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Angiotensin II type 1 receptor blockade in early cirrhosis

To the Editor:

We read with great interest the article by Debernardi-Venon and collaborators, evaluating the hemodynamic response and variations in serum markers of liver fibrosis of twelve months' administration of candesartan in Child A/B cirrhotic patients without ascites [1]. The authors found that angiotensin II type 1 receptor (AT1R) blockade induced a significant decrease in portal pressure, assessed as hepatic venous pressure gradient (HVPG), with 25% of the patients showing a decrease greater than 20%. The authors also observed a significant correlation between the reductions in HVPG and serum concentrations of hyaluronic acid. In the aforementioned study, candesartan was well tolerated in compensated cirrhotics with low plasma renin activity. The lack of severe adverse reactions was also observed in a previous report of losartan in preascitic cirrhosis [2]. In our opinion the main strength of this study is the simultaneous evaluation of hemodynamic and antifibrotic effects of AT1R blockade in humans.

AT1R blockers have been used in the treatment of portal hypertension with diverse results. Losartan at doses of 25 mg per day induced a decrease in HVPG equal or greater than 20% in more than 40% of the patients in different studies without serious clinical adverse effects [3–6]. Nevertheless, higher doses of losartan did not achieve a good hemodynamic response but produced a decrease in arterial pressure and glomerular filtration rate in patients with moderate liver disease [7]. Irbesartan at doses of 150 and 300 mg showed a variable hemodynamic response, but induced hypotension and impaired renal function in patients with Child B or C cirrhosis [8–10].

Several factors may affect the effects of AT1R blockers in cirrhosis, including administered doses [11], length of the therapy and degree of liver disease, as the authors observed [1]. In addition, genetic factors may influence the response to these drugs as well. We have found a relationship between the AT1R A1166C polymorphisms and the therapeutic response to losartan in compensated cirrhosis [5]. It would be of great usefulness to analyse AT1R A1166C polymorphism in this population to test these preliminary results.

AT1R blockade may be potentially harmful in advanced cirrhosis, where the renin angiotensin system is activated as an endocrine homeostatic mechanism to maintain arterial pressure in a context of hyperdynamic circulation. In contrast, in patients with early cirrhosis these drugs seem to be well tolerated. Moreover, AT1R blockers have shown inhibition of activated hepatic stellate cells contraction [12] antifibrotic effect [13,14] and natriuretic effect [15] in patients with severe fibrosis or early cirrhosis. These arguments make these drugs good candidates for pharmacological treatment of portal hypertension in patients with early cirrhosis, selected, perhaps, on based genetic profiles.

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