Use of Terlipressin in Liver Transplant Candidates

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Abstract: The use of terlipressin in the treatment of hepatorenal syndrome type 1 (HRS-1) in patients with advanced cirrhosis wait-listed for liver transplant (LT) has been controversial. Successful treatment lowers patients' Model for End-Stage Liver Disease (MELD) score and hence their LT priority. Terlipressin's potential ischemic side effects and risks for respiratory failure in susceptible patients lend support to directly proceed to LT. However, responders to terlipressin have better post-LT survival with lower incidences of post-LT chronic kidney disease and need for renal replacement therapy (RRT). Available data suggest that terlipressin responders have not all been impacted negatively. HRS-1 itself confers a greater negative effect on survival when compared with patients with the same MELD score but without HRS-1; therefore, various countries except the United States have strategies to preserve the wait-list position of terlipressin responders. The MELD lock strategy uses the patient's pre-terlipressin MELD score to maintain their wait-list position indefinitely; a modified MELD lock system requires re-evaluation of the patient's eligibility status every 3 months. Patients taking long-term terlipressin for recurrent HRS are treated as needing RRT in assessing their LT priority. The United States considers that more data are needed before devising its own system for managing wait-listed terlipressin responders. Current data suggest that treating and reversing HRS in wait-listed patients is the appropriate course of action. This article will review the pros and cons of using terlipressin in LT wait-listed patients with HRS and the various strategies practiced by different countries to ensure equitable access to LT.

Keywords
Acute kidney injury, albumin, hepatorenal syndrome, inflammation, vasoconstrictor, terlipressin

Renal dysfunction is a common life-threatening complication of decompensated cirrhosis, occurring in approximately 26% to 50% of patients admitted to the hospital.[1-3] Acute renal dysfunction, now referred to as acute kidney injury (AKI), is generally divided into functional or structural types. Functional causes of AKI include volume-responsive hypovolemic AKI such as prerenal azotemia or non–volume-responsive cases such as hepatorenal syndrome (HRS), whereas structural causes of AKI include diseases such as glomerulonephritis, acute tubular necrosis, or postrenal bladder outlet obstruction.

Table 1. Diagnostic Criteria and Types of HRS

Diagnostic criteria for HRS			
• Cirrhosis with ascites • sCr >1.5 mg/dL (133 μmol/L) • No full or partial response after at least 2 days of diuretic withdrawal and volume expansion with albumin • Absence of shock • No current or recent treatment with nephrotoxic drugs • Absence of parenchymal kidney disease as indicated by absence of proteinuria, microhematuria, and abnormal renal ultrasonography			
Types of HRS			
2007 definition[4]		**2015 definition[5]**	
HRS-1	Doubling of initial sCr to >2.5 mg/dL (226 μmol/L) in less than 2 weeks PLUS Fulfilling all other diagnostic criteria for HRS	HRS-AKI	Increase in sCr ≥0.3 mg/dL (≥26.5 μmol/L) within 48 hours OR increase in sCr ≥50% from baseline within the prior 7 days PLUS Fulfilling all other diagnostic criteria for HRS
HRS-2	Slow rise in sCr to 1.5 to 2.5 mg/dL (133 to 226 μmol/L) with a steady progressive course PLUS Fulfilling all other diagnostic criteria for HRS	HRS-NAKI	HRS-AKD eGFR <60 mL/min for <3 months in the absence of structural causes OR <50% increase in sCr using last available sCr within 3 months as baseline HRS-CKD[61] eGFR <60 mL/min for >3 months in the absence of structural causes PLUS Fulfilling all other diagnostic criteria for HRS

eGFR, estimated glomerular filtration rate; HRS, hepatorenal syndrome; HRS-1, hepatorenal syndrome type 1; HRS-2, hepatorenal syndrome type 2; HRS-AKD, hepatorenal syndrome–acute kidney disease; HRS-AKI, hepatorenal syndrome–acute kidney injury; HRS-CKD, hepatorenal syndrome–chronic kidney disease; HRS-NAKI, hepatorenal syndrome–non-acute kidney injury; sCr, serum creatinine.

