The Current Management of Hepatorenal Syndrome–Acute Kidney Injury in the United States and the Potential of Terlipressin

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Acute kidney injury (AKI) in the setting of cirrhosis (hepatorenal syndrome [HRS]–AKI) is a severe and often fatal complication of end-stage liver disease. The goals of treatment are to reverse renal failure and prolong survival in patients who are critically ill. However, interventions have limited efficacy, and mortality rates remain high. In the United States, the mainstay of pharmacologic therapy consists of the off-label use of vasoconstrictive agents in combination with plasma expanders, a strategy that produces modest effects. Liver transplantation is the ultimate solution but is only an option in a minority of patients because contraindications to transplantation are common and organ availability is limited. Renal replacement therapy is a temporary option but is known to confer an extremely poor short-term prognosis in patients with HRS-AKI and at best serves as a bridge to liver transplantation for the minority of patients who are transplantation candidates. The high mortality rate associated with HRS-AKI in the United States is a reflection of the suboptimal standard of care. Improved therapeutic options to treat HRS-AKI are sought. Terlipressin is a drug approved in Europe for treatment of HRS-AKI and supported by recommendations for first-line therapy by some liver societies and experts around the world. This review article will discuss the substantial unmet medical need associated with HRS-AKI and the potential benefits if terlipressin was approved in the United States.

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Defining Hepatorenal Syndrome

Hepatorenal syndrome (HRS)–acute kidney injury (AKI), a dire consequence of end-stage liver disease, is a functional, progressive kidney failure that is potentially reversible but most often rapidly fatal. HRS-AKI is observed in hepatic failure of any cause, but most often occurs in the setting of advanced cirrhosis.[1,2] In advanced cirrhosis, portal hypertension reduces portal blood flow, which results in the release of vasodilators and blood pooling in the splanchnic circulation. This causes activation of both the renin-angiotensin-aldosterone system and the sympathetic nervous system.[3-5] The intense renal vasoconstriction with predominant peripheral arterial vasodilation

Abbreviations: AASLD, American Association for the Study of Liver Diseases; AE, adverse event; AKI, acute kidney injury; CHRSR, confirmed hepatorenal syndrome reversal; CKD, chronic kidney disease;

TABLE 1. Morbidity and Mortality Associated With HRS-AKI

Consequences of HRS-AKI	Supporting Data
Increased mortality	The mortality rate was 36.9% in a prospective cohort study of 120 patients with HRS-AKI[15]
	Mortality rate of 50% 2 weeks after diagnosis, approaching 100% "within 3 months"[16]
	Without treatment, median survival was calculated to be approximately 11 days, with a survival probability of 25% after 30 days[17]
	Without treatment, >80% mortality at 3 months and a median survival of <4 weeks[18]
ICU admission	In patients with cirrhosis, 50% of ICU admissions were attributed to HRS-AKI[18]
Hospital readmission	Up to a third of patients with HRS-AKI who are discharged from the hospital are readmitted within 30 days[19]

(mainly in the splanchnic circulation) that follows is considered the hallmark feature of HRS.[6] In the United States, at least 633,000 adults are afflicted with cirrhosis, which represents 0.3% of the population.[7] The estimated annual incidence for HRS type 1 (HRS-1; the previously used term for HRS-AKI) in the United States ranges from 9000 patients to more than 35,000 patients.[8-12] Although these rates technically classify HRS-AKI as rare, the literature regards it as a "relatively frequent problem." Approximately 20% of hospitalized patients with cirrhosis experience HRS-AKI.[13] Previous studies have found that 18% of patients with advanced cirrhosis develop HRS-AKI after 1 year of follow-up, and this proportion more than doubles to 39% after 5 years.[14]

The continuum of kidney damage that occurs in HRS-AKI, initially reversible, can lead to permanent damage, ultimately in the form of irreversible renal failure if left untreated. Although recommendations for early and rapid interventions are widely accepted, favorable outcomes are seldom achieved. Current treatment options, particularly in the United States, are generally ineffective, and better options to manage HRS-AKI are sought. The purpose of this article is to discuss the substantial unmet medical need associated with HRS-AKI and delineate ways to improve therapy for this disease.

Cr, creatinine; FDA, Food and Drug Administration; FENa, fractional excretion of sodium; HRS, hepatorenal syndrome; HRS-1, hepatorenal syndrome type 1; HRS-2, hepatorenal syndrome type 2; HRSR, hepatorenal syndrome reversal; ICA, International Club of Ascites; ICU, intensive care unit; IV, intravenous; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; REVERSE, Randomized, placEbo-controlled, double-blind study to confirm the reVERSal of hepatorenal syndromE type 1 with terlipressin; RRT, renal replacement therapy; sCr, serum creatinine; SD, standard deviation; SIRS, systemic inflammatory response syndrome; VHRSR, verified hepatorenal syndrome reversal.

