Renin inhibition in portal hypertension: Novel indication beyond cardiovascular diseases?

Aliskiren {2(S),4(S),5(S),7(S)-N-(2-carbamoyl-2-methylpropyl)-5-amino-4-hydroxy-2,7-diisopropyl-8-[4-methoxy-3-(3-methoxypropoxy) phenyl]-octanamide hemifumarate}, a direct renin inhibitor, is recognized for its efficacy in lowering systemic blood pressure.1 The vasodilatory effect of aliskiren can be related to the upregulation of endothelial nitric oxide synthase (NOS) expression by enhanced NOS mRNA stability, as well as by post-transcriptional modification.2

In liver cirrhosis, the formation of regeneration nodules and fibrotic bands in response to acute and chronic liver injuries increase intrahepatic vascular resistance. Enhanced intrahepatic vascular tone also is associated with the phenomenon. As a result, portal venous flow is hindered from efficiently entering the liver. To divert the stagnant portal blood flow, an array of portosystemic collateral vasculature gradually develops. At the same time, the peripheral and splanchnic vasodilatation leads to a reduced total peripheral vascular resistance, increased splanchnic blood flow and portal blood flow, an array of portosystemic collateral vasculature gradually develops. This is the so-called hyperdynamic circulatory state. Moreover, the reduced total vascular resistance elicits an inadequate intravascular volume, which triggers the activation of the renin-angiotensin-aldosterone axis. Excessive sodium and water retention subsequently can induce edema, ascites formation, hepatic hydrothorax, and even hepatorenal syndrome.3 Throughout the entire process, an uneven distribution of NOS expression and NO synthesis has been noticed. NO, an endothelium-derived potent vasodilatory substance, is a major contributor to splanchnic and systemic vasodilatation, which leads to the hyperdynamic circulatory syndrome in portal hypertension.4 Meanwhile, a functional deficit or decreased NO synthesis in the intrahepatic microcirculation is also noted. Intrahepatic vasorelaxation in response to receptor-dependent and -independent endothelial NOS agonists, such as acetylcholine and calcium-ionophore A23187, is significantly reduced.2 Endothelial NOS activity is also found to be decreased in experimental liver cirrhosis.6 It has also been reported that a markedly enhanced intrahepatic vasoconstrictile response to angiotensin II was found in cirrhotic rats.8 On the other hand, NO also participates in vascular responsiveness in portosystemic collateral vascular bed. Acute NOS inhibition increases vascular tone and suppresses acetylcholine-induced dilatations of portosystemic collaterals in portal hypertensive rats.9 The long-term blockade of NO synthesis further increases portosystemic collateral resistance and alleviates portal-systemic shunting.9 Additionally, NO may be involved in the development and dilatation of collaterals. It has been suggested that the process of portosystemic collateralization involves both neoangiogenesis and opening of preexisting venous channels.10 For both events, NO is of crucial importance.

Since liver cirrhosis and portal hypertension are often accompanied by renin-angiotensin-aldosterone axis activation, the potential effect of renin inhibition deserves further clarification. To address the real contribution of aliskiren in this disease, its influences on different vascular bed are to be concerned. In the current study, Hsieh et al11 revealed that aliskiren decreased portal pressure in cirrhotic rats, which is attributed to the amelioration of the angiotensin II-induced intrahepatic vasoconstriction. Furthermore, the intrahepatic vasodilatory response to acetylcholine is improved in cirrhotic rats treated with aliskiren. This sophisticated work reveals that low-dose aliskiren treatment (20 mg/kg/day) for 2 days reduced portal pressure and intrahepatic resistance, whereas systemic blood pressure was not significantly decreased. This is quite noteworthy since excessive blood pressure reduction could be harmful in cirrhotic patients with hyperdynamic circulation with systemic hypotension. In a recent survey, Chang et al found that aliskiren decreased portal pressure in PVL rats12 as well as in cirrhotic rats.13 Aliskiren significantly decreased SMA resistance and increased SMA and left adrenal vein (the most prominent intra-abdominal portosystemic collateral vessel in rodents) eNOS mRNA expression. In addition, using an in situ portosystemic collateral vascular perfusion model, preincubation of aliskiren attenuated the collateral vasoconstrictive effects of AVP.12 Apart from the well-known systemic arterial blood pressure lowering effect, indication of a portal hypotensive effect of aliskiren is encouraging. Portal pressure is determined by portal venous inflow, intrahepatic vascular resistance and portosystemic collateral vascular resistance. Taking the results of current and recent investigations into consideration, it can be inferred that aliskiren reduces portal pressure via intrahepatic resistance and portosystemic collateral vascular resistance reduction.
Another potentially beneficial effect of aliskiren is the alleviation of fibrosis. Aliskiren ameliorates renal inflammation and fibrosis induced by unilateral ureteral obstruction in mice. The activation of the renin-angiotensin-aldosterone axis, especially angiotensin II, increases transforming growth factor-β (TGF-β) and α-SMA expression in kidney (TGF-β is a key factor involved in the progression of interstitial fibrosis elicited by renal injury). It is also worth noting that in animal models with nonalcoholic steatohepatitis, angiotensin II type 1 receptor blocker inhibits activation of hepatic stellate cells, oxidative stress, expression of TGF-β, expression of collagen genes, and liver fibrosis. It remains unclear as to whether direct renin inhibition also exerts antifibrotic effect and further investigation is necessary.

In conclusion, the latest animal studies demonstrate that aliskiren exerts its portal hypotensive effect via reducing intrahepatic and portosystemic collateral vascular resistance, which has not been proved in the past. Nevertheless, caution should be exercised when extrapolating the results of animal experiments and their associated data into clinical practice. Further study is essential to address the efficacy of aliskiren and its safety in a clinical setting.

Hui-Chun Huang
Faculty of Medicine, National Yang-Ming University
School of Medicine, Taipei, Taiwan, ROC

Division of Gastroenterology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC

Corresponding author. Dr. Hui-Chun Huang,
Division of Gastroenterology,
Department of Medicine, Taipei Veterans General Hospital,
201, Section 2, Shih-Pai Road, Taipei 112, Taiwan, ROC.
E-mail address: hchuang2@vghtpe.gov.tw

References