Adapted from Salerno et al,[4] Angeli et al,[5] and Angeli et al.[61]

Hepatorenal syndrome type 1 (HRS-1),[4] now referred to as hepatorenal syndrome–acute kidney injury (HRS-AKI)[5] (Table 1), is the most severe form of AKI. Although much less common than prerenal azotemia and acute tubular necrosis with an annual incidence of 12.1%, HRS-AKI has an in-hospital mortality rate of 24.5% and a 90-day mortality rate of 49%.[3] This article will review the merits and drawbacks of using terlipressin (Terlivaz, Mallinckrodt Pharmaceuticals) to treat HRS-AKI in patients with advanced cirrhosis wait-listed for liver transplant (LT).

Pathophysiology of Hepatorenal Syndrome

The pathophysiology of HRS-AKI is quite complex. In brief, there is systemic and splanchnic arterial vasodilatation with paradoxical renal vasoconstriction. The former is related to overexpression of vasodilators in the splanchnic and systemic circulations and reduced responsiveness to vasoconstrictors, whereas the latter is related to increased sensitivity to overactive vasoconstrictor systems.[6] The resultant splanchnic and systemic arterial vasodilatation also means that the effective arterial blood volume and mean arterial pressure (MAP) are decreased; hence, renal perfusion is also reduced, resulting in relative renal hypoperfusion.[6,7] Inflammation also plays a significant part in the pathogenesis of HRS-AKI. This is related to increased bacterial translocation in the gut, transferring pathogen-associated molecular patterns[8] from the gut lumen into the splanchnic circulation, as well as damage-associated molecular patterns from tissue injury,[9] inciting an inflammatory cascade,[10] contributing to renal microcirculatory dysfunction and renal tubular damage (Figure). Therefore, the management of HRS-AKI involves correction of hemodynamic abnormalities using vasoconstriction together with albumin as an adjunctive therapy to reduce the extent of inflammation as well as to improve the effective arterial blood volume.[11]