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The Impact of Renal Failure on Morbidity and Mortality in Cirrhosis

A diagnosis of HRS-AKI confers a relatively short survival period. The literature indicates mortality rates ranging from 36% to 100%, with patients more likely to die if there are delays in therapy.[15-18] Aside from the risk of death, HRS-AKI is associated with additional deleterious consequences (Table 1). Patients with HRS-AKI who are hospitalized are likely to require intensive care and, if discharged, have high readmission rates.[19,20] These facts underscore the importance of timely diagnosis and effective intervention.

Diagnosis

Previously, HRS was classified by the International Club of Ascites (ICA) as either type 1 (HRS-1) or type 2 (HRS-2),[21] but the nomenclature has recently evolved. The original definition of HRS-1 required that the diagnosis be established at an advanced stage of AKI, with a final serum creatinine (sCr) cutoff value of >2.5 mg/dL. However, treatment efficacy proved to be limited if initiated in such advanced stages.[22,23] The new terminology, per the consensus of the ICA, delineates HRS-1 and HRS-2 by the presence or absence of AKI, respectively. HRS-1 is now referred to as HRS-AKI and defined by changes in sCr and/or urinary output, among other diagnostic criteria that are detailed in Table 2. To encourage early and rapid interventions, this new definition of HRS-AKI eliminates the final sCr cutoff value of ≥1.5 mg/dL and instead recommends treatment even when increases in sCr are small. Urinary output has also been added to the definition but because of challenges in sample collection is only recommended if a catheter is present.[24] This discussion will focus on HRS as it relates to AKI (HRS-AKI) in the setting of cirrhosis. HRS without AKI, formerly HRS-2, is a diagnosis in the setting of chronic kidney disease and is beyond the scope of this article.

As reflected in the diagnostic criteria, once HRS-AKI is suspected, it is important to differentiate HRS-AKI from structural kidney injury—acute tubular necrosis–AKI. This is considered a "real clinical challenge" because the most commonly used assessment for renal function—sCr—is a marker of kidney filtration and therefore cannot differentiate functional disease (ie, HRS-AKI) from structural disease (ie, acute tubular necrosis–AKI). The utility of novel urinary biomarkers, which reflect structural injury, in combination with changes in filtration is under investigation for this purpose. Based on available data, the ICA has identified interleukin-18, kidney injury molecule-1, liver type fatty acid–binding protein, and neutrophil gelatinase-associated lipocalin as promising biomarkers, but their availability is not widespread, nor is usage standardized. Another alternative is to evaluate the fractional excretion of sodium, but questions remain regarding appropriate cutoffs to distinguish between the 2 processes.[24,25]

Additional factors decrease the utility of sCr measurements in HRS-AKI. Creatine is synthesized in the liver before storage in muscles, where it is phosphorylated to creatinine (Cr). Cr is filtered in the glomeruli and, to a lesser extent, excreted through the proximal tubule. In patients with cirrhosis, Cr levels are lower because of decreased production from hepatic impairment, protein calorie malnutrition, and muscle wasting. Elevated bilirubin levels may interfere with Cr assays, and true values may not be elucidated in the laboratory. Finally, wide variations in sCr may be observed in patients experiencing ascites attributed to large-volume paracentesis and volume expansion.[26] In summary, it is important to take these factors into consideration and recognize that normal sCr levels do not always reflect normal renal function in patients with cirrhosis. Fortunately, there is ongoing research for better biomarkers to accurately define renal function and aid in the diagnosis of HRS-AKI. Studies have demonstrated that cystatin C may be a better marker of renal function in patients with cirrhosis because it is produced by all nucleated cells. Serum cystatin C levels are not significantly affected by race, age, muscle mass, or liver function.[27] Data indicate that estimated glomerular filtration rate based on serum cystatin C, in comparison to sCr, provides a more accurate estimation and earlier detection of chronic kidney disease.[28]

TABLE 2. ICA Diagnostic Criteria for HRS-AKI*[24]

- Cirrhosis, acute liver failure, acute-on-chronic liver failure
- Increase in sCr, ≥0.3 mg/dL within 48 hours or ≥50% from baseline value and/or urinary output ≤0.5 mL/kg of body weight for ≥6 hours (requires use of a urinary catheter)
- No full or partial response for ≥2 days of diuretic withdrawal and volume expansion with albumin (dosed at 1 g/kg of body weight/day†)
- Absence of shock
- No current or recent treatment with nephrotoxic drugs
- In the absence of CKD, assess for parenchymal disease, as indicated by proteinuria >500 mg/day, microhematuria (>50 red blood cells per high power field), urinary injury biomarkers (if available) and/or abnormal renal ultrasonography
- Suggestion of renal vasoconstriction, with FENa <0.2% (levels <0.1% are considered highly predictive)

*All criteria must be met for the diagnosis of HRS-AKI.
†Maximum 100 g/day.

