SGLT2 Inhibitors: A New Dawn for Recurrent/Refractory Cirrhotic Ascites

Yuan Gao1, Lai Wei2, Dorothy Da Zhang3, Yu Chen1 and Bing Hou*1

1Department of Hepatology, Youan Hospital, Capital Medical University, Beijing, China; 2Hepatopancreabiliary Center, Beijing Tsinghua Changgung Hospital, Tsinghua University, Beijing, China; *Xenorn MedInfo Center, Beijing, China


To the editor,

There remains a huge unmet need for treatment of cirrhotic ascites. In this letter, we propose that the sodium-glucose cotransporter-2 (SGLT2) inhibitor may be a promising complement for current therapeutic strategies.

Ascites is the commonest complication of decompensated cirrhosis, and it significantly deteriorates quality of life and shortens survival. Loop diuretics and mineralocorticoid receptor antagonists are the mainstay of pharmacological treatments, but decades of use have brought little survival benefit. Moreover, recurrent or refractory ascites often leads to unplanned re-hospitalization for patients with uncompensated cirrhosis and consequently causes a substantial economic burden.

Renin-angiotensin-aldosterone-system (RAAS) overactivation and a subsequent reduction in urinary sodium excretion are the pivotal mechanisms of ascites formation.1 Thus, the pharmacological treatment aims to achieve a negative sodium balance by promoting natriuresis. By inhibiting the sodium-potassium-chloride cotransporter 2 and then increasing sodium chloride concentration in the luminal fluid of distal convoluted tubule, loop diuretics exert their prominent natriuretic effect during the acute phase of ascites treatment. However, prolonged use of loop diuretics can induce renal adaptation, which increases reabsorption of sodium in the distal segments of the nephron and results in a gradual decline in net sodium excretion. With reduced sodium excretion, the diuretic effect of loop diuretics would be greatly attenuated, which is termed “braking phenomenon.”2 Consequently, diuretics acting on distal nephron segments, such as loop diuretics or mineralocorticoid receptor antagonists, frequently fail during the treatment of advanced ascites, even in patients with normal renal function. Given the above, novel treatments for recurrent/refractory cirrhotic ascites are needed.

SGLT2 inhibitors have shown promise as a treatment of ascites. They belong to a class of oral medications used to treat type 2 diabetes that act through inhibiting the reabsorption of glucose and sodium in the proximal convoluted tubule, which results in a significant decrease in sodium concentration in distal nephron segments.4 Consequently, SGLT2 inhibitors may also be suitable for treating recurrent/refractory cirrhotic ascites.5

More seriously, the dose-dependent hyperkalemia and gynecomastia may lead to drug dose reduction or discontinuation. Notably, in ascitic condition, sodium reabsorption is increased mainly at the proximal convoluted tubule, which results in a significant decrease in sodium concentration in distal nephron segments.4 Consequently, SGLT2 inhibitors may facilitate normalization of RAAS (Table 1). If so, such drugs would complement current pharmacological treatments for ascitic patients. Given that the benefits of SGLT2 inhibitors in patients with advanced heart failure are independent of glycaemia, they merit further investigation in patients with cirrhotic ascites regardless of the presence or absence of comorbid diabetes.

Safety is always the first priority when a new class of agents is introduced into the treatment of cirrhotic ascites. Current data show that the risks of liver dysfunction or hypoglycemia associated with SGLT2 inhibitors in patients without diabetes are not greater than those associated with placebo.7 Moreover, hepatic impairment has no appreciable impact on the pharmacokinetics of SGLT2 inhibitors.10 Initial dip of estimated glomerular filtration rate and mild blood pressure drop observed with SGLT2 inhibitors have raised concerns of hepatorenal syndrome, but such changes are not found to alter the state of RAAS.6

Abbreviations: RAAS, renin-angiotensin-aldosterone-system; SGLT2, sodium-glucose cotransporter-2.

*Correspondence to: Bing Hou, Xenorn MedInfo Center, No. 30 Xueyuan Road, Beijing 100083, China. ORCID: https://orcid.org/0000-0002-4613-1095. Tel/Fax: +86-10-88443312, E-mail: hou_bing@hotmail.com

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It is encouraging that regression of ascites and lower extremity edema have been reported after treatment of patients with cirrhosis and comorbid diabetes with SGLT2 inhibitors without obvious adverse events. The correction of hyponatremia observed in these case reports suggests that SGLT2 inhibitors may facilitate normalization of RAAS (Table 1). If so, such drugs would complement current pharmacological treatments for ascitic patients. Given that the benefits of SGLT2 inhibitors in patients with advanced heart failure are independent of glycaemia, they merit further investigation in patients with cirrhotic ascites regardless of the presence or absence of comorbid diabetes.

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Letters to the Editor
Although SGLT2 inhibitors seem unlikely to trigger hepatorenal syndrome in absence of an aggravation of RAAS status, an exploratory study is need to investigate their effects on sodium excretion and neurohormonal changes among patients with cirrhotic ascites. As SGLT2 inhibitors prompt urinary glucose excretion, there may be concerns of an increased risk of urogenital infection in cirrhotic patients, who are generally immunocompromised. Given that the amount of glucose excreted following administration of SGLT2 inhibitors is dependent on the plasma glucose level, this uncommon complication might be less pronounced in cirrhotic patients, especially those with normal plasma glucose level. Nevertheless, the issue should be taken into account in future clinical trials.

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Conflict of interest

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Author contributions

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