# *Selected Summaries*

## Albumin administration in patients with cirrhosis: Should it be done routinely?

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SUMMARY

This open-label, investigator-initiated, pragmatic, randomized controlled trial aimed at investigating the effect of long-term administration of human albumin (HA) infusions in patients with cirrhosis and persistence of ascites despite receiving moderate doses of diuretics (i.e. anti-aldosteronic drugs ≥200 mg/day and furosemide ≥25 mg/day). After inclusion in the trial, they were randomized to receive diuretics in the above doses (standard medical treatment, SMT), or SMT and HA (40 g twice weekly for the first 2 weeks, and then 40 g weekly) for up to 18 months. The primary end-point was 18-month mortality. In all, 440 patients were randomly assigned to the 2 treatments. Of these, 431 patients were included in an intention-to-treat analysis (218 in SMT and HA, and 213 in SMT alone). Thirty-eight (17.4%) of the 218 patients in the SMT and HA group, and 46 (21.6%) of the 213 patients in the SMT group died. On time-to-event analysis, the 18-month survival was significantly higher in the SMT and HA group than in the SMT group (Kaplan–Meier estimates 77% *v*. 66%; p=0.028), with a 38% reduction in the mortality hazard ratio (0.62; 95% CI 0.40–0.95). The requirement of paracentesis and the incidence of complications such as spontaneous bacterial peritonitis (SBP), other bacterial infections, renal dysfunction and hepatic encephalopathy were significantly lower in the SMT and HA group. HA infusion was deemed more cost-effective in the overall analysis when compared to SMT alone.

COMMENT

The administration of HA is associated with improvement in outcomes of several specific complications of cirrhosis. Among patients with cirrhosis and SBP, particularly those with serum bilirubin level ≥4 mg/dl or those with serum creatinine ≥1 mg/dl, administration of HA is associated with a reduction in the incidence of type 1 hepatorenal syndrome (HRS) and in mortality.[1] A recent meta-analysis of randomized controlled trials in patients with cirrhosis undergoing large-volume paracentesis for ascites reported HA to be superior to plasma expanders or vasoconstrictors not only in preventing post-paracentesis circulatory dysfunction but also in lowering adverse outcomes related to hyponatraemia and mortality.[2] Therefore, the recent clinical practice guidelines from the European Association for Study of the Liver (EASL) recommend an infusion of HA in patients with cirrhosis who are undergoing large-volume paracentesis.[3] HA is also a part of the standard management protocol for patients with HRS.[3] The mechanisms of the beneficial effects of HA include plasma volume expansion and its anti-oxidant and anti-inflammatory properties.[4] However, the long-term effects of administration of HA in patients with cirrhosis and ascites in the absence of these specific indications are largely unknown.

There have been only 2 previous prospective studies on the impact of HA infusion in the management of decompensated cirrhosis.[5,6] In 1 of these, Gentilini *et al*. followed up 126 patients who received either low-sodium diet and diuretics (*n*=63) or additional HA infusions (25 g/week; *n*=63) for 36 months. The patients in the HA group had a lower cumulative probability of developing ascites (19%, 56% and 69% *v*. 30%, 79% and 82% at 12, 24 and 36 months, respectively) and of hospital readmission

(15%, 56% and 69% *v*. 27%, 74% and 79%, respectively). However, the survival was similar in the 2 groups. In a subsequent study, Romanelli *et al*. randomized 100 consecutive patients with ascites to receive either diuretics alone or diuretics with HA (in a dose of 25 g/week of HA in the first year followed by 25 g/week every fortnight) for a median duration of 84 months. This long-term administration of HA was associated with a net gain of 16 months in mean adjusted survival time, and a reduced rate of re-accumulation of ascites (51% *v*. 94%).[5] However, both these studies had small sample sizes, which precluded a generalized recommendation of routine long-term HA infusion in patients with decompensated cirrhosis.

