EDITORIAL

Treatment of Hepatorenal Syndrome-Acute Kidney Injury: Advances Made but Challenges Remain

Hepatorenal syndrome–Acute kidney injury (HRS-AKI) is common in patients with cirrhosis and liver transplantation remains the definitive therapy for such patients. Vasoconstrictors have been associated with reversal of HRS-AKI. Terlipressin is the most studied drug and has been used for more than 15 years across the globe, except in the United States. Recently, a multicenter trial from North America (CONFIRM) reported a significant benefit in HRS-AKI reversal with terlipressin, following which the Food and Drug Administration has approved its use in the United States.[1] However, the adverse events due to terlipressin are not uncommon and preclude its use in patients with high Model for End-stage Liver Disease (MELD) score and in those with acute on chronic liver failure Grade 3.[2] Noradrenaline, or a combination of octreotide and midodrine have also been reported to have efficacy, while adverse events have been encountered with such therapies. To that end, a comprehensive meta-analysis, particularly considering the recent approval of terlipressin in the United States, was required to assess the comparative efficacy and safety of the various vasoconstrictors in HRS-AKI. In this issue, Singal et al performed a metanalysis that included 16 studies and 1244 patients with HRS-AKI, randomized to an intervention with a vasoconstrictor regimen (mean age 50.3 years, 67.5% males, serum creatinine of 3.07 mg/dL, and MELD score of 30.9) or a placebo or another vasoconstrictor regimen (mean age 54.0 years, 67.4% males, serum creatinine of 3.11 mg/dL, and MELD score of 30.6).[3] All patients received intravenous albumin infusion for volume expansion. The first comparison was between terlipressin and placebo in 7 randomized controlled trials (454 patients) wherein odds of HRS-AKI reversal were 3.3-fold higher with terlipressin but without a benefit on liver transplant (LT) free patient survival. Further, in comparison of Norepinephrine (NE) with terlipressin in 6 randomized controlled trials with a pool of 312 patients, there was similar HRS-AKI reversal rate, LT free survival and serious adverse event (SAE) rate. In contrast, comparing either terlipressin or NE with midodrine and octreotide, there was 91% lower odds of HRS-AKI reversal with the latter combination. Non-responders had higher mean MELD score (29 vs 27.8), $P = .014$ and serum creatinine (3.5 vs 3.1), $P = .027$.

Serious adverse events are known to occur following any of the therapeutic modalities which then are confounded by the serious condition of advanced liver disease. The SAE rate with terlipressin or NE or midodrine/octreotide was similar across the eligible studies.[3] Many of the adverse events, such as pulmonary edema may be precipitated due to precarious fluid balance in cirrhosis with HRS-AKI. Overzealous use of intravenous albumin may also be responsible for fluid overload. The CONFIRM study has highlighted the risk of pulmonary edema in patients treated with terlipressin and albumin.[1,2] However, Asian data have reported a lower incidence of pulmonary overload, possibly due to a lower dose of terlipressin and albumin than the trials while using a bolus regimen.[4,5] In addition, continuous infusion of low dose terlipressin may have prevented decompensation of heart failure, even in those with underlying cardiac dysfunction.[6]

Lastly, although 7 studies in this metanalysis examined baseline patient variables predicting response to treatment, we still do not have adequate clinical or biochemical predictors of terlipressin/NE response in HRS-AKI. It appears that baseline renal function (serum creatinine level) and liver disease severity (MELD score) determine response to vasoconstrictors.[7,8] Use of non-selective beta blockers and diuretics, sepsis, and cholestasis may impair renal function in advanced cirrhosis by reducing effective circulating blood volume, systemic inflammation, or promoting bile salt-related direct tubular damage. In addition, there may be genetic factors, metabolic stress, presence of covert cardiomyopathy, undiagnosed intrinsic renal disease like diabetic kidney disease, and immunoglobulin A nephropathy, which may affect response to vasoconstrictor therapy in HRS-AKI.[8–10]