Liver Transplantation

Liver transplantation (LT) is considered the optimal treatment for patients with HRS-AKI because it corrects the underlying liver failure that underlies reversible HRS-AKI, thereby curing both.[29,30] In reality, this is rarely realized because most patients have contraindications to transplantation, organ

availability is limited, and factors adversely impact prioritization of patients with HRS-AKI who are listed for LT.

The Organ Procurement and Transplantation Network is the unified transplantation network in the United States under the auspices of the United Network for Organ Sharing. According to the Organ Procurement and Transplantation Network policy for LT, each adult LT candidate (≥18 years old) is assigned a score based on the Model for End-Stage Liver Disease (MELD) scoring system, which prioritizes patients for liver allocation. The factors involved in this calculation are sCr, bilirubin, and international normalized ratio values, and, in patients with MELD scores >10, sodium levels.[31] MELD score is a prediction of 90-day mortality; the higher the score, the higher the mortality rate.

Unfortunately, the MELD scoring system often provides a disservice to patients with HRS-AKI on transplantation waiting lists. Patients with HRS-AKI have demonstrated worse survival expectancy than other populations with cirrhosis with equivalent MELD scores.[18,32] This is because patients with elevated sCr from HRS-AKI have worse prognoses than patients with AKI because of parenchymal nephropathy.[32,33] In Italy, the Italian Liver Allocation Policy was recently revised to reflect relevant critical issues and conceptual advances, one being "the inequity of a purely MELD-based system governing organ allocation." The revised policy now considers HRS an exception,[34] but to date, no such policy revision has been implemented in the United States. Finally, data demonstrate that effective pharmacological treatment of HRS-AKI improves specific components of the MELD system (ie, sCr, sodium), reducing the score and adversely affecting the priority of patients on the waiting list for liver allocation who remain quite ill and still require life-saving LT. Nevertheless, this should not be a reason to withhold treatment in patients with HRS-AKI who are LT candidates, as the benefits of effective management far exceed the risk of decreased priority for LT. An update to amend the allocation policy to allow patients with HRS-AKI to maintain priority for liver allocation in the setting of effective therapy would be ideal, but more advances in this field are needed. For example, the availability of validated biomarkers to differentiate HRS-AKI from the pool of other kidney disorders (eg, parenchymal AKIs) is essential to avoid the mislabeling of patients and downstream implications on kidney allocation.

Renal Replacement Therapy

Renal replacement therapy (RRT) is a temporary option to potentially bridge the limited number of eligible LT candidates with HRS-AKI to transplantation. Associated risks and poor outcomes, however, make RRT a suboptimal solution for such patients. RRT in patients who are critically ill is complicated by high morbidity and mortality rates. Survival with RRT in patients with end-stage liver disease presenting with HRS-AKI is short, and the overall benefit is not well documented. In LT candidates, a 59% mortality rate in patients requiring >7 days of in-hospital continuous RRT has been observed.[35]

Patients with RRT are also at risk for general acute complications, such as intradialytic hypotension, increased risk of cardiac events, and complications related to venous access (including bleeding and infections).[15] Patients with decompensated cirrhosis present additional physiologic challenges that impair adequate volume management during RRT.[15] Portal hypertension and splanchnic vasodilation result in decreased effective circulating volume and low mean arterial pressure; both impact volume management.[36] Continuous RRT involves intensive care unit (ICU) care, immobilization, anticoagulation, and subsequent bleeding risks. Intermittent RRT is complicated by hemodynamic instability attributed to rapid fluid and solute shifts,[37] resulting in intradialytic hypotension and cerebral edema.

