Patient Subset Analysis of the REVERSE Phase lll Study: The Impact of Terlipressin Treatment on Rates of Transplant, Dialysis, and Survival in Patients with Hepatorenal Syndrome

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Introduction

- Hepatorenal syndrome-acute kidney injury (HRS-AKI, formerly known as HRS type 1 [HRS-1]) is a dangerous but potentially reversible form of AKI occurring in patients with advanced cirrhosis that can cause early mortality without treatment or a liver transplant[1]
- Advanced AKI that requires renal replacement therapy (RRT) is associated with very poor patient survival[1,2]
- The American Association for the Study of Liver Diseases (AASLD) recommends use of the synthetic vasopressin analog terlipressin, in combination with albumin, for the treatment of patients with HRS-AKI[2,3]
- In the REVERSE clinical study (NCT01143246), terlipressin in combination with albumin significantly lowered serum creatinine (SCr) in patients with HRS compared with albumin alone ($P < .001$); furthermore, survival was significantly correlated with a decrease in SCr ($P < .001$)[4]
- Successful pharmacological treatment of HRS improves Model for End-Stage Liver Disease (MELD) score components (eg, SCr); and, as a result, lowers patient liver transplant prioritization[1]

Aim of the Study

- To determine the impact of terlipressin on liver transplantation, RRT requirement, and survival in a subgroup of patients with HRS-AKI who were enrolled in the REVERSE study and potentially eligible for liver transplantation

Methods

- REVERSE was a Phase lll, randomized, double-blind, placebo-controlled study that enrolled a total of 196 patients with HRS in North America (terlipressin, n = 97; placebo, n = 99)[4]
- This post hoc analysis included patients from REVERSE who were potential liver transplant candidates as per the following criteria:
  - Aged ≤ 70 years
  - Enrolled at a site in the United States
  - Absence of hepatocellular carcinoma
  - Absence of alcohol-related hepatitis
- Patients were evaluated for their renal outcomes during treatment (up to 24 hrs after the last dose of study drug) and categorized as follows:
  - HRS reversal (defined as ≥ 1 SCr value ≤ 1.5 mg/dL while on treatment)
  - Partial response (PR, defined as a SCr decrease > 0.3 mg/dL from baseline)
  - No Response (NR, defined as worsening [increase in SCr], no change, or minimally improved SCr [decrease ≤ 0.3 mg/dL] from baseline to the end of treatment [EOT]; no RRT)
  - RRT (those patients who stopped treatment due to RRT)
- Clinical status including survival, liver transplant status, and RRT requirement were assessed at 30-day, 60-day, and 90-day post treatment and categorized as follows:
  - Alive without liver transplantation, without RRT
  - Alive with liver transplantation, without RRT
  - Alive with liver transplantation, with RRT
  - Alive without liver transplantation, with RRT
  - Dead
- MELD score and SCr value prior to liver transplantation were evaluated by treatment group

Results

Baseline Demographics and Characteristics

- A total of 125 patients (terlipressin, n = 66; placebo, n = 59) satisfied criteria for this analysis
- Patient demographics and clinical characteristics at baseline were similar between treatment arms (**Table 1**)
- Baseline mean MELD scores (± standard deviation [SD]) in the terlipressin and placebo arms were similar (33.16 ± 6.16 and 32.67 ± 5.13, respectively)

Table 1. Baseline Patient Demographics and Clinical Characteristics, REVERSE Population Subset[a]

Characteristic	Terlipressin (n = 66)	Placebo (n = 59)	*P* value[b]
Age (years), median (range)	57.5 (34.8–68.4)	55.9 (30.6–69.3)	.293
Male sex, n (%)	32 (48.5)	36 (61.0)	.162
SCr, mg/dL	3.6 ± 0.98	3.8 ± 1.20	.322
Total bilirubin, mg/dL	10.3 ± 10.54	11.8 ± 12.59	.479
MAP, mm Hg	74.5 ± 12.18	74.8 ± 10.57	.889
Child-Pugh score, median (range)	10 (7–15)	10 (7–15)	.558
MELD score	33.2 ± 6.16	32.7 ± 5.13	.656

Data are presented as the mean ± SD unless otherwise noted.

