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Early Diagnosis and Treatment with Terlipressin for Adults with Hepatorenal Syndrome Improves Clinical Outcomes and Reduces Healthcare Resource Utilization

Juan F. Gallegos-Orozco[1], Jacqueline G. O'Leary[2], Gautham Reddy[3], Khurram Jamil[4], Jas Bindra[5], Ishveen Chopra[6], John Niewoehner[4], Xingyue Huang[4]

[1]University of Utah, Salt Lake City, UT, USA; [2]Dallas Veteran Affairs Medical Center, Dallas, TX, USA; [3]University of Chicago Medicine, Chicago, IL, USA; [4]Mallinckrodt Pharmaceuticals, Bridgewater, NJ, USA; [5]Falcon Research Group, North Potomac, MD, USA; [6]Manticore Consultancy, Bethesda, MD, USA

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BACKGROUND

- Hepatorenal syndrome (HRS, also referred to as HRS-1 and HRS-acute kidney injury [AKI]) is a potentially reversible form of AKI[1,2]
- Terlipressin (TERLIVAZ®), a synthetic vasopressin analog that binds to vasopressin receptors, acts as a systemic vasoconstrictor,[3] thereby counteracting the splanchnic arterial vasodilation associated with HRS-1 and restoring blood flow to the kidneys[2]
  - Terlipressin is currently the only Food and Drug Administration-approved medication indicated to improve kidney function in adult patients with HRS with rapid reduction in kidney function[4]
  - Terlipressin plus albumin is recommended as the first-line treatment for patient with HRS-1, per the European Association for the Study of the Liver guidelines,[5] and is the preferred vasoconstrictor therapy recommended by the American Association for the Study of Liver Diseases guidelines[6]
- Early detection is an integral part of improving prognosis in conditions such as HRS, where a patient's rapidly deteriorating kidney function often leads to a need for renal replacement therapy (RRT) and liver transplantation sooner rather than later[7,8,9]
  - However, shortage of kidneys and livers leads to long waitlist for transplant
  - Early identification of AKI and early treatment for patients with HRS-AKI may lead to better clinical outcomes for patients[7,10]
  - Better renal function pre-liver transplant is associated with better post-transplant outcomes
- Analysis of 3 North American clinical trials showed greater benefit from terlipressin for patients with lower serum creatinine (SCr) levels at diagnosis, emphasizing the importance of early identification and treatment of HRS[7]
- To date, studies have not examined impact of early diagnosis (SCr <3 mg/dL) and treatment of HRS on healthcare resource utilization (HCRU) and costs

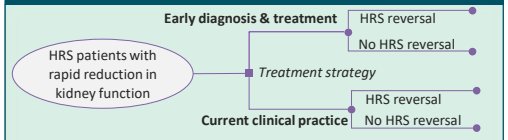
OBJECTIVE

To evaluate the potential impact of a national strategy for an early HRS diagnosis and terlipressin treatment in the United States (US)

METHODS

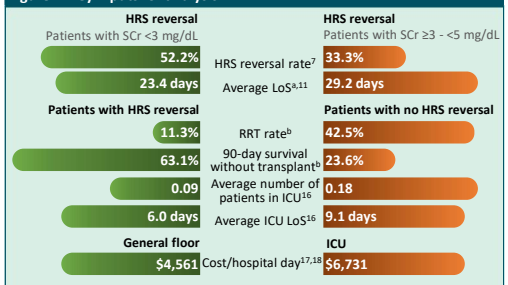
- A decision-analytic model was developed to compare various scenarios (**Figure 1**), assessing the distribution of patients across 3 different SCr groups at the time of HRS diagnosis[7]
  - **Current clinical practice scenario**: patients were grouped by SCr level based on the CONFIRM trial (<3 mg/dL: 45%; ≥3 to <5 mg/dL: 55%)[11]
  - **Early diagnosis and treatment scenario**: distribution of patients was assumed (<3 mg/dL: 85%; ≥3 to <5 mg/dL: 15%) based on the results of an HRS medical chart review study from the United Kingdom[12]
- Model only assessed terlipressin on-label treatment, hence patients with SCr ≥5 mg/dL or grade 3 acute-on-chronic liver failure (ACLF) were excluded
  - **Terlipressin HRS reversal rate for the on-label population (SCr <5 mg/dL and ACLF grade 0 to 2):** 52.2% for SCr <3 mg/dL and 33.3% for SCr ≥3 to <5 mg/dL; generated from the CONFIRM trial[11]
- The annual HRS incidence of 50,000 adults (Premier Healthcare Database)[13] was used to assess the impact of the early diagnosis and treatment strategy
- Values for key model inputs are presented in **Figure 2**
- All outcomes for each scenario were calculated separately (**Table 1**)

Figure 1. Schematic of the decision-analytic model



Abbreviations: HRS, hepatorenal syndrome

Figure 2. Key inputs for analysis



[a] Patients with SCr <5 and acute-on-chronic liver failure range of 0-2 were only considered
[b] Sourced from pooled analysis of 3 RCTs (OT-0401,[14] REVERSE,[15] and CONFIRM[11])
Abbreviations: HRS, hepatorenal syndrome; ICU, intensive care unit; LoS, length of stay; RCT, randomized controlled trial; RRT, renal replacement therapy; SCr, serum creatinine