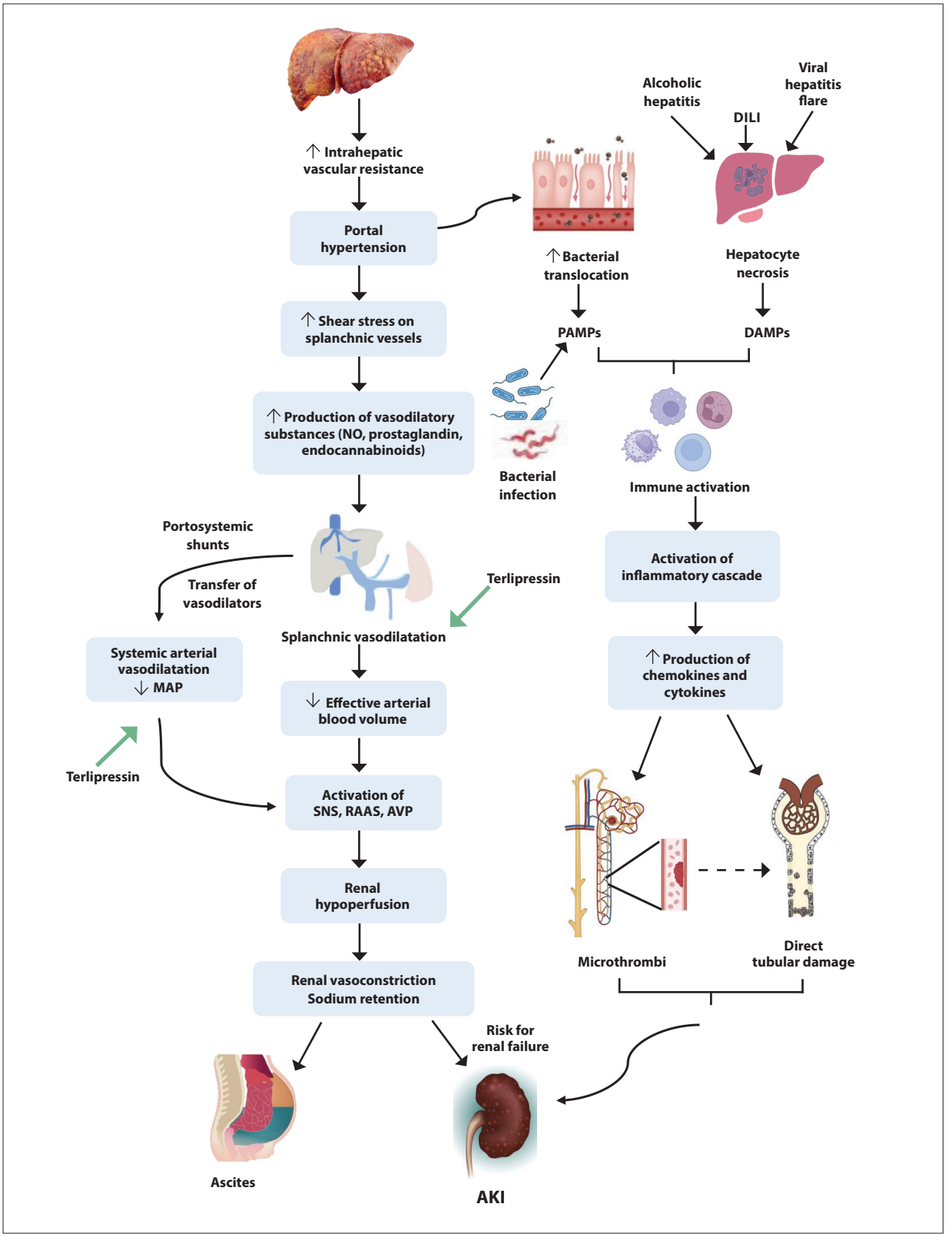

Figure. Pathophysiology for hepatorenal syndrome and sites of action for terlipressin.

AKI, acute kidney injury; AVP, arginine vasopressin; DAMPs, damage-associated molecular patterns; DILI, drug-induced liver injury; MAP, mean arterial pressure; NO, nitric oxide; PAMPs, pathogen-associated molecular patterns; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system.

Terlipressin

Terlipressin is a peptide prodrug[12,13] of lysine vasopressin, which is a nonselective agonist of both human V_1 and V_2 receptors.[12] V_1 receptors are found on the vascular smooth muscles of the systemic, splanchnic, and renal circulations, inducing vasoconstriction with activation.[14] V_2 receptors are found in the distal tubule and collecting ducts of the kidney, acting to mobilize aquaporin channels leading to water retention.[14] Lysine vasopressin binds to V_1 approximately 6-fold stronger compared with V_2 receptors.[13] Therefore, when terlipressin is administered and converted into lysine vasopressin in the circulation, there is a net effect of arteriolar vasoconstriction in the splanchnic circulation, leading to reduced portal inflow and thus decreased portal pressure. Terlipressin also increases the systemic arterial blood pressure, resulting in an elevated MAP and hence improved renal perfusion. In the kidneys, terlipressin reduces the renal arterial resistance and increases renal perfusion pressure also via mechanisms that decrease activation of the renin-angiotensin-aldosterone system.[15] By lowering portal pressure, terlipressin can also reduce the extent of the abnormal bacterial translocation in the gut, indirectly reducing the extent of inflammation that contributes to the development of HRS (Figure). Therefore, terlipressin is the most commonly used vasoconstrictor in the management of HRS-AKI.[16]

