

	Odds Ratio (95% CI)	*P*-value
Presence of a precipitating event (Ref: No)	0.288 (0.10 to 0.87)	.027
Albumin use (Ref: No or unknown)	2.717 (1.29 to 5.70)	.008
Baseline AKI severity (Ref: Severe)[b]		
Mild	2.462 (1.11 to 5.44)	.026
Moderate	2.288 (1.06 to 4.95)	.036

Abbreviations: AKI, acute kidney injury; CI, confidence interval.
[a] Complete response, decrease from the day before treatment initiation to a level of ≤1.5 mg/dL; partial response, SCr decreased ≥20% from the day before treatment initiation to a level >1.5 mg/dL; no response, SCr decreased <20% from the day before treatment initiation.
[b] Mild AKI, SCr <2.25 mg/dL <24 hrs prior to treatment initiation; moderate AKI, SCr ≥2.25 mg/dL and <3.5 mg/dL) <24 hrs prior to treatment initiation; Severe AKI, SCr ≥3.5 mg/dL.

DISCUSSION

- The results of this study highlight the importance of albumin use and timely treatment with terlipressin when SCr is mildly or moderately elevated in patients with HRS-AKI to optimize patient outcomes.
- This study represents the largest "real world" population experience of terlipressin for HRS, and thus holds great value in bridging clinical trial data into the hands of clinicians.
- The diagnosis of HRS-AKI was at the discretion of the treating clinicians and will have deviated from existing guidelines.
  - For example, only 68% of patients were reported as having received intravenous albumin which is part of the 2015 Ascites Club diagnostic criteria for HRS and would have been required as part of any clinical trial.[7]

CONCLUSIONS

- Prompt diagnosis and treatment of HRS-AKI, prior to reaching SCr of 3.5 mg/dL, absence of a precipitating event, and use of albumin improve the likelihood of HRS reversal.

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