Table 1. Calculation of outcomes

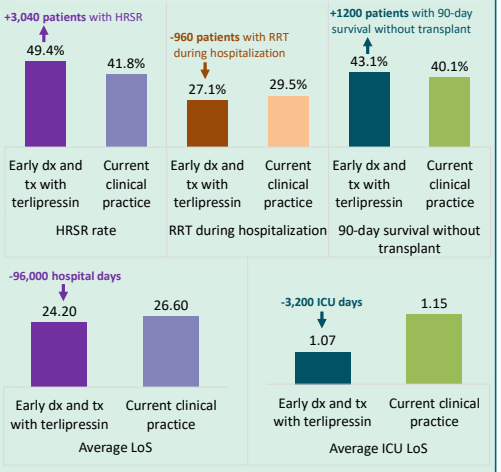
Clinical outcomes	
Overall HRSR rate	[HRSR rate$_{SCr<3\ mg/dL}$ × Proportion of patients$_{SCr<3\ mg/dL}$] + [HRSR rate$_{SCr\geq3-<5\ mg/dL}$ × Proportion of patients$_{SCr\geq3-<5\ mg/dL}$]
Healthcare resource utilization	
RRT rate during hospital	[Overall HRSR rate × RRT rate$_{HRSR}$] + [(1 – Overall HRSR rate) × RRT rate$_{NHRSR}$]
Day-90 survival without transplant rate	[Overall HRSR × Day-90 TFS rate$_{HRSR}$] + [(1 – Overall HRSR rate) × Day-90 TFS rate$_{NHRSR}$]
Average ICU days	[Overall HRSR rate × Average number of patients in ICU$_{HRSR}$ × Average LoS days$_{HRSR}$] + [(1 – Overall HRSR rate) × Average number of patients in ICU$_{NHRSR}$ × Average LoS days$_{NHRSR}$]
Average LoS	[HRS reversal rate$_{SCr<3\ mg/dL}$ × Average LoS$_{SCr<3\ mg/dL}$] + (HRS reversal rate$_{SCr\geq3-<5\ mg/dL}$) × Average LoS$_{SCr\geq3-<5\ mg/dL}$
Cost of care	
Overall cost	[Average ICU days × Cost per ICU day] + [(Average LoS$_{General\ floor}$ – Average ICU days) × Cost per day$_{General\ floor}$]

Abbreviations: HRS, hepatorenal syndrome; HRSR, HRS reversal; ICU, intensive care unit; LoS, length of stay; NHRSR, no HRS reversal; RRT, renal replacement therapy; SCr, serum creatinine; TFS, transplant-free survival

RESULTS

- Early HRS diagnosis and treatment with terlipressin yields 3,040 greater HRS reversals compared to the current clinical practice (**Figure 3**)
  - Consequently, early treatment strategy results in a higher 90-day survival without transplant and a lower RRT rate during hospitalization compared to the current clinical practice
- This strategy also leads to fewer intensive care unit (ICU) days and a shorter overall hospital length of stay (LoS)
- Further, a reduction in hospitalization, including ICU stay, results in $11,504 savings per person and total annual national savings of $460.2 million in the US (2023 US dollars)

Figure 3. Incremental benefit with early dx and tx with terlipressin



[a] Assumes 80% of patients meet terlipressin label criteria out of the annual incidence of 50,000 adults (based on the Premier Healthcare Database) with hepatorenal syndrome in the United States. The incremental benefit is calculated based on the difference between the scenarios multiplied by the 40,000 patients (80% of 50,000).
Abbreviations: dx, diagnosis; HRSR, hepatorenal syndrome reversal; ICU, intensive care unit; LoS, length of stay; RRT, renal replacement therapy, tx, treatment

DISCUSSION

Study Limitations

- This analysis relies on efficacy data from published randomized clinical trials, which may not be generalizable to all the adult HRS population in the US
- Treatment-related adverse event data was not considered in this analysis
- Costs for hospital LoS and ICU use were considered;[17,18] further costs were sourced from published literature, which may result in under- or over-estimation of costs

Study Implications

- HRS is a life-threatening condition; delayed diagnosis and treatment can lead to rapid deterioration and increased mortality
- **Reversible in Early Stages:** In its early stages, HRS may be reversible with appropriate therapy; identifying HRS early provides a window of opportunity to intervene and potentially restore kidney function
- **Improved Patient Outcomes:** Timely diagnosis and treatment can significantly improve patient outcomes by preventing renal failure and its associated complications, such as fluid overload, electrolyte imbalances, and infection
- **Enhanced Quality of Life (QoL):** Early intervention can help maintain or improve patient's QoL by preserving kidney function, reducing need for RRT, and preventing hospitalizations
- **Preventing Progression:** Early identification and treatment can prevent the progression of HRS to more advanced stages, which are often more challenging to manage and have a poorer prognosis
- **Transplantation Eligibility:** For patients who are candidates for liver transplantation, addressing HRS promptly can help them maintain eligibility for transplantation and improve their chances of a successful outcome
- **Cost Savings:** Timely management of HRS can reduce healthcare costs by minimizing expensive and intensive treatments (RRT and liver transplantation)
- **Optimal Medication Timing:** Some medications, such as vasoconstrictors like terlipressin, are more effective when administered early in the course of HRS, emphasizing the importance of early diagnosis

CONCLUSIONS

- Early diagnosis and treatment of HRS with terlipressin shows improved clinical outcomes and reduced HCRU compared to the current clinical practice
  - Early diagnosis and treatment of HRS with terlipressin results in costs savings of $11,120 per person compared to the current clinical practice
- Study findings highlight the significant need to identify and treat patients with HRS early when they often have lower SCr levels to improve patient outcomes and reduce healthcare costs
- Further studies are needed to evaluate long-term clinical and economic outcomes of early diagnosis and treatment of HRS with terlipressin

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DISCLOSURES

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