Terlipressin and Hepatorenal Syndrome

Multiple randomized controlled trials have assessed the use of terlipressin with albumin vs albumin alone for the treatment of HRS-AKI.[17-20] However, these trials recruited patients based on the 2007 International Club of Ascites' definition of HRS-1, which is a rapidly progressive form of HRS with doubling of serum creatinine (sCr) to greater than 2.5 mg/dL in less than 2 weeks.[4] Terlipressin acetate was administered as a bolus dose of 1 mg intravenously every 4 to 6 hours, together with 20 to 40 grams of albumin per day, for a maximum of 14 days or until HRS reversal, defined as sCr of less than 1.5 mg/dL, whichever came first.[21] Three of the trials were conducted in North America and exclusively recruited patients with HRS-1,[17,19,20] whereas the trial in Spain included patients with both HRS-1 and HRS type 2.[18] All of the enrolled patients had a baseline sCr between 3.5 mg/dL and 3.9 mg/dL and Model for End-Stage Liver Disease–sodium (MELD-Na) score between 32 and 33. The HRS reversal rate with terlipressin was 24% to 44% with 3 of the 4 studies showing statistical significance.[17-19] The HRS recurrence rate varied between 5.3% and 17%.[17-20] All of the trials reported no difference in overall and transplant-free survival at 90 days between terlipressin plus albumin vs albumin alone. A lower pretreatment MELD-Na score and sCr of less than 5 mg/dL predicted response to terlipressin and albumin.[22] A lower baseline serum bilirubin of less than 10 mg/dL and a sustained increase of MAP by greater than 5 mm Hg with terlipressin also predicted response.[23-25] Other predictors of response included a lower stage of acute-on-chronic liver failure (ACLF),[26] a change in the renal resistive index by greater than 5% on day 3 of treatment,[27] and a pretreatment urinary neutrophil gelatinase-associated lipocalin level of less than 220 ng/mL, a marker of renal tubular damage.[28] Patients with systemic inflammatory response syndrome[29] and those with alcoholic hepatitis as the trigger for HRS also responded better to terlipressin.[17] Trials have consistently shown that responders to vasoconstrictor therapy, especially those with HRS reversal, had better transplant-free and overall 90-day survival compared with nonresponders.[30] Even a partial response was associated with improved survival.[31] Terlipressin can also be administered as a continuous infusion of 2 mg/day to a maximum of 8 mg/day. Terlipressin infusion has been shown in 2 studies to decrease adverse events without compromising efficacy.[30,32]

The use of terlipressin is not without complications. It is a vasoconstrictor and therefore could potentially cause ischemia in patients with a history of ischemic conditions.[21] The use of terlipressin has also been shown to be associated with an increased incidence of respiratory failure, especially in patients with multi-organ failure such as those with grade 3 ACLF (≥3 organ failures).[33] Predictors of respiratory failure with terlipressin use include a high baseline international normalized ratio, a high pretreatment MAP, or a low pretreatment oxygen saturation of less than 90% on pulse oximetry while on room air. Given the fact that patients with a pretreatment sCr of greater than 5 mg/dL have a very poor response rate to terlipressin, various academic societies have recommended that terlipressin should not be given to patients with grade 3 ACLF, baseline sCr of greater than 5 mg/dL, or oxygen saturation of less than 90%.[34,35]

Hepatorenal Syndrome–Acute Kidney Injury and Liver Transplantation

LT remains the definitive treatment for HRS-AKI, as this procedure corrects the portal hypertension, liver failure, and resulting kidney injury. Therefore, patients with HRS-AKI should be evaluated and placed on the LT list once eligible.[36-38] LT resolves HRS-AKI in 75.8% of cases with a mean time of 13 ± 2 days.[39] Patients who receive a living donor LT have an even higher renal recovery rate of 86% at 3 months.[40] Patient outcomes post-LT are greatly improved with 100% 180-day survival[40] and 97% 1-year survival regardless of the therapy received or the success

Table 2. Arguments for and Against Using Terlipressin in Liver Transplant Candidates

Arguments for treatment with terlipressin	Arguments against treatment with terlipressin
• Responders will have time to wait for a donor organ to be available • Terlipressin use decreases the risk of HRS-AKI progression while waiting for a donor organ • Responders to terlipressin have improved transplant-free survival • Terlipressin use decreases the requirement for pre- and posttransplant RRT • Terlipressin use decreases the likelihood of CKD development posttransplant • HRS-AKI reversal pretransplant will improve posttransplant graft and patient survival	• Responders will have lower MELD-Na score and therefore have lower priority on the transplant waiting list • Responders' lower MELD-Na score may make them drop off the liver transplant waiting list altogether • Responders have increased waiting time for a donor organ • Patients with advanced disease may develop respiratory failure with terlipressin use • HRS reversal rate is higher with liver transplant without prior terlipressin than with terlipressin alone

CKD, chronic kidney disease; HRS, hepatorenal syndrome; HRS-AKI, hepatorenal syndrome–acute kidney injury; MELD-Na, Model for End-Stage Liver Disease–sodium; RRT, renal replacement therapy.

or failure of HRS reversal.[41] However, donor organs are scarce, and a long wait time from HRS-AKI diagnosis to LT has been identified as a negative prognostic factor in patient outcomes.[42] Therefore, it has been recommended that vasoconstrictor therapy, especially terlipressin, should be used to manage patients with HRS-AKI while waiting for LT.[34]

