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

To the Editor:

We would like to thank the authors for their interest in our study. The main conclusion of our trial was that treatment with midodrine and albumin, in patients with cirrhosis and ascites on the waiting list for liver transplantation (LT), was neither associated with a decrease in the incidence of complications of cirrhosis nor with improved survival.[1] We agree with Singh *et al.* that this conclusion should be considered in the context of the specific characteristics of our study, which we clearly indicate in the discussion of our manuscript: i) patients awaiting LT, and ii) a specific dose and duration of treatment.

Although our study was designed for long-term treatment, overall median duration of treatment was 80 days because of a high rate of transplantation in both groups. First, this reflects the difficulty of performing interventional studies in the population of patients on the waiting list for LT. Nonetheless, we considered that patients awaiting LT were an ideal target population as they could be the group that would benefit most from a treatment that could improve the natural history of the disease as a bridge to LT. Second, considering the duration of treatment in our study and the recently published results of the ANSWER trial,[2] we agree that our results do not completely rule out a possible benefit of long-term treatment with albumin in the entire population of patients with cirrhosis. However, we believe that our findings suggest that treatment should not be recommended to those patients with cirrhosis, either on the waiting list or not, in whom treatment duration is expected to be short.

In our study, treatment was administered until LT or death. In addition, there were no significant differences in the percentage of patients transplanted in both groups and study treatment was not associated with the probability of transplantation in the univariate analysis. Therefore, we considered that a competing risk analysis was not necessary in this setting and that it would not have changed the final results.

With respect to midodrine, in our trial this drug was administered at the recommended dose and schedule, which is starting at a low dose and increasing the dose based on changes in mean arterial pressure to a maximum of 30 mg/day. In fact, in the studies cited in this letter,[3,4] midodrine was used at a lower dose than the maximum used in our trial (22.5 mg/day and 12.5 mg/day, respectively). In our opinion, the major drawback of midodrine treatment was not only that the effect of treatment on mean arterial pressure was not strong enough, but that it was not persistent. In keeping with these results, in the study by Singh *et al.* they showed that treatment with midodrine is associated with a significant increase in mean arterial pressure at 1 month; however, there is no significant increase at 3 and 6 months.

In conclusion, in view of our results and the recent findings from the ANSWER trial, an interesting debate has arisen on whether treatment with long-term albumin at higher doses could be beneficial for a specific population of patients with cirrhosis and ascites. We believe that defining the target population of patients with cirrhosis that could really benefit from this treatment should be the major goal of future studies.

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Conflict of interest

PG has worked on advisory boards for: Grifols, Promethera, Martin Pharmaceuticals, Ferring Pharmaceuticals and Novartis. He has received research funding from Mallinckrodt. ES and CS have nothing to disclose.

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.2018.12.026.

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Author names in bold designate shared co-first authorship

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