



Albumin administration for refractory ascites in cirrhotic patients

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A recent article published in *Liver International* reported that long-term administration of albumin to cirrhotic patients with refractory ascites improved survival and reduced inpatient hospitalization (1). In addition to reducing complications associated with liver cirrhosis, such as ascites and spontaneous bacterial peritonitis (SBP), long-term albumin administration also reduced complications such as hepatic encephalopathy and non-SBP infection. These findings indicated that long-term albumin infusion therapy may benefit cirrhotic patients, not only by improving hemodynamics but also by enhancing the scavenging of toxic substances, thereby improving patient prognosis.

Albumin, the most abundant protein in human plasma, has multiple biologic activities. For example, albumin is the main regulator of plasma as oncotic pressure; binds to and transports other biological molecules; has antioxidant, antithrombotic and immunomodulatory activities; and stabilizes endothelial cells (2). Albumin binds to furosemide in blood and transports it to the kidneys, which secrete furosemide into the proximal tubules, the sites of its activity. Albumin can enhance the response to diuretics in cirrhotic patients with hypoalbuminemia (3). Thus, albumin is effective in improving symptoms in cirrhotic patients with ascites. Furthermore, clinical studies have shown the usefulness of albumin administration to cirrhotic patients under some conditions. For example, albumin administration after large volume paracentesis was effective in preventing paracentesis-induced circulatory dysfunction (PICD) (4). A meta-analysis found that albumin supplementation significantly reduced the incidence of PICD, as well as hyponatremia, an independent prognostic indicator in cirrhotic patients (5). Furthermore, albumin

was more effective than volume expanders such as dextran and polygeline, suggesting that the activity of albumin is due to more than its preservation of oncotic pressure (4). To prevent PICD, clinical practice guidelines recommend the administration of 6–8 g of albumin per liter of ascites to remove more than 5 L of ascites (6,7). Moreover, albumin was found to prevent the development of hepatorenal syndrome, a life-threatening complication frequently found after SBP in cirrhotic patients (8). Administration of albumin together with antibiotics was more effective at reducing renal dysfunction in patients with SBP than antibiotics alone (9). Albumin supplementation (1.5 g/kg of body weight at diagnosis and 1.0 g/kg on day 3) is recommended in patients with SBP (7,10). Taken together, these findings indicate that albumin can improve the prognosis of patients with decompensated cirrhosis under specific situations. However, it is unclear whether long-term administration of albumin improves prognosis and prolongs survival in cirrhotic patients.

Clinical studies assessing the effect of long-term albumin administration have shown limited and unclear benefits. One trial found that administration of 25 g albumin per week for 1 year and 25 g every 2 weeks for the following 2 years reduced the recurrence of ascites and readmissions, but did not improve survival (3). However, long-term follow-up of these patients for seven years found that albumin improved transplant-free survival (11). More recently, the large scale randomized ANSWER trial, involving over 400 cirrhotic patients, assessed the efficacy of long-term albumin administration (12). In this trial, administration of 40 g albumin twice weekly for two weeks and 40 g weekly for up to 18 months, together with diuretics, enhanced serum albumin concentration;

reduced liver-related complications, such as SBP, hepatic encephalopathy, hepatorenal syndrome and hyponatremia; and showed survival benefits, with overall 18-month survival rates of 77% in the treated group and 66% in the control group (hazard ratio, 0.62; 95% confidence interval: 0.40–0.95, $P=0.028$) (12). Moreover, long-term albumin administration was more cost-effective than standard medical therapy alone, as the former reduced the need for hospitalization (12). The present study by Di Pascali *et al.* found that administration of 20 g albumin twice weekly (40 g per week) also reduced 24-month mortality rates in cirrhotic patients with refractory ascites (1). In contrast, another recent randomized study found that administration of 40 g albumin every 15 days plus midodrine for one year did not prevent complications of cirrhosis and did not improve the survival of cirrhotic patients (13). These findings suggest that only albumin doses greater than 40 g per week have survival benefit in cirrhotic patients.

However, the limited supply of blood-derived albumin and the potential risk of blood-derived pathogens are unsolved issues in long-term use of albumin. The clinical application of recombinant human albumin has been tested, but its cost effectiveness, biochemical properties and safety remain to be determined (14,15). Further studies are needed to test the clinical usefulness of human recombinant albumin. In such situations, long-term albumin administration may be considered for patients with decompensated cirrhosis in the upper ranks of those awaiting liver transplantation. Studies are also needed to test the effectiveness of albumin administration combined with transjugular intrahepatic portosystemic shunt, which effectively improves portal hypertension and reduces refractory ascites and mortality in cirrhotic patients (16).

Evidence has established the effectiveness of long-term albumin administration. Long-term administration of more than 40 g per week albumin may improve survival in patients with decompensated cirrhosis. Further studies are needed to develop a useful form of recombinant albumin, to optimize dose and administration and to select the most suitable candidates for long-term albumin treatment.

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