The Controversy Regarding the Use of Terlipressin in Liver Transplant Candidates

The Arguments Against Terlipressin Use in Liver Transplant Candidates

LT allocation worldwide is mainly based on the patient's MELD score, which is calculated using their sCr, international normalized ratio, and serum bilirubin. Serum sodium is involved in the calculation if the MELD-Na score is used. Treatment of HRS-AKI using terlipressin can result in HRS reversal in approximately one-third of patients, decreasing sCr to less than 1.5 mg/dL in responders, with a corresponding decrease in their MELD score. This lowers priority for LT and may disadvantage responders on the LT waiting list compared with nonresponders. If their MELD score falls too low with terlipressin use, the patient may drop off the LT waiting list altogether. Furthermore, responders have an HRS-AKI recurrence rate of 5.3% to 17%,[17-20] which will require retreatment. Therefore, there is some merit to the argument that patients with HRS-AKI should proceed directly to LT without vasoconstrictor therapy, especially because LT can yield a much higher HRS-AKI reversal rate than vasoconstrictor therapy. Furthermore, the use of terlipressin with albumin, especially in patients with advanced disease, may contribute to the development of respiratory failure,[33] potentially making the patient too ill for LT.

The Arguments for Terlipressin Use in Liver Transplant Candidates

The strategy of proceeding directly to LT without pharmacotherapy increases the risk of HRS-AKI progression, which demands the use of renal replacement therapy (RRT) while on the waiting list. This has the downstream adverse effects of bleeding, infections, and cardiac events, further increasing morbidity and mortality. Progression of HRS-AKI also increases the risk of HRS-AKI nonreversal following LT and therefore further need for RRT post-LT. It has been estimated that for each additional day of pretransplant RRT, there is an increased risk of HRS-AKI nonreversal post-LT of 6%.[39] Requirement for RRT for LT recipients has a negative impact on graft and patient survival compared with those who do not need RRT.[43] Therefore, it stands to reason to try to recover renal function with pharmacotherapy before LT.

The CONFIRM study in North America showed that there was a reduction in MELD score in HRS-AKI patients who responded to terlipressin, but there was no delay in terlipressin responders receiving LT.[17] In contrast, an Italian study reported a longer wait time for terlipressin responders to receive a LT (median of 37 days vs 17 days for nonresponders; P=.041) owing to a mean 6-point decrease in MELD score; however, responders to terlipressin had better 30-day transplant-free survival.[44] In another study that only enrolled HRS-AKI patients who were eligible to be assessed or wait-listed for LT, the use of terlipressin was associated with lower end-of-treatment sCr and MELD score.[32] Complete response was observed in 64% of patients. Among the 16 patients who underwent LT, 10 were terlipressin complete responders, 1 was a partial responder, and 5 were nonresponders by 90 days after terlipressin, suggesting that response did not delay LT. Further analysis of various terlipressin

Table 3. Various Strategies to Preserve Wait-List Priority for Transplant Candidates Receiving Terlipressin

MELD lock	Pretreatment MELD-Na score is locked without expiration Pros • Protects wait-list priority for terlipressin responders in the short and long term Cons • May give unfair advantage to patients with access to terlipressin and those with a durable response to terlipressin without recurrence of HRS-AKI • Will disadvantage patients who have increases in MELD-Na score owing to other causes such as infection or bleeding
Modified MELD lock (quarterly update)	Pretreatment MELD-Na score is locked until the next update after 3 months Pros • Protects wait-list priority for terlipressin responders within 3 months Cons • May give unfair advantage to patients with access to terlipressin and those with a durable response to terlipressin without recurrence of HRS-AKI • Will disadvantage patients who have increases in MELD-Na score owing to other causes such as infection or bleeding
Patients with recurrent HRS-AKI requiring long-term terlipressin	• Long-term terlipressin is regarded as equivalent to receiving RRT in the computation of the MELD-Na score • Ensures patients with recurrent HRS-AKI maintain wait-list priority

HRS-AKI, hepatorenal syndrome–acute kidney injury; MELD, Model for End-Stage Liver Disease; MELD-Na, Model for End-Stage Liver Disease–sodium; RRT, renal replacement therapy.

studies showed that the use of this treatment significantly reduced the need for RRT in the post-LT period.[45,46] The patients who received terlipressin pre-LT were also less likely to develop chronic kidney disease in the post-LT period.[32] Therefore, there have been calls for early use of terlipressin in appropriate patients with HRS-AKI to avoid RRT,[47,48] as the early use of terlipressin and albumin to reverse HRS-AKI before LT potentially provides more benefits than harm.