The ANSWER (The human AlbumiN for the treatment of aScites in patients With hEpatic ciRrhosis) study is an open-label, randomized pragmatic (designed to study the effectiveness of an intervention in a real-life practice setting) trial, which aimed to assess the impact of long-term administration of HA. This multicentre trial, conducted in 33 Italian centres, included patients with cirrhosis who had uncomplicated ascites despite ongoing diuretic treatment; those with refractory ascites, recent complications, prior transjugular intrahepatic portosystemic shunt (TIPS) or liver transplant were excluded. The intervention group was initially given 40 g of albumin twice a week and then weekly infusions of this dose in addition to SMT, while the comparator group received SMT alone. The study included patients irrespective of the cause of liver disease. Importantly, patients with a high Child–Turcotte–Pugh score and high Model for End-Stage Liver Disease score were also included in this study. The mean albumin concentration was <3.5 g/dl, and comparable in the 2 groups. The primary end-point was 18-month mortality, and the secondary end-points were a reduction in paracentesis requirement and in complications of cirrhosis; in addition, a cost-effectiveness analysis of HA administration was also done. Any patient in either group who needed 3 or more paracentesis over a 1-month period were excluded henceforth and their data censored from that point onwards.

In the intervention arm, there were 38 deaths, 19 liver transplants, 6 TIPS and 18 patients underwent 3 or more paracentesis over a 1-month period, whereas in the SMT these numbers were 46, 18, 8 and 42, respectively. The follow-up was shorter in the SMT group (since a higher proportion of these patients required 3 or more paracentesis). On Kaplan–Meier survival analysis, the 18-month all-cause mortality rate, which was the primary end-point, was significantly lower in the patients with albumin infusion. It may be emphasized that the actual difference in mortality rates at the end of 18 months in the 2 groups was quite small (SMT and HA 17.4% [38/218] and SMT 21.6% [46/213]), i.e. a mere 4%—much smaller than the assumed 15% reduction in mortality which the authors used to calculate the sample size.

There was no difference in the requirement of TIPS and liver transplantation between the 2 groups. Serum albumin concentration during the follow-up period was higher and requirement for paracentesis was lower in the intervention arm, with fewer patients in the HA arm developing refractory ascites. The incidence of ascites-related complications, i.e. SBP, non-SBP related sepsis and hepatic encephalopathy, was also significantly lower in the group who received HA. The authors specifically looked at the incidence of variceal bleeding, since some previous anecdotal case series have shown an increase in this complication in patients with decompensated cirrhosis who receive albumin. In the ANSWER trial, the overall incidence of variceal bleeding was comparable in the 2 groups, although the incidence of bleeding secondary to portal hypertensive gastropathy was higher in patients receiving HA. Thus, more data may be necessary on the safety of long-term HA in patients with variceal and portal hypertensive bleeding.

The quality of life, as assessed by the EQ-5D questionnaire and a visual-analogue scale, showed a significantly smaller decline in the HA arm over the period of follow-up. In addition, the administration of HA was deemed more cost-effective than SMT. These calculations included the costs of liver-related hospitalizations, paracenteses and of HA administration. The authors report that the cost of HA administration was counterbalanced by the reduction in the number of hospitalizations for complications of cirrhosis. However, there is no mention whether the cost of travel expenses for weekly infusions or of wages lost because of this were included in the analysis. An overall cost–benefit analysis covering all the direct as well as indirect costs needs to be undertaken before the routine use of HA can be recommended. Moreover, it is unclear whether infusion of smaller amounts of albumin would also be equally effective in preventing the complications of cirrhosis; this needs to be explored in future studies. It may also be useful to study the use of albumin in patients with acute-on-chronic liver failure, a sicker group of patients with increased propensity for infections and a high short-term mortality.[7]

Although this study did show an overall benefit of long-term administration of HA in patients with decompensated cirrhosis, it has some limitations. The predominant cause of cirrhosis (in 338 [78.4%] of the 431 patients analysed) was viral or alcohol. In patients with hepatitis C, oral direct-acting antiviral agents (DAA) have been associated with improvement in overall outcomes, with at least some patients showing recovery from a decompensated disease to a compensated state.[8] Similarly, abstinence from alcohol is associated with improvement in outcomes. The current study enrolled patients before DAAs became available, and it does not provide any details of abstinence. Further, it was an open-label trial, with no placebo being administered to the control group. Thus, subjects in the intervention group were administered HA by nursing personnel either in an outpatient or a home-care setting, and had a contact with healthcare personnel every week; those in the SMT group did not have such contact. Hence, the former group had the advantage of any potential complication being recognized earlier and treated in time. Ideally, the number of healthcare contacts in the 2 groups should have been similar, with the patients in the SMT group also seen as frequently by the healthcare personnel.