Although HRS-AKI is thought to be reversible with LT, post-LT renal function may be adversely affected. Data indicate that the longer patients are maintained on RRT while awaiting transplantation, the higher the risk of nonrecovery of renal function after LT. In 1041 LT recipients on RRT at the time of transplantation, 707 recipients (67.9%) had spontaneous recovery of renal function after LT. Patients who recovered spontaneously had a significantly shorter course of RRT in the pretransplant time period (15.6 versus 36.6 days; $P < 0.001$). Recovery of renal function was observed in 70.8% and 11.5% of recipients on RRT for <30 days and >90 days, respectively.[38] In another study, 2112 adult transplantation recipients who received acute RRT for ≤90 days before LT were assessed. The adjusted renal nonrecovery risk increased by 3.6% per day of pretransplantation RRT ($P < 0.001$).[39] According to the United Network for Organ Sharing criteria, if patients require dialysis for ≥6 weeks before LT, they are candidates for simultaneous kidney/LT because of this risk of renal nonrecovery.[40]

Pharmacologic Therapy

Currently, there are no approved medications for treating HRS-AKI in the United States. Therapeutic alternatives are needed for the minority of patients who are critically ill and awaiting LT and the majority of patients who are ineligible for LT. At present, the mainstay of pharmacologic therapy consists of plasma expanders to increase intravascular volume and, in combination with vasoconstrictors, reverse splanchnic vasodilatation. This is thought to improve the systemic circulation and increase arterial pressure,[26] leading to increased renal perfusion pressure, glomerular filtration rate, and overall renal function.[41,42]

VOLUME EXPANSION

Albumin is considered a crucial plasma expander for the treatment of HRS-AKI. Albumin maintains or increases cardiac output even in the most advanced phases of liver disease.[15] Preclinical studies indicate that albumin may also have anti-inflammatory properties. However, in a recent study in the United Kingdom, during which 777 patients with cirrhosis were given the standard of care dose of albumin (median of 20 g/patient) or increased albumin (to a target of ≥30 g/L), albumin did not reduce the incidences of infection, kidney dysfunction, or death.[43]

VASOCONSTRICTORS

The vasoconstrictive component of treatment can occur via several mechanisms. Alpha-adrenergic receptor agonists, including norepinephrine and midodrine, act by binding to alpha-1-adrenergic receptors on vascular smooth muscle cells, leading to vasoconstriction. The somatostatin analog octreotide inhibits the release of glucagon and other vasodilator peptides, leading to vasoconstriction in splanchnic, portal, and systemic circulations.[44] Vasopressin and vasopressin analogs (ornipressin, terlipressin) bind to V1 receptors of vascular smooth muscle cells, leading to vasoconstriction, mainly of the splanchnic circulation.[41,45] Despite the lack of approved indications in HRS-AKI by the US Food and Drug Administration (FDA), vasoconstrictors that are commonly administered with albumin in the United States include midodrine and octreotide. The adrenergic agonist norepinephrine is also used to treat HRS-AKI, but its administration requires ICU care. Thus, it is often used in patients with severe HRS-AKI. Terlipressin, a vasopressin analog, is commonly used in combination with albumin for HRS-AKI management around the world but is currently unavailable in the United States.

Potential Adverse Events of Pharmacologic Therapy

VOLUME EXPANDERS

Excessive resuscitation with albumin can contribute to intravascular volume overload and cardiopulmonary compromise, necessitating careful administration and monitoring in patients with decompensated cirrhosis and portal hypertension.

VASOCONSTRICTORS

The most frequent adverse reactions seen in controlled trials of midodrine were supine and sitting hypertension, paresthesia, and pruritus (mainly of the scalp), chills, urinary urge, urinary retention, and urinary frequency.[42] In patients treated with octreotide, common adverse reactions include nausea, diarrhea, headache, arthralgia, asthenia, hyperhidrosis, peripheral swelling, increased serum glucose, emesis, abdominal discomfort, dyspepsia, sinusitis, and osteoarthritis.[46] The combination of midodrine and octreotide is advantageous in that it can be administered outside of the ICU.

Norepinephrine is often associated with reversible cardiac and digital ischemia.[47] Intensive hemodynamic monitoring is required with norepinephrine infusion, and as mentioned previously, it should only be administered in the ICU setting.[48]

Efficacy of Pharmacologic Therapy

Although the off-label use of midodrine and octreotide, as well as norepinephrine, in HRS-AKI is widespread, much of the data are based on small, nonrandomized studies. Few data exist on the comparative efficacy of these drugs. In recent years, the first meta-analysis of HRS-1 (the accepted nomenclature at the time for HRS-AKI) was published and provided some insight into the comparative efficacy of available agents. The

authors identified 13 randomized controlled trials that enrolled 739 adults with HRS-1. All of the studies compared the efficacy of vasoactive drugs, in combination with albumin, to placebos. The primary outcome was reduction in short-term mortality. Secondary outcomes included reversal of HRS, relapse of HRS after initial reversal, and adverse events (AEs). Terlipressin studies were included in this meta-analysis.[49]

Table 3 compares the findings of the meta-analysis to the recommendations from the American Association for the Study of Liver Diseases (AASLD) practice guidelines for HRS-AKI.[50,51] As demonstrated in the table, the authors of the meta-analysis dispute the practice guidelines and suggest terlipressin should be adopted as a first-line therapy in the management of HRS-AKI.[48] In the absence of better alternatives, however, clinicians in the United States generally follow these guidelines for HRS-AKI management. Midodrine and octreotide, in combination with albumin, has become the regimen of choice based on availability and ease of administration despite the lack of data. Although norepinephrine has proven benefits, ICU administration is impractical, and therefore its use is uncommon.

