

# Long-term albumin administration in decompensated cirrhosis

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Cirrhosis of the liver is one of the common mortality and morbidity cause worldwide. 170,000 individuals die from cirrhosis per year in Europe (1,2). It has a heavy burden on health care costs. Once cirrhosis decompensates, such as ascites, gastrointestinal bleeding, hepatorenal syndrome and encephalopathy, prognosis is poor and median survival time is about 2 years (3,4). There is no sole approach to prevent and/or treat all of the complications. Each complications are treated by various therapeutic strategies individually. Actually, we need overall therapeutic approaches to prevent and/or treat all of the complications, thus improving quality of life and survival, reducing hospital admissions and health care costs.

Hypoalbuminemia, prominent finding of cirrhosis, has various pathophysiological mechanisms on developing complications of cirrhosis such as ascites. Hypoalbuminemia causes ascites formation, not only by reducing plasma oncotic pressure, but also by reducing effective plasma volume (5). Reduced effective arterial volume due to peripheral vasodilation is an important pathophysiological mechanism of ascites formation, causing renal sodium and water retention (6). Therefore effect of human albumin administration might result from blood volume expansion, thus reducing activated vasoconstrictor and sodium retaining mechanisms and improving renal perfusion.

In a multicentre randomised, parallel, open-label, pragmatic trial -Long term albumin administration in decompensated cirrhosis- (ANSWER) by Caraceni et al, about effect of long term human albumin (HA) administration to cirrhotic patients with uncomplicated ascites, was pub-

lished in *The Lancet* in the previous year. This trial was funded by Italian Medicine Agency. It was done in 33 academic and non-academic Italian hospitals. The trial was monitored by an external contract research organisation and overseen by a data safety and monitoring board of physicians not involved in the study. They enrolled the patients with uncomplicated ascites ongoing diuretic treatment with an antialdosteronic drug (at a dose  $\geq 200$  mg/day) and furosemide (at a dose  $\geq 25$  mg/day), stable for 4 days before enrollment. The main exclusion criteria were patients with refractory ascites, transjugular intrahepatic portosystemic shunt (TIPS), active hepatocellular carcinoma, liver transplantation, ongoing alcohol abuse, extrahepatic organ failure and albumin use for the treatment of ascites in the month preceding enrollment. They enrolled 440 patients ongoing standard medical treatment (SMT) (treatment with an antialdosteronic drug at a dose  $\geq 200$  mg/day and furosemide at a dose  $\geq 25$  mg/day). They randomized the patients (1:1) to either SMT or SMT plus HA administration. Twenty percent HA was administered at a dose of 40 g twice weekly for the initial 2 weeks and 40 g weekly thereafter. The patients were assessed monthly for up to 18 months or study interruption or death. At each visit clinical, laboratory, instrumental data (if needed) were collected by the attending physicians. The trial was interrupted when patients underwent transplantation or TIPS, needed 3 or more therapeutic paracenteses per month, or refused to continue in the trial, or because of medical judgement. At the end of the trial 213 patients in SMT group and 218 patients in SMT plus HA group were eligible for intention to treat analysis. The primary endpoint was 18 months mortality.

There were 38 (21.6%) deaths in SMT plus HA group and 46 (17.5%) deaths in SMT group. The 18-month all cause mortality rate was significantly lower in SMT plus HA group than in SMT group. 0.27 deaths per person 18-months (95% CI 0.19-0.37) in SMT plus HA group,

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0.44 deaths per person 18-months (95% CI 0.32-0.80) in SMT group, leading to an incidence rate ratio of 0.61 (95% CI 0.39-0.96;  $p=0.027$ ). Consistently, Patients in SMT plus HA group had a significantly higher 18-month probability survival than patient in SMT group, corresponding to a 38% reduction in the mortality hazard ratio (0.62 [95% CI 0.40-0.95]) see figure 3 on [ncbi.nlm.nih.gov/pubmed/29861076](https://pubmed.ncbi.nlm.nih.gov/pubmed/29861076) Long-term albumin administration in decompensated cirrhosis (ANSWER): an open-label randomised trial. *Lancet* 2018; 391: 2417-29. In the trial univariate and multivariate analysis showed that age, viral cause of cirrhosis, Child-Pugh and Model for End Stage Liver Disease were independent predictors of all cause mortality whereas SMT plus HA was the sole protective factor see figure 4b on [ncbi.nlm.nih.gov/pubmed/29861076](https://pubmed.ncbi.nlm.nih.gov/pubmed/29861076) Long-term albumin administration in decompensated cirrhosis (ANSWER): an open-label randomised trial. *Lancet* 2018; 391: 2417-29.

As secondary outcomes, the SMT plus HA group also had significantly reduced incidence rates of paracentesis (HR 0.33 [95% CI 0.19- 0.58];  $p<0.0001$ ), refractory ascites (HR 0.43 [95% CI 0.29-0.62];  $p<0.0001$ ), spontaneous bacterial peritonitis or other bacterial infections, episodes of renal dysfunction, hepatorenal syndrome type 1, and hepatic encephalopathy grade 3-4, whereas the incidence rate of gastro-oesophageal variceal bleeding was similar in the two groups see figure 7 on [ncbi.nlm.nih.gov/pubmed/29861076](https://pubmed.ncbi.nlm.nih.gov/pubmed/29861076) Long-term albumin administration in decompensated cirrhosis (ANSWER): an open-label randomised trial. *Lancet* 2018; 391: 2417-29. SMT plus HA was associated with a better quality of life and fewer hospital admissions than the SMT group, contributing to a favourable incremental cost-effectiveness ratio. The expected result of long-term HA administration to patients with decompensated cirrhosis is conventionally believed to be a better management of ascites than SMT, as convincingly shown by the ANSWER study. However, and more importantly, it shows that long-term HA treatment also reduces the incidence of potentially fatal com-

plications of end-stage liver disease, ultimately leading to an improved survival. Notably, this therapeutic approach appears to be cost-effective.

Paolo Caraceni et al. attempted to find out whether long-term HA administration might be an overall therapeutic approach for decompensated cirrhotic patients. Their trial's outcomes don't mean that long-term HA administration is an overall therapeutic approach for decompensated cirrhotic patients, but trial's outcomes are striking. This trial might modify HA use from targeting specific complications to a more comprehensive approach aimed at slowing down the progression of decompensated cirrhosis. Long-term HA administration requires the use of health-care services and a careful patient compliance. However, the clinical advantages achieved and the favourable results of cost-effectiveness analysis can justify the implementation of this management strategy. Future research should clarify whether some patient subgroups would benefit most from long-term HA treatment and whether different doses and timing schedules might be more effective than those used in the present study.

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