Table 2 summarizes the various pros and cons of using terlipressin in LT wait-listed candidates.

Possible Solutions

HRS reversal with terlipressin is still associated with high mortality without any survival advantage because of the presence of liver dysfunction; therefore, patients with HRS-AKI still require LT as definitive treatment for their liver failure. To resolve the controversy over potential delay in LT with terlipressin use in patients with HRS-AKI, many countries around the world have adopted policy changes to provide a more equitable donor organ allocation. More than a decade ago, Europeans proposed to use the pretreatment MELD score to maintain LT priority for patients with HRS-AKI.[49] This has evolved into several decision-making algorithms to address the issue of disadvantaging treatment responders on the transplant waiting list.[50]

Model for End-Stage Liver Disease Lock Strategy

The MELD lock strategy involves locking the pretreatment MELD score without expiration. This was proposed because 30-day survival was only 60% in HRS responders to terlipressin without LT,[44] which was far inferior to greater than 90% in patients who received placebo following LT in the largest terlipressin trial.[17] This strategy was first adopted by Italy followed by Spain. Switzerland likewise adopted a version of the MELD lock system in its organ allocation policy. The advantage of this strategy is that it protects the wait-list priority for HRS-AKI treatment responders or partial responders who may otherwise miss LT offers owing to a reduction in their MELD score after treatment. The opponents to this proposal argue that linking terlipressin use to a MELD lock strategy would give an unfair advantage to patients who have access to terlipressin, which may not be universal in all regions.[50] Opponents argue that allowing patients who have a durable response to terlipressin without recurrence of HRS-AKI to maintain their priority on the waiting list is an unfair strategy, as these patients may no longer need

LT with their improved renal function, and that insisting on this strategy will increase the disparity of health care access. The fact that both Italy and Spain have an opt-out system for organ donation may offset some of the health care access disparity, as availability of donor organs is presumably higher.[51] Finally, patients whose MELD score is increased owing to infection, gastrointestinal bleeding, or other forms of decompensation would not be able to move ahead on the waiting list despite worsening of their clinical status.

Quarterly Model for End-Stage Liver Disease/United Kingdom End-Stage Liver Disease Score Update

France employs a modified MELD lock strategy[52] in that the MELD score is updated every 3 months instead of every week. The United Kingdom uses a combination of the United Kingdom End-Stage Liver Disease (UKELD) score as well as a transplant benefit score,[53] which are also updated every 3 months. This strategy protects against reduction in the MELD/UKELD score after effective HRS-AKI therapy in the short term. The same arguments about the advantages and disadvantages of the MELD lock strategy can also be applied here until the MELD score is updated in 3 months. France has an opt-in system for organ donation, whereas the United Kingdom has a soft opt-out system.

Hepatorenal Syndrome–Acute Kidney Injury Requiring Long-Term Vasoconstrictor Therapy

Patients with HRS-AKI who initially respond to terlipressin may have recurrent HRS-AKI once the terlipressin is discontinued. Recurrent HRS-AKI has been defined as relapse of HRS more than once within 72 hours after treatment discontinuation.[54] These patients usually require retreatment with terlipressin. Several countries have adopted the use of continuous long-term terlipressin for greater than 30 days in the management of patients with recurrent HRS-AKI until LT,[55] as this treatment regimen has been reported to yield other benefits for these patients.[56,57] Angeli and Gines proposed that long-term treatment with terlipressin and albumin should be equivalent to receiving RRT in the calculation of the MELD score.[49] This would ensure that patients with recurrent HRS-AKI maintain their wait-list priority, as their MELD score most likely will fall with long-term terlipressin use. For quite some time, Australians have also been practicing long-term terlipressin infusions for patients with HRS-AKI while waiting for LT.[53] They do not use a MELD lock system nor equate the use of long-term terlipressin with RRT in the calculation of the MELD score. Rather, they prioritize patients on long-term continuous terlipressin infusion depending on clinical need, response to terlipressin, duration of terlipressin therapy, and functional status.[58] They reported similar renal recovery and survival at 180 days comparable with patients who received LT without HRS-AKI.[59]

Table 3 details the pros and cons of the various strategies to preserve wait-list priority for transplant candidates receiving terlipressin.