Use of Terlipressin in Patients With HRS-AKI

Terlipressin is approved in Europe for the treatment of HRS-1, and efficacy is supported by controlled studies,[52,53] including the recently published CONFIRM trial in the United States,[54] and is endorsed by 2 liver society guidelines.[30,55] In contrast to the AASLD guidelines (Table 3), the European Association for the Study of the Liver Practice Guidelines recommends terlipressin and albumin as a first-line therapy for HRS-1 (now HRS-AKI).

Terlipressin is a prohormone of lysine-vasopressin and, via a tissue peptidase mechanism, causes prolonged release of lysine-vasopressin, thereby prolonging the half-life.[56] This allows for administration in divided doses of 1 mg intravenously every 6 hours for up to 14 days,[54] with alternative modes of delivery currently being studied. Terlipressin is selective for both V1 and V2 receptors. Stimulation of the V1 receptors causes splanchnic and extrarenal vasoconstriction, reducing splanchnic blood flow and portal pressure, ameliorating hyperdynamic circulation, and improving the effective circulatory volume and renal perfusion pressure. Stimulation of the V2 receptors increases water reabsorption in the renal collecting ducts, which may result in hyponatremia.[30] The AE profile is safe enough that ICU administration is unnecessary.

Terlipressin is under investigation in the United States for FDA approval for HRS-AKI. It has been evaluated in 3 phase 3 studies. OT-0401 and REVERSE (Randomized, placEbo-controlled, double-blind study to confirm the reVERSal of hepatorenal syndromE type 1 with terlipressin) are 2 multicenter, randomized phase 3 clinical studies comparing treatment with terlipressin plus albumin to placebo plus albumin in patients with HRS-1 (currently HRS-AKI).[56] A summary of both studies is included in Table 4.[57,58] The larger CONFIRM study was subsequently performed to confirm the efficacy and safety

TABLE 3. Meta-Analysis Data on HRS-1* Compared With the AASLD Practice Guidelines, Treatment, and Recommendations

Therapeutic Strategy	AASLD Recommendation[48]	Corresponding Meta-Analysis Finding[49]
Midodrine/octreotide plus albumin	Should be considered in the treatment of HRS-1*	Low-quality evidence supports this recommendation
		Data demonstrate no significant benefit for short-term survival
		Data demonstrate no significant benefit in reversing HRS-1
Norepinephrine plus albumin	Can be considered in the ICU	There is low confidence in estimates suggesting any survival benefit
		Superior to midodrine plus octreotide with albumin for reversal of HRS, and as such this strategy might be beneficial in reversing HRS-1
Terlipressin plus albumin	Currently under review by the FDA	Might reduce short-term mortality compared with placebo
		Superior to midodrine plus octreotide with albumin for reversal of HRS-1

*At the time of the meta-analysis and creation of the practice guidelines, the accepted nomenclature was HRS-1 (currently HRS-AKI).

