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

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,7 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 colleagues6 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.6 Another less robust, much smaller, single-centre study had also shown lower mortality with chronic albumin than with SMT.7 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
Diabetes mortality in the USA: winning the battle but not the war?

A worldwide epidemic of type 2 diabetes is underway. In 2017, the International Diabetes Federation estimated that 425 million people had diabetes globally, an increase of 274 million since 2000, and that 4 million excess deaths were attributable to diabetes, compared with about 2 million in 2000.\(^1\) \(^2\) Death rates in people with diabetes are higher than in people of similar sex and age without diabetes, and the differences are directly or indirectly attributable to diabetes. Death rates are highest in those who have had diabetes for a long time, and mainly result from its serious vascular complications, which lead to excess deaths especially from cardiovascular disease, renal disease, and infections.\(^1\)

In The Lancet, Edward Gregg and colleagues\(^1\) examined changing rates, relative risk, and causes of death in people with and without diagnosed diabetes in the USA from 1988 to 2015. In keeping with global trends, the number of people diagnosed with diabetes in the USA tripled during this period, reaching 21.1 million or 9.1% in the population aged 20–79 years by 2010–15. Among people with diabetes, the number of deaths increased from 278,401 to 658,479 per year. The main conclusion of the Article is that age–sex adjusted death rates fell consistently both in people with and without diabetes, but the rate of decline was greater in those with diabetes than without. Mortality rates in people with diabetes declined by 20.1% per decade versus 10.7% in those without, more so in men than in women, but still remained more than 60% higher in those with diabetes. The relative risks