Firstly, this metanalysis suggests that terlipressin is at least as efficacious as NE in HRS-AKI reversal, although a better transplant-free survival could not be demonstrated with any of the regimens., In addition, use of octreotide and midodrine in combination was less efficacious than either terlipressin or NE. However, there remain several unanswered questions. While LT free survival is not favorably influenced by therapy, it would be important to assess if there are any “protective” renal benefits of such therapy by way of decreased need for renal replacement therapy, rate of simultaneous liver/kidney transplant, or the need for renal transplant post liver transplant. In addition, as there is heterogeneity in dosing, mode of administration, site of administration (intensive care unit vs floor), the criteria for increasing infusion rate or total daily dose of terlipressin or NE, or the mode of continuous infusion vs bolus administration of terlipressin requires more prospective clinical data on response or SAEs in HRS-AKI in different Asian or Western cohorts while adjusting for confounders and baseline clinical characteristics. Lastly, we need robust data on predictors of long-term benefits of response and survival, thus enabling prioritization of patients for liver transplantation in those with cirrhosis and HRS-AKI.

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References

1. Wong F, Pappas SC, Curry MP, et al. Terlipressin plus albumin for the treatment of type 1 hepatorenal syndrome. N Engl J Med 2021;384(9):818–828.
2. Wong F, Pappas SC, Reddy KR, et al. Terlipressin use and respiratory failure in patients with hepatorenal syndrome type 1 and severe acute-on-chronic liver failure. Aliment Pharmacol Ther 2022;56(8):1284–1293.
3. Singal A, Palmer G, Melick L, et al. Vasoconstrictor therapy for Acute kidney injury hepatorenal syndrome: a meta-analysis of randomized studies. Gastro Hep Advances 2023;2(4):455–464.
4. Kulkarni AV, Ravikumar ST, Tevethia H, et al. Safety and efficacy of terlipressin in acute-on-chronic liver failure with hepatorenal syndrome-acute kidney injury (HRS-AKI): a prospective cohort study. Sci Rep 2022;12(1):5503.
5. Arora V, Maiwall R, Rajan V, et al. Terlipressin is superior to noradrenaline in the management of acute kidney injury in acute on chronic liver failure. Hepatology 2020;71(2):600–610.
6. Cavallin M, Piano S, Romano A, et al. Terlipressin given by continuous intravenous infusion versus intravenous boluses in the treatment of hepatorenal syndrome: a randomized controlled study. Hepatology 2016;63(3):983–992.
7. Seo YS, Park SY, Kim MY, et al. Lack of difference among terlipressin, somatostatin, and octreotide in the control of acute gastroesophageal variceal hemorrhage. Hepatology 2014;60(3):954–963.
8. Piano S, Schmidt HH, Ariza X, et al. Association between grade of acute on chronic liver failure and response to terlipressin and albumin in patients with hepatorenal syndrome. Clin Gastroenterol Hepatol 2018;16(11):1792–1800.e3.
9. Premkumar M, Devurgowda D, Vyas T, et al. Left ventricular diastolic dysfunction is associated with renal dysfunction, poor survival and low health related quality of life in cirrhosis. J Clin Exp Hepatol 2019;9(3):324–333.
10. Nazar A, Pereira GH, Guevara M, et al. Predictors of response to therapy with terlipressin and albumin in patients with cirrhosis and type 1 hepatorenal syndrome. Hepatology 2010;51(1):219–226.

Received February 14, 2023. Accepted February 14, 2023.

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Conflicts of Interest:
This author discloses the following: K.R.R.: Advisor: Spark Therapeutics, Novo Nordisk, Mallinckrodt, Genfit; Research support (paid to Institution: Mallinckrodt, Sequana, Grifols, BioVie, BMS, Intercept, Exact Sciences, HCC-TARGET, NASH-TARGET. The remaining author discloses no conflicts.

Funding:
The authors report no funding.

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2772-5723
https://doi.org/10.1016/j.gastha.2023.02.005