TABLE 4. High-Level Overview of Phase 3 Terlipressin Studies

	CONFIRM[54]	REVERSE[60]	OT-0401[59]
Inclusion criteria and randomization	Adult patients with cirrhosis, ascites, and HRS-1 (based on the 2019 ICA criteria as rapidly deteriorating renal function to SCr ≥2.25 mg/dL, with actual or projected doubling of sCr within 2 weeks and without improvement in renal function [<20% decrease in sCr 48 hours after both diuretic withdrawal and albumin-fluid challenge], in adult patients with cirrhosis and ascites) randomized to 14 days‡ of terlipressin 1 mg IV every 6 hours + albumin (n = 199) or placebo + albumin (n = 101)	Adult patients with cirrhosis, ascites, and HRS-1 (based on the 2007 ICA criteria) randomized to 14 days* of terlipressin 1 mg IV every 6 hours + albumin (n = 97) or placebo + albumin (n = 99)	Patients with HRS-1 randomized to 14 days† of terlipressin 1 mg IV every 6 hours + albumin (n = 56), placebo + albumin (n = 56), or placebo + albumin (n = 56)
Primary endpoint	VHRSR, defined as >2 consecutive sCr values ≤1.5 mg/dL at least 2 hours apart and alive without RRT for at least 10 days after the second sCr value ≤1.5 mg/dL	CHRSR, defined as >2 on-treatment sCr values <133 μmol/L at least 48 (±8) hours apart without intervening RRT or LT	Treatment success on day 14, defined as a decrease in sCr level to ≤1.5 mg/dL for at least 48 hours without dialysis, death, or relapse of HRS-1
Primary efficacy results	A total of 63 (31.7%) patients treated with terlipressin achieved VHRSR versus 17 (16.8%) treated with placebo ($P = 0.006$)	CHRSR observed in 19/97 patients (19.6%) receiving terlipressin versus 13/99 patients (13.1%) receiving placebo ($P = 0.22$)	Treatment success with terlipressin was double that with placebo (25% versus 12.5%; $P = 0.09$)
Safety results	AEs of any severity, including serious AEs, were reported in 88% of participants in the terlipressin group versus 88.9% of those in the placebo group Terlipressin resulted in more AEs, including abdominal pain, nausea, diarrhea, and respiratory failure Death within 90 days attributed to respiratory disorders occurred in 11% of the participants in the terlipressin group versus 2% of those in the placebo group AE-related dose interruptions were similar in both groups (terlipressin, 7%; placebo, 7.1%), whereas the rate of permanent treatment discontinuations attributed to AEs was higher in the terlipressin group (12%) than in the placebo group (5.1%)	There was a similar number of AEs in each group, but patients in the terlipressin group had more ischemic events	One nonfatal myocardial infarction occurred with terlipressin, but the total AE rate was similar to that of placebo

*Unless the following occurred: CHRSR (defined as 2 sCr values ≤1.5 mg/dL at least 40 hours apart on treatment without RRT or LT or sCr at or above baseline on day 4).
†Unless treatment success, death, dialysis, or transplantation occurred.
‡Unless the following occurred: VHRSR, RRT, LT, or sCr at or above baseline on day 4.

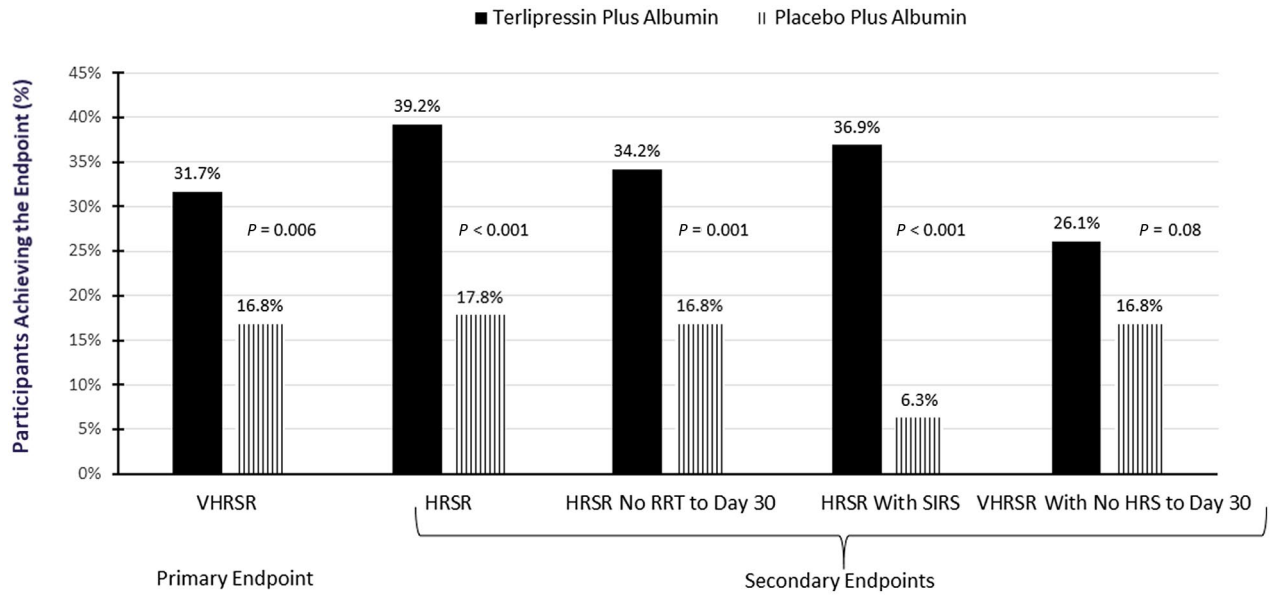

FIG. 1. Primary and secondary outcomes of participants treated with terlipressin versus placebo in the phase 3 CONFIRM trial.[54] HRSR was defined as a decrease in sCr to ≤1.5 mg/dL.

of terlipressin plus albumin versus albumin alone in patients with well-defined HRS-1.[54] Terlipressin demonstrated efficacy and a favorable safety profile in all 3 studies (Table 4).[54,59,60]

