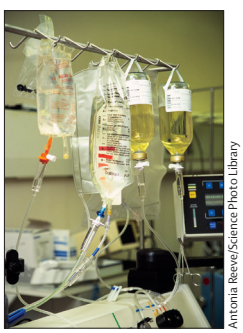
Long-term albumin in cirrhosis: is it the ANSWER?



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Ascites is the most frequent complication of cirrhosis and carries the worst prognosis.[1] Although its development might be delayed by non-selective β-blockers,[2] once ascites develops the patient progresses to refractory ascites, hyponatraemia, and renal dysfunction.[3] This progression is due to worsening of portal pressure and worsening of the vasodilatory–hyperdynamic circulatory state, leading to progressive decrease in effective blood volume, cardiac dysfunction, and renal perfusion.[4] Inflammation from overt or covert (bacterial translocation) infections is a major driver of progression.

Diuretics and large-volume paracenteses (LVP), the most common therapies for ascites, are merely symptomatic treatments because they act downstream of the pathogenic cascade by either counteracting sodium retention or by removing fluid through a needle. Ideal therapies should act upstream of the cascade and would be instituted before the patient develops refractory ascites. Albumin could be one such therapy. Albumin not only increases intravascular volume but also has anti-inflammatory and vasoconstrictive properties.[5]

In *The Lancet*, Paolo Caraceni and colleagues[6] report the findings of the ANSWER trial, a large multicentre, Italian, open-label study that compared weekly intravenous albumin infusions (n=218) with standard medical therapy (SMT, diuretics and LVP as needed; n=213) in patients with decompensated cirrhosis; 68% of patients were men with a median age of 61 years and a median Model for End-Stage Liver Disease score of 12·5, in whom ascites persisted despite diuretic therapy, but who did not meet criteria for refractory ascites.[7]

18-month mortality, the primary outcome, was significantly lower in patients randomly assigned to receive albumin (0·27 [95% CI 0·19–0·37]) than those randomly assigned to receive SMT (0·44 [95% CI 0·32–0·80]). This 38% reduction in mortality was associated with a significant reduction in the number of LVPs required and, importantly, with a reduction of other complications of ascites, such as refractory ascites, hyponatraemia, and hepatorenal syndrome.

Even though a mechanistic explanation for the results is not provided, the ANSWER trial is proof of concept that reversing pathogenic mechanisms upstream of the cascade by improving one or all of the pathogenic mechanisms (effective arterial blood volume, vasodilatation, and inflammation) will offset downstream deleterious effects, not only regarding ascites formation but also regarding complications of ascites.

The main question is whether evidence is sufficient to change clinical practice. This is an important point, particularly given the scarcity and cost of albumin and the fact that synthetic volume expanders do not have albumin's additional benefits.[8] Another less robust, much smaller, single-centre study had also shown lower mortality with chronic albumin than with SMT.[9] However, both are open-label studies. The absence of a placebo group is associated with inherent biases including the intensity of medical supervision and the subjectivity of some of the outcomes, such as the need for LVP. In fact, preliminary results of a multicentre randomised trial showed no differences in survival between patients on albumin (40 g every 15 days) plus midodrine (a vasoconstrictor) compared with a double-placebo.[10]

In whom would chronic intravenous albumin be indicated? The ANSWER trial included only about a third of patients screened; most patients who were excluded were already on intravenous albumin, had refractory ascites, or had hepatocellular carcinoma. Patients with cirrhosis enrolled in the study were heterogeneous; half had ascites as the sole decompensating event, identifying patients with a significantly lower mortality than the other half who had additional decompensating events.[1] Furthermore, a third had hyponatraemia and about 20% had a history of spontaneous bacterial peritonitis or infections, both poor prognostic indicators. Also, although a substantial number of patients had hepatitis C cirrhosis, and because direct-acting antivirals were not available at the time of the study, only a minority received anti-hepatitis C therapy, which is likely to change the course of the disease. As acknowledged by the authors,[6] data on the specific subpopulation of patients that derived the most benefit from albumin are necessary.

What dose and frequency of albumin infusion would be recommended? The ANSWER trial used a dose of 40 g twice weekly for 2 weeks, and then 40 g weekly for up to 18 months. However, doses as low as 25 g every 2 weeks appear to be equally effective.[9]

Cost-effectiveness analysis in the ANSWER trial estimated direct health-care costs and concluded that chronic albumin was cost-effective, mostly because hospital admissions and paracenteses were prevented. However, the economic burden (and quality of life) associated with patients' weekly travel to the study site was not considered and the feasibility of at-home infusions could be further explored.

Importantly, the place of transjugular intrahepatic portosystemic shunt (TIPS), a one-time procedure, compared with chronic albumin in the management of these patients needs to be assessed, ideally in the setting of randomised trials. TIPS, which also acts upstream of the pathogenic cascade by relieving sinusoidal hypertension and by replenishing the intravascular volume, has been shown in a prospective trial to reduce mortality in patients with ascites requiring two LVPs in a minimum 3-week interval.[11]

The ANSWER trial is an important trial, showing that a pathophysiological therapy for ascites results in better outcomes than traditional symptomatic therapy. It raises issues that will stimulate further research and eventually result in a change of practice.

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I have received personal fees from Grifols, Biovie, and Ferring, outside the area of work commented on here.

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