Title: Terli or Not Terli: Examining the Role of Terlipressin for Reversal of HRS-AKI

Presenter:
Benjamin Herrmann, PharmD
PGY1 Pharmacy Resident
UPMC Presbyterian

Date: 04/05/2023

Learning Objectives:
1. Define hepatorenal syndrome and its pathophysiology
2. Describe the current treatment options for hepatorenal syndrome
3. Discuss the evidence for the use of terlipressin in hepatorenal syndrome-acute kidney injury
4. Identify an appropriate place in therapy for terlipressin

Abstract:
Hepatorenal syndrome is a serious complication of advanced liver cirrhosis. The hallmark of hepatorenal syndrome (HRS) is peripheral arterial/splanchnic vasodilation, coupled with intense renal vasoconstriction leading to decreased renal perfusion. This decreased renal perfusion leads to a potentially reversible acute kidney injury (AKI). However, when left untreated, this disease is associated with a mortality rate of nearly 50% within 2 weeks up to 80% by 30 days. The only curative treatment for hepatorenal syndrome is liver transplant; however, treatment with norepinephrine in combination with albumin has been our historically preferred treatment for HRS in patients unable to receive transplants or as a bridging therapy to transplant. Terlipressin, a vasopressin analogue prodrug, recently received approval from the FDA for the indication of HRS reversal. While current guidelines recommend the use of terlipressin for HRS reversal, questions still exist about the safety and efficacy of the medication. More data is needed to better identify an optimal place in therapy and monitoring parameters for this newly-approved therapy.

References:

1. Greenberger NJ. Hepatorenal Syndrome. In: Greenberger NJ, Blumberg RS, Burakoff R. eds. CURRENT Diagnosis & TreatmentL Gastroenterology, hepatology, & endoscopy. 3e New York, NY: McGraw Hill; 2016. https://accessmedicine.mhmedical.com/content.aspx?bookid=1621&sectionid=105187091 (Accessed 2023 February 1)
2. Mukhtar NA, Khalili M. Liver Disease. In: Hammer GD, McPhee SJ. Pathophysiology of disease: An introduction to clinical medicine. 8e New York, NY: McGraw Hill; 2019. https://accesspharmacy.mhmedical.com/content.aspx?bookid=2468&sectionid=198222693. (Accessed 2023 February 1)
3. Erly B, Carey WD, Kapoor B, et al. Hepatorenal syndrome: a review of pathophysiology and current treatment options. *Semin Intervent Radiol*. 2015;32:445-454.
4. Flamm SL, Brown K, Wadei HM, et al. The current management of hepatorenal syndrome – acute kidney injury in the United States and the potential of terlipressin. *Liver Transplant.* 2021;27:1191-1202.
5. Biggins SW, Angeli P, Garcia-Tsai G, et al. Diagnosis, evaluation, and management of ascites, spontaneous bacterial peritonitis an hepatorenal syndrome: 2021 practice guidance by the American Association for the Study of Liver Diseases. *Hepatology*. 2021;74(2):1014-1038.
6. Wadei HM, Mai ML, Ahsan N, Gonwa TA. Hepatorenal syndrome: Pathophysiology and management. *Clin J Am Soc Nephrol*. 2006:1066-1079.

7. Pichler RH, Swenson ER, Leary PJ, Paine CH. Terlipressin: hopes fulfilled or dashed? *Clin J Am Soc Nephrol*. 2022;17:140-142.
8. Bajaj JS, OLeary JG, Lai JC, et al. Acute-onchronic liver failure guidelines. *Am J Gastroenterol*. 2022;00:1-28.
9. Wong F, Pappas SC, Curry MP, et al. Terlipressin plus albumin for the treatment of type 1 hepatorenal syndrome. *N Engl J Med*. 2021;384:818-828.
10. 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.
11. Boyer TD, Sanyal AJ, Wong F, et al. Terlipressin plus albumin is more effective than albumin alone in improving renal function in patients with cirrhosis and hepatorenal syndrome type 1. *Gastroenterology*. 2016;150:1579-1589.
12. Piano S, Gambino C, Vettore E, et al. Response to terlipressin and albumin is associated with improved liver transplant outcomes in patients with hepatorenal syndrome. *Hepatology*. 2021;73(5):1909-1918
13. Singh H, Jindal A, Sharma MK, Sarin SK. Early versus standard initiation of terlipressin for HRS-AKI in ACLF patients – a randomized controlled trial (ETERLI). *J Clin Exp Hepatol*. 2022;12(2):S29-30.
14. Terlipressin (Terlivaz) package insert. Bedminster, NJ: Mallinckrodt Hospital Products Inc.; 2022 Sept.

Audience Response Questions:

1. Hepatorenal syndrome can best be defined by:
    a. Toxins released from the liver lead to ATN
    b. Peripheral arterial vasodilation and intense renal vasoconstriction leading to decreased renal perfusion
    c. Kidneys' inability to remove hepatotoxins from the blood leading to acute liver failure
    d. Simultaneous use of both nephrotoxic and hepatotoxic medications leading to liver and kidney dysfunction

2. Which is a benefit of using terlipressin over norepinephrine in treatment of HRS-AKI?
    a. Terlipressin can be administered on a general medicine floor while norepinephrine must be given in the ICU
    b. Terlipressin is associated with fewer respiratory and ischemic adverse reactions than norepinephrine
    c. Multiple large randomized controlled trials have shown terlipressin is more effective in reversing HRS-AKI than norepinephrine
    d. None of the above is true, terlipressin should never be used

3. Which of the following is a curative treatment for HRS-AKI?
    a. Norepinephrine + Albumin
    b. Terlipressin + Albumin
    c. TIPS Procedure
    d. Liver Transplant