In CONFIRM, patients were to have "well-defined" HRS-1 based on the modified criteria outlined by the ICA in adult patients with cirrhosis and ascites[21] (Table 4). The demographic and baseline clinical characteristics of patients in CONFIRM were similar among treatment groups and indicate a population of patients with advanced HRS-AKI, including the mean baseline sCr, which was 3.5 mg/dL for both the terlipressin and placebo groups.[54] In addition, 42.2% of participants in the terlipressin group and 47.5% in the placebo group met the criteria for systemic inflammatory response syndrome (SIRS),[54] a group typically associated with poor outcomes.[59] As depicted in Fig. 1, CONFIRM demonstrated that patients with HRS-AKI treated with terlipressin plus albumin experienced a significantly greater reversal of worsening renal function compared with patients treated with albumin alone (placebo group), including patients with SIRS. Furthermore, although similar percentages of participants in each treatment group were admitted to the ICU, patients in the terlipressin group required 6.4 days of ICU care compared with 13.2 days in the placebo group (Table 5).[60]

Post hoc analyses of CONFIRM examined how terlipressin use affects RRT after LT in this population. Through 90 days of follow-up, 23.1% (46/199) of patients treated with terlipressin and 28.7% (29/101) of patients treated with placebo underwent LT. After transplantation, the rate of RRT in patients who received terlipressin was significantly lower than those who received placebo (19.6% [9/46] versus 44.8% [13/29], respectively; $P = 0.03$). The overall 90-day survival rate for transplantation in the terlipressin group was 100% (46/46) compared with 93.1% (27/29) in the placebo group, but the differences were not statistically significant.[61] A separate post hoc intention-to-treat analysis was conducted to assess the incidence of RRT among CONFIRM survivors. The cumulative incidences of the need for RRT for the terlipressin group at days 14, 30, and 90 were 23%, 26%, and 29%, respectively, compared with 35%, 36%, and 39%, respectively, for patients assigned to the placebo group ($P = 0.03$, 0.07, and 0.10, respectively). Among the survivors, significantly fewer patients treated with terlipressin remained dependent on RRT at days 14, 30, and 90 (22%, 26%, and 30%, respectively) compared with those treated with placebo (39%, 43%, and 46%; $P < 0.01$, $P = 0.03$, and $P = 0.05$, respectively). The 90-day RRT-free survival rate was 35% in the terlipressin group versus 30% in the placebo group ($P = 0.08$), with a numerically longer median number of RRT-free days in the terlipressin group (20 versus 11 days).[62] These analyses indicate that treatment with terlipressin

TABLE 5. Terlipressin-Treated Participants in CONFIRM Had a Shorter Length of ICU Stay[62]

	Terlipressin (n = 199)	Placebo (n = 101)
Incidence of ICU admission, n (%)	31 (15.6)	14 (13.9)
Length of study site hospital stay, days, mean (SD)	24.5 (19)	24.8 (18.2)
Length of ICU stay, days, mean (SD)	6.4 (5.5)	13.2 (15.9)
Survival in ICU-admitted participants (alive and without RRT or transplantation by day 14), n (%)	9/31 (29)	1/14 (7.1)

and albumin for patients with HRS-1 significantly decreases the need for RRT after LT, decreases the rate of RRT among survivors, and improves RRT-free survival.[61,62] Of note, a previous study in patients with HRS-AKI demonstrated that terlipressin and albumin reduced the need for RRT after LT and reduced the risk of chronic kidney disease at 1 year after LT.[63]

With regard to AEs in the CONFIRM trial, more patients in the terlipressin group experienced abdominal pain, nausea, and diarrhea as well as respiratory failure (14%) than in the placebo group (5%). The higher incidence of respiratory failure and acute respiratory failure in the terlipressin group is possibly related to the known cardiovascular and pulmonary effects of terlipressin and increased preload from aggressive hydration with albumin.[45,64-66] A total of 9 patients (4.5%) in the terlipressin group died during the treatment period versus 1 (1%) in the placebo group; the most common cause of death during the treatment period was respiratory failure (3% for terlipressin and none for placebo). Furthermore, patients in the terlipressin group were more likely to develop respiratory failure and die from respiratory disorders within 90 days (11% versus 2%), which likely contributed to the observed mortality difference.[54]

Interpretations of Terlipressin Data and Recommendations From the Expert Panel

A new drug application for terlipressin use in HRS-1 (the nomenclature at the time of filing) has been reviewed by the FDA. The agency issued a complete response letter requesting more information to support the benefit-risk ratio. The committee noted that an exploratory analysis of treatment effects on clinical outcomes showed terlipressin was not associated with improved survival compared with placebo and raised safety concerns regarding respiratory failure events.[67]

