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Commentary

Renin-angiotensin-aldosterone system in cirrhosis: There's room to try!

In liver diseases, the role of the renin-angiotensin-aldosterone system (RAAS) has been extensively studied. It is well known that in cirrhosis, RAAS activates as a compensatory response to the systemic and splanchnic arterial vasodilation, leading to renal water and sodium retention and therefore contributing to the increase in portal blood flow. Moreover, angiotensin II enhances intrahepatic resistance by promoting the proliferation and contraction of hepatic stellate cells and inducing the profibrogenic processes in the liver [1]. The increase of portal blood flow and intrahepatic resistance due to the activation of RAAS eventually participates in the onset of portal hypertension, indicating the role played by this system in the development of the complications of cirrhosis.

At present, non-selective beta-blockers are the main pharmacological therapy available for the long-term treatment of portal hypertension whenever a hyperdynamic circulation characterized by high cardiac output and low peripheral vascular resistance has developed [2,3]. However, a significant proportion of patients fail to achieve an optimal response or are not eligible for treatment [4], therefore new therapeutic strategies should be implemented and RAAS is potentially an optimal target. In fact, several experimental and clinical studies have evaluated the effect of RAAS inhibitors on portal pressure, but the results are not univocal. The meta-analysis by Tandon et al. [5] showed that treatment with angiotensin II receptor blockers (ARBs) or angiotensin converting enzyme inhibitors (ACEIs) results in a reduction of hepatic venous pressure gradient (HVPG), which is significant only in patients with Child Pugh A cirrhosis. This suggests that while these drugs could be useful in the early stages of the disease, they may lose their efficacy in the more advanced stages of cirrhosis, when it is unlikely that their hemodynamic and antifibrotic effects are able to hinder the severe alterations already established (Fig. 1). Emerging evidences address the role of a local intrahepatic RAAS, that seems to be particularly relevant at earlier stages of cirrhosis [1], which may explain the different effects of ARBs and ACEIs according to the disease progression. Moreover, in addition to the "classical" axis of the RAAS, an alternate axis has been characterized, which includes ACE2, a structural homologue of ACE, its product angiotensin-(1–7) and the Mas receptor, whose effects counterbalance those mediated by the classical axis, e.g. inducing vasodilation and counteracting fibrogenesis [6]. This parallel axis, which seems to have a secondary role in physiology, may be particularly important in a pathological condition such as cirrhosis [7]. Since evidences suggest that ARBs and ACEIs not only inhibit the classical axis, but also stimulate the activity of the alternate RAAS axis [8], the effects of RAAS blockers on the ACE2-angiotensin-(1–7)-Mas arm in liver diseases need further evaluation. Indeed, in advanced cirrhosis, an upregulation of ACE2 in the splanchnic vascular district [7] may promote vasodilation, further triggered by RAAS blockers, and increase portal venous inflow. Nonetheless, in patients with evidence of advanced liver damage, the use of blockers of RAAS should be carefully evaluated, since they could be responsible for severe hypotension and acute renal failure.

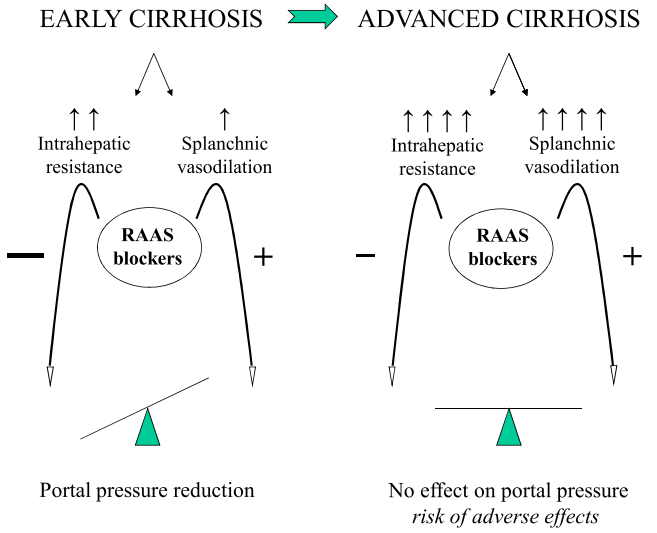

Fig. 1. RAAS blockers may have a different effect on portal pressure along the hemodynamic changes characterizing 'early' (compensated with/without varices) vs 'advanced' (decompensated or further decompensated) cirrhosis.

In this context, it has been hypothesized that a genetic component related to RAAS activity may affect the progression of chronic liver diseases and the development of the related complications. An insertion/deletion (I/D) polymorphism of the ACE gene is associated with different activation of RAAS. Indeed, ACE and angiotensin II levels are higher in DD than II homozygotes while are intermediate in ID heterozygotes [9].

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The influence of ACE genotypes on the evolution of fibrosis in hepatic diseases has been investigated in a few clinical studies, still with discordant results, even opposite to what could be expected based on the known RAAS effects [10]. To date only one study evaluated the hemodynamic effects of ACE polymorphism in cirrhosis, showing that patients with esophageal varices and alcoholic cirrhosis had a higher prevalence of the ACE-I allele [11].

In this issue of *Digestive and Liver Disease*, Annicchiarico et al. address the intriguing and novel topic of the impact of ACE gene polymorphism on portal hypertension in liver cirrhosis [12]. They report that patients who carry ACE-I allele had a higher HVPG, an increased prevalence of large gastro-esophageal varices, and had more often previously experienced variceal hemorrhage. These results are of note, even if there are some major limitations in the paper that have been, at least in part, acknowledged also by the authors themselves. First of all, the very limited number of patients enrolled in the study does not provide robust data to draw conclusions in such a multi-faceted and complex subject. It is unlikely that in patients with cirrhosis, ACE gene polymorphism alone might justify so marked differences in HVPG values (18.7 ± 6.4 mmHg in patients carrying ID and II genotypes vs 10.3 ± 6.3 mmHg in DD genotype carriers) and the mean of HVPG is unexpectedly low in DD-patients, considering that most of them (20 out of 24) had gastro-esophageal varices which are likely to develop when HVPG is over the threshold of 10 mmHg [2]. Moreover, their data are not supported by measurements of angiotensin II and aldosterone levels and a longitudinal follow-up would be necessary to challenge the association of the polymorphism with hard clinical endpoints.

On the other hand, despite the aforementioned caveats, this manuscript opens potential new insights on the debated topic of the influence of RAAS blockers on cirrhosis outcome. The association of ACE-hypofunctional polymorphism with the severity of cirrhosis at presentation apparently seems in contrast to the assumed beneficial effect of ACEIs or ARBs in this clinical setting. If the results of this study are confirmed in future large clinical trials, we may speculate that in advanced stages of cirrhosis, the lack of ACE expression due to the ACE-I allele presence becomes determinant in the splanchnic district, where a fully functional ACE2 may be responsible for a vasodilator effect of ACEIs and ARBs in this district. In a much larger cohort of patients than the one of the present study, it would be interesting to conduct a sub-analysis of the effect of these drugs on portal pressure and blood flow in patients with compensated vs decompensated cirrhosis, according to ACE polymorphism.

Conflict of interest

None declared.

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