Future Directions for Terlipressin Use in Liver Transplant Candidates

Almost all of the randomized controlled trials on the use of terlipressin in the treatment of HRS-AKI were conducted in patients who had HRS-1. However, the newer definition of HRS-AKI[5] proposed by the International Club of Ascites diagnoses HRS-AKI at a lower sCr than HRS-1. Starting treatment of HRS-AKI at a lower sCr may lead to an improved response rate with potential for better posttransplant patient and renal outcomes. As shown by a recent study that used a continuous infusion of terlipressin in transplant wait-listed candidates who were diagnosed using the newer definition of HRS-AKI, a complete response rate of 64% was observed,[32] which is significantly higher than the complete response rate of 39% in patients who had HRS-1 and received bolus injections of terlipressin.[17] These 2 aspects of terlipressin use in HRS-AKI patients will need to be confirmed in future studies. Furthermore, the published studies on terlipressin use in HRS-AKI were not powered to assess survival, as HRS-AKI is a rare disease. However, with HRS-AKI diagnosed at a lower sCr, more patients with renal dysfunction will be diagnosed with HRS-AKI, with the potential for sufficient patients to be included in larger studies to assess the effects of terlipressin on survival.

Terlipressin is approved in the United States as a treatment for HRS-AKI, but it is not universally used as the first-line treatment for HRS-AKI owing to cost and financial strain. If cost was removed as a consideration, the use of terlipressin in the appropriate patients on the LT waiting list should not be a difficult decision. However, there is no broad experience on the use of terlipressin for HRS-AKI in the United States owing to high expenses with potential adverse events and no benefits in up to 60% of patients (ie, nonresponders) who receive terlipressin. This is particularly true for patients with a MELD score of at least 35, who are unlikely to respond to terlipressin. Whether these patients should be completely excluded from terlipressin use and directly referred for LT or be considered on an individual basis is an issue that needs to be decided in future policy directions. This is especially relevant for patients with alcoholic cirrhosis who may respond to corticosteroid therapy and recover from their hepatic insult and thus their renal function if supported. Therefore, rather than implementing any of

the policies listed, a task force has been proposed to structure a multipronged approach to solve this dilemma.[51] The task force has proposed leveraging the United Network for Organ Sharing database to model changes in MELD and wait-list priority while simultaneously setting up a registry of patients with HRS-AKI treated with terlipressin to measure utilization and outcomes. The results will be compared with patients with HRS-AKI who do not receive terlipressin to try to learn about barriers to terlipressin use. The task force also plans to assess patient and provider attitude toward the impact of terlipressin use in the transplant wait-listed population. Once objective data are obtained, the task force will be in a better position to advise how best to handle terlipressin responders and their wait-list priority.

Summary

HRS is the most severe form of AKI in patients with decompensated cirrhosis with high mortality rates even after effective treatment using vasoconstrictors and albumin. Vasoconstrictor treatment improves renal outcomes but has no survival advantage at 90 and 180 days. LT remains the definitive treatment for HRS-AKI. Current available data favor treating HRS-AKI with vasoconstrictors with the aim of recovering renal function before LT to ensure the best outcomes for these patients. Different strategies have been proposed to protect the LT wait-list position of patients who have successfully achieved HRS reversal. However, recommending any policy change in North America is premature for HRS-AKI responders without real-world evidence. Preliminary data suggest that terlipressin responders do not have significant delays in receiving a LT.[32] Additionally, even a delay in receiving a LT did not appear to impact post-LT outcomes.[44] With the newer HRS-AKI diagnostic criteria introduced 10 years ago,[5] the number of patients who have been diagnosed with HRS-AKI compared with the previous 2007 criteria has doubled,[60] and patients are being diagnosed earlier in the course of HRS-AKI. This means that HRS-AKI therapy can be started earlier in the disease course and likely will improve outcomes, which can be the focus of future studies. Future prospective data on the response of real-world patients to terlipressin, recurrence rates, and transplantation rates will help to settle the controversy of whether to use terlipressin in LT candidates. Until then, current data suggest that treating and reversing HRS-AKI in wait-listed patients has more advantages than disadvantages.

Disclosures

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