[a] ITT population excluding those aged > 70 years, not in the USA, or with hepatocellular carcinoma or alcohol-related hepatitis.

[b] *P* values were determined using a Fisher's exact test or a Chi-square test.

ITT, intent-to-treat; MAP, mean arterial pressure; MELD, Model for End-Stage Liver Disease; SCr, serum creatinine; SD, standard deviation; USA, United States of America.

Clinical Outcomes

- Renal outcomes at the EOT indicated that numerically more patients in the terlipressin arm had a confirmed HRS reversal (18.0% vs 16.4%, $P = .8122$) or an improvement in SCr (34.4% vs 23.6%, $P = .2024$) compared to placebo (**Table 2**)

Table 2. Outcomes at the EOT (up to Day 14), REVERSE Population Subset[a]

Status	Terlipressin (n = 61)[b]	Placebo (n = 55)[b]	*P* value[c]
Confirmed HRS reversal[d]	11 (18.0)	9 (16.4)	.8122
SCr lower than baseline	21 (34.4)	13 (23.6)	.2024
SCr same, or higher than baseline	22 (36.1)	24 (43.6)	.4052
RRT	7 (11.5)	7 (12.7)	.8363
Dead	0	2 (3.6)	.2226

Data are presented as n (%).

[a] ITT population excluding those aged > 70 years, not in the USA, or with hepatocellular carcinoma or alcohol-related hepatitis.

[b] Nine patients were excluded from this analysis: 6 patients did not receive treatment (terlipressin, n = 3; placebo, n = 3); and 3 patients did not have a postbaseline SCr values on/before the treatment stop date/time (terlipressin, n = 2; placebo, n = 1).

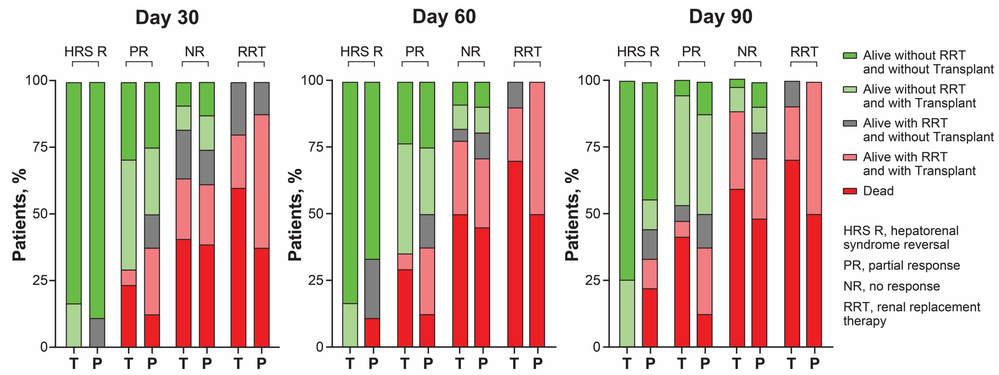
[c] *P* values were determined using a Fisher's Exact Test or Chi-square test.

[d] Confirmed HRS reversal (2 SCr values of ≤ 1.5 mg/dL collected ≥ 40 hours apart while on treatment).

EOT, end of treatment; HRS, hepatorenal syndrome; ITT, intent-to-treat; RRT, renal replacement therapy; SCr, serum creatinine; USA, United States of America.

- There was a similar decrease from baseline to the EOT (up to Day 14) in mean MELD scores (± SD) among patients who achieved HRS reversal in either treatment arm (terlipressin, -4.4 ± 2.95; placebo, -5.6 ± 4.12; $P = .503$)
- Among patients who achieved HRS reversal (n = 21/125), survival outcomes progressively diminished over time from Day 30, 60, and 90 for the placebo group; whereas, in the terlipressin group at Day 90, 100% (12/12) of patients were alive and RRT-free, compared to only 55.6% (5/9) of patients in the placebo group (**Figure 1**)
- Survival outcomes progressively worsened as response status diminished from complete response/HRS reversal to PR, NR, or the need for RRT (**Figure 1**)
- Roughly 50% of partial responders were alive without RRT at Day 90 (terlipressin, 47.1% [8/17]; placebo, 50.0% [4/8]) compared to < 20% of non-responders (terlipressin, 13.6% [3/22]; placebo, 19.4% [6/31]) (**Figure 1**)
- Among patients who received RRT (n = 18), the percent of patients alive on Day 90 without a liver transplant was 10.0% (1/10) for patients in the terlipressin arm and 0% (0/8) for those in the placebo arm (**Figure 1**)

