Elsevier Editorial System(tm) for Journal of Hepatology

Manuscript Draft

Manuscript Number: JHEPAT-D-18-01644

Title: MACHT - a re-evaluation of the role of albumin infusions for advanced liver disease

Article Type: Invited Editorial

Section/Category: Clinical portal hypertension

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MACHT - a re-evaluation of the role of albumin infusions for advanced liver disease

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No conflict of interests

No financial support was provided for this piece of work

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Albumin has long been an important option in the treatment of patients with cirrhosis and ascites. Albumin improves circulatory function; and is recommended for use in hepatorenal syndrome, spontaneous bacterial peritonitis, as well as in preventing post paracentesis circulatory dysfunction following large volume paracentesis (LVP)[2]. Albumin also has beneficial immunomodulatory and endothelial effects[3]. Therefore many centers use albumin as an unproven, but seemingly effective agent as an adjuvant to chronic diuretic therapy for ascites in patients with cirrhosis. In particular, patients regarded to have the greatest potential benefit are those with chronic renal insufficiency who tolerate diuretic therapy poorly. Midodrine, an α-adrenergic agonist, has been shown to improve systemic and renal hemodynamics in patients with ascites[4]. However a meta-analysis of 10 trials using midodrine to treat ascites showed no beneficial effect on survival and when used as an alternative to albumin in LVP, the mortality was higher for midodrine than albumin[5]. Furthermore the addition of the somatostatin analogue, octreotide to midodrine was not superior to albumin in preventing ascites recurrence compared to albumin[6].

Albumin use is not without controversy[7]. Two different conclusions have been reached by separate groups conducting meta- analyses for use of albumin in large volume paracenteses. One group concluded that there was insufficient evidence that albumin infusion after LVP significantly lowered mortality in hepatocellular carcinoma-free patients with advanced liver disease[8] and the other that albumin reduced morbidity and mortality compared with alternative treatments[9]. Moreover, large scale trials in critical care patients without liver disease have shown no survival benefit[10, 11]. Indeed many countries experience albumin shortages. Albumin is many times more expensive than other intravenous fluids and the possibility of a transmission of diseases remain. Therefore an evidence-based re-evaluation of the role of albumin in cirrhosis is required. The MACHT trial (**m**idodrine and **a**lbumin for **c**irr**h**otic patients in the waiting list for liver **t**ransplantation) in the current issue of this *Journal*, the recently completed ANSWER (The human Albumin for the treatmeNt of aScites in patients With hEpatic cirrhosis)[12] and soon to complete ATTIRE[13] will hopefully guide clinical practise.

The MACHT trial conducted by Sola et al at the centre with the best record of performing clinically important trials in advanced liver disease, showed that in patients with cirrhosis awaiting liver transplantation, treatment with midodrine and albumin (40g every 2 weeks) slightly suppressed the vasoconstrictor activity, but neither prevented complications of cirrhosis nor improved survival. This was a double blinded placebo controlled trial using opaque bags and intravenous sets to administer albumin or placebo. However, only 9 patients were treated for the entire year and the median length of treatment was 80 days. This demonstrates how challenging these studies are, in particular "natural history" studies in liver transplant candidates as transplantation frequently interrupts the

course of the patients' disease. Therefore the results of this important study should be considered in light of these qualifications.

How should we interpret the findings that treating decompensated cirrhosis patients on the waiting list for liver transplantation with albumin and midrodine neither reduced complications of cirrhosis nor improved survival? Certainly, given their notable achievement with regard to blinding, midodrine and albumin should not be prescribed for patients with a likely 3 month or less wait on the transplant list. However the ANSWER trial did demonstrate a survival benefit with a treatment regimen of 40g of albumin weekly rather than every two weeks[12]. The MACHT authors detected suppression, but not normalization, of the activity of the renin-angiotensin-aldosterone system and perhaps a greater dose of albumin or longer duration of treatment is required to benefit patients. It should be noted that the control group in ANSWER received no fluid or weekly medical care introducing an inherent bias in intensity of medical supervision that was not the case in this study. The forthcoming PRECICIOSA[14] trial (Effects of Long-Term Administration of Human Albumin in Subjects With Decompensated Cirrhosis and Ascites) in which the treatment arm will receive 1.5 g/kg body weight albumin (maximum 100 g per subject) every 10 ± 2 days may clarify this; although this will not be a blinded placebo controlled trial. The difficulties for patients attending weekly for outpatient albumin therapy will also need to be addressed in future trials and perhaps community-based infusions may be possible.

In conclusion, this is one of an ongoing series of extremely important and well-conducted randomized clinical trials from The Barcelona Liver Unit. This study demonstrates that 40g albumin every 2 weeks had no clinically important benefit in contrast to the recent unblinded ANSWER trial which administered albumin weekly. Remarkably for a therapy first administered in 1941[15], we are still uncertain of its exact role in clinical care but these recent studies have stimulated huge interest that will lead to improvements in management of patients with advanced cirrhosis.

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