However, there are no approved therapies for HRS-AKI in the United States, and the current off-label options are generally ineffective. Thus, in the United States, there is a significant unmet medical need, and terlipressin addresses that need for a subpopulation of those with HRS-AKI. This recommendation is based on the careful interpretation of terlipressin data in the 3 registration trials. Per the old ICA criteria that dictated CONFIRM study eligibility, many patients were enrolled at advanced stages of HRS, resulting in late treatment interventions and poor outcomes. Nevertheless, primary and secondary endpoints were consistently met in patients treated with terlipressin and albumin compared with placebo and albumin in phase 3 studies. However, it is clear that further defining the population that has greatest benefit will improve the benefit-risk parameters.

The CONFIRM study demonstrated that significantly more patients treated with terlipressin achieved verified HRS reversal than in those receiving placebo, an extremely important outcome. Considering a cohort of patients (n = 99) with access to LT from a previously published study of terlipressin plus albumin versus albumin alone, 35 of whom received LT, the 180-day survival rates for patients who received transplants were 100% in those who received terlipressin plus albumin versus 94% in those who received albumin alone. This study also reported that the 180-day survival rate in the nontransplant group was 34% in those who received terlipressin plus albumin versus 17% in those who received albumin alone. The survival rate was significantly better for those achieving a reversal of HRS versus those who did not (47% versus 4%; $P < 0.001$) and for those who received LT compared with those who achieved HRS reversal (97% versus 47%; $P < 0.001$). These data reinforce that LT is optimal for HRS-AKI. However, the majority of patients with HRS-AKI are ineligible for LT or a donor organ is unavailable if they are eligible. HRS-AKI reversal with an effective therapy such as terlipressin is a meaningful strategy to improve survival.[63]

The effects of terlipressin on RRT-related outcomes are also important to consider. RRT is a provisional management strategy for HRS-AKI known to confer an extremely poor prognosis and at best serves as a bridge to

LT for the small number of patients who are transplantation candidates. Data on the use of RRT in patients with HRS-AKI indicate that it is associated with increased mortality, a risk of serious complications, a threat of renal nonrecovery after LT, poor quality of life, and high costs. The benefits of terlipressin and albumin use on RRT alone should be considered a significant and clinically meaningful outcome when managing this serious disease for which there are no approved therapies.

The safety issues that are of concern have been infrequently encountered or successfully managed in patients treated with terlipressin for many years in Europe. Efforts to mitigate AEs and optimize favorable outcomes involve a better understanding of patient selection, including timing of therapy (ie, administering to the appropriate patients at the appropriate time), careful candidate selection, dosing method and titration, as well as the correct use of albumin and fluid monitoring. In the CONFIRM study, the majority (83%) of patients treated with terlipressin received albumin because of the advanced degree of HRS. There was likely an increase in afterload (from terlipressin use) and an increase in preload (from albumin use) that resulted in pulmonary edema and, ultimately, respiratory failure. It is plausible that if terlipressin were given earlier in the disease process (ie, at lower Cr levels), using the current consensus definition of HRS, it would potentially lead to higher rates of HRS reversal and lower incidences of respiratory failure. Appropriate patient selection would include patients early in the disease process with the avoidance of patients with cardiopulmonary issues. Careful administration of albumin is also necessary, with vigilance for fluid overload or impending respiratory failure. Future investigations with terlipressin should be designed to assess populations that optimize benefit from terlipressin and minimize toxicity.[68]

Conclusions

HRS-AKI is no longer a rare condition given the tremendous increase in the number of patients with advanced liver disease in the United States, and clinicians should be attentive to the development of HRS-AKI in patients with cirrhosis. Early diagnosis and interventions involving specialists (in particular, nephrologists) are essential to improve outcomes, but HRS-AKI is often rapidly fatal under any circumstances without effective interventions. LT remains the most effective intervention, but few patients with HRS-AKI undergo transplantation. RRT is a temporary life-saving intervention but may ultimately worsen outcomes, especially if implemented for long periods, and increase the risk of renal insufficiency after LT. In terms of pharmacologic therapy, vasoconstriction and plasma expansion are necessary therapeutic interventions. The agent of choice for volume resuscitation is albumin, and judicious use is encouraged. No vasoconstrictors are approved for HRS-AKI, yet midodrine/octreotide has become the mainstay of therapy despite the lack of evidence of therapeutic efficacy. Terlipressin, approved in Europe for the treatment of HRS-AKI and supported by recommendations for first-line therapy by some liver societies and experts around the world, would constitute a beneficial option for many patients with HRS-AKI were it available in the United States.

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