Figure 1. Clinical Status at the End of Follow-Up (Day 30, Day 60, and Day 90) by Renal Outcomes During Treatment, REVERSE Population Subset



Eight patients were excluded: in the terlipressin arm, 3 were not treated, and 2 received 1 dose of treatment and only had a baseline SCr value; in the placebo arm, 3 were not treated.
P, placebo; T, terlipressin.

- By Day 90, more than one-third of patients in each treatment arm had received a liver transplant: terlipressin, 34.8% (23/66), and placebo, 42.4% (25/59) ($P = .388$)
  - Prior to liver transplantation, patients in the terlipressin and placebo arms had comparable MELD scores (**Table 3**)

Limitations

- These results are derived from a retrospective analysis with a small sample size; therefore, the data should be interpreted with caution
- Additionally, long-term follow-up data were not collected

Table 3. Last Measurements of MELD Score and SCr Prior to Liver Transplantation, REVERSE Population Subset[a]

Status	Terlipressin (n = 13)[b]	Placebo (n = 8)[b]	*P* value[c]
SCr, mg/dL	2.6 ± 0.75	3.5 ± 1.86	0.276
MELD score	34.2 ± 5.41	31.7 ± 5.96	0.365

Data are presented as the mean ± SD.

[a] ITT population excluding those aged > 70 years, not in the USA, or with hepatocellular carcinoma or alcohol-related hepatitis.

[b] The data were missing for some patients who had received a liver transplant.

[c] A Kruskal-Wallis test or ANOVA was used to calculate the *P* value.

ANOVA, analysis of variance; ITT, intent-to-treat; MELD, Model for End-Stage Liver Disease; SCr, serum creatinine; SD, standard deviation; USA, United States of America.

Conclusions

- This subgroup analysis of the REVERSE study demonstrated clinical benefits among patients who achieved HRS reversal
  - Patients who achieved HRS reversal had a higher survival rate by Day 90 compared with those who had a partial response or no response, or those who received RRT
- Roughly 50% of partial responders were alive without RRT at Day 90 compared to < 20% of non-responders
- Without liver transplantation, patients who received RRT had low rates of survival
- Although MELD scores decreased with HRS reversal, the overall rate of liver transplantation did not seem to be adversely affected

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Conflicts of Interest

Samuel H. Sigal has received grant/research support from Eli Lilly, Gilead, Intercept, and Mallinckrodt Pharmaceuticals, and is a consultant for Gilead and Mallinckrodt Pharmaceuticals. Arun Sanyal has received grant/research support from AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Intercept, Madrigal, Merck, Novartis, Novo Nordisk, and Pfizer; is a consultant for Akero, Alnylam, AstraZeneca, Biocellvia, Boehringer Ingelheim, Eli Lilly, Fibronest, Fractyl, Genentech, Gilead, Glaxo Smith Kline, Hemoshear, Histoindex, Intercept, Inventiva, Madrigal, Merck, Northsea, Novartis, Novo Nordisk, Path-AI, Pfizer, Regeneron, Roche, Target Pharmasolutions, Takeda, and Tern; holds sock in Durect, GenFit, Hemoshear, Inversago, and Tiziana; and has received royalties from Elsevier and UpToDate. Mark Wong has received speaking and teaching fees from Gilead. Brendan M. McGuire has received grant/research support from Arrowhead, Disc, and Mallinckrodt Pharmaceuticals. Bilal Hameed has received grant/research support from CymaBay, Gilead, Intercept, Madrigal, Pliant Therapeutics, Novo Nordisk, and Salix; is an advisor for the Chronic Liver Disease Foundation (CLDF), Mallinckrodt Pharmaceuticals, and Pleiogenix; is a consultant for Gilead and Pioneering Medicine VII, Inc; and holds stock in Pleiogenix. Khurram Jamil is an employee of Mallinckrodt Pharmaceuticals.

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