Patients in either group who required 3 or more paracentesis per month were taken out of the study and their data were censored from that point onwards. This was, as would be expected, commoner in the SMT arm than in the HA arm. Thus, the dropout rate was higher in the SMT arm, and this may have influenced the results. The patients who dropped out for this reason would have continued to live for a long duration, albeit with frequent need for paracentesis. Whether they should be excluded in an analysis that compares survival in the 2 groups is a moot point.

Other issues relate to the lack of information on whether the patients had the standard recommended daily intake of dietary proteins. The cost-effectiveness analysis in the study assumed that HA cost was reimbursed, which may not be the case in many countries. In India, where 20 g of HA costs around ₹4000, the HA strategy would cost approximately ₹416 000 per year. This is several times the gross national income in India. Thus, this

strategy may not be feasible for routine use for our patients. Though this study analysed data for 18 months of follow-up, once HA treatment is begun, it would need to be continued for life, and hence a longer-term analysis of cost considerations would have been preferable.

In conclusion, despite the benefit of long-term HA administration on the prognosis of patients with cirrhosis who have ascites, these results need to be validated in other populations given the high cost of this treatment. Moreover, cost-effectiveness analyses of long-term HA infusion needs to be done in different settings, particularly in developing countries where the cost of treatment is borne largely by the patients. Future studies should identify subgroups of patients who may benefit the most from this intervention to better target this costly treatment. Till then, recommending long-term albumin infusion to all patients with decompensated cirrhosis may not be justified.

*Conflicts of interest.* None declared

## REFERENCES

1 Sort P, Navasa M, Arroyo V, Aldeguer X, Planas R, Ruiz-del-Arbol L, *et al.* Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med* 1999;**341:**403–9.
2 Bernardi M, Caraceni P, Navickis RJ, Wilkes MM. Albumin infusion in patients undergoing large-volume paracentesis: A meta-analysis of randomized trials. *Hepatology* 2012;**55:**1172–81.
3 European Association for the Study of the Liver. EASL clinical practice guidelines for the management of patients with decompensated cirrhosis. *J Hepatol* 2018;**69:**406–60.
4 Arroyo V, García-Martinez R, Salvatella X. Human serum albumin, systemic inflammation, and cirrhosis. *J Hepatol* 2014;**61:**396–407.
5 Romanelli RG, La Villa G, Barletta G, Vizzutti F, Lanini F, Arena U, *et al.* Long-term albumin infusion improves survival in patients with cirrhosis and ascites: An unblinded randomized trial. *World J Gastroenterol* 2006;**12:**1403–7.
6 Gentilini P, Casini-Raggi V, Di Fiore G, Romanelli RG, Buzzelli G, Pinzani M, *et al.* Albumin improves the response to diuretics in patients with cirrhosis and ascites: Results of a randomized, controlled trial. *J Hepatol* 1999;**30:**639–45.
7 Shalimar, Rout G, Jadaun SS, Ranjan G, Kedia S, Gunjan D, *et al.* Prevalence, predictors and impact of bacterial infection in acute on chronic liver failure patients. *Dig Liver Dis* 2018;pii:S1590-8658(18)30757-6.
8 Gupta S, Rout G, Patel AH, Mahanta M, Kalra N, Sahu P, *et al.* Efficacy of generic oral directly acting agents in patients with hepatitis C virus infection. *J Viral Hepat* 2018;**25:**771–8.

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evaluate the association between self-reported medication adherence

there were 675 deaths over a median follow-up of 6 years. The CKD