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Midodrine and albumin in decompensated cirrhosis: Down but not out. . .

To the Editor:

We read with interest the study by Solà *et al.* the MACHT trial (midodrine and albumin for cirrhotic patients in the waiting list for liver transplantation) where the authors evaluate the efficacy of midodrine and albumin in patients with decompensated cirrhosis.[1] We congratulate the authors for conducting the sole placebo-controlled trial in this field. The authors conclude that midodrine and albumin (M + A group) did not prevent complications of cirrhosis or improve the survival in decompensated cirrhosis. However, we suggest a note of caution when interpreting the results.

The most important limitation is the fact that most patients did not receive the experimental treatment for a sufficient duration (overall median, 80 days; midodrine and albumin group median, 63 days). In fact, most of the study population was transplanted at a median of 42 days and only 9 patients received the study drugs for a duration of 1 year. Also, just 58% of the patients in the midodrine/albumin group received the maximum dose of midodrine (30 mg/day), while 42% received a lower dose (15 mg/day) during the study. This led to a suboptimal increment in mean arterial pressure. We have previously demonstrated a significant increase in mean arterial pressure, decrease in plasma renin activity and better control of ascites after 1 month of midodrine therapy in 40 patients with refractory/recurrent ascites.[2] In this study, patients with refractory/recurrent ascites were administered midodrine at a dose of 7.5 mg thrice daily.[2] In another recent study in 78 patients with refractory ascites, there was better control of ascites and a significant increase in mean arterial pressure with a mean dose of 12.5 ± 2.5 mg/day of midodrine.[3]

The authors also conclude that there were no significant differences in the probability of developing complications of cirrhosis during the study period. Although associated with a minor clinical impact, the current study did find that the episodes of hyponatremia and renal failure were more severe in patients in the placebo group compared to the M + A group. The mean peak serum creatinine during episodes of renal failure was 1.2 ± 0.3 *vs.* 1.5 ± 0.4 mg/dl in patients from the M + A group and placebo group, respectively ($p = 0.01$). Although they defined the renal failure as an increase in serum creatinine ≥50% with respect to baseline values, with a final value ≥1.5 mg/dl, yet many of the patients in the placebo group are likely to meet the revised criteria of acute kidney injury for diagnosing renal failure.[4] Similarly, the mean trough serum sodium concentration during hyponatremia episodes was 134 ± 3 *vs.* 129 ± 5 mEq/L in patients from the M + A group and placebo group, respectively ($p = 0.04$).

Interestingly, the findings of the current study are in contrast to the recently published ANSWER trial (The human albumin for the treatment of ascites in patients with hepatic cirrhosis).[5] Serum albumin levels in the current study were unchanged between the treatment and placebo groups, whereas in the ANSWER trial there was a significant increase in mean serum albumin concentration from a baseline concentration of 3.1 g/dl to about 4 g/dl within 1–2 months with no change in the standard care group. It appears the dose of albumin was adequate to suppress the renin-angiotensin-aldosterone system, but was inadequate to bring about significant changes in various complications and mortality.

While the authors have correctly performed liver transplantation in decompensated cirrhosis, the study design of this trial does not permit the conclusion of the authors because of the confounding caused by the performance of liver transplantation. In fact, the results of the study could be different in other settings, such as in centers with longer liver transplant waiting list time or in patients not eligible for liver transplantation. Also, the large number of 'dropouts' (those who underwent liver transplantation) suggest other options such as the competing risk approach analysis (considering liver transplant as a competing risk for complications of cirrhosis or death) could lead to more reliable interpretations.

Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2018.11.008.

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