OTHER

Position paper

AISF: Italian Association for the Study of the Liver (*Associazione Italiana Studio del Fegato*); **SIMTI**: Italian Society of of Transfusion Medicine and Immunohaematology (*Società Italiana di Immunoematologia e Medicina Trasfusionale*)

AISF-SIMTI position paper on the appropriate use of albumin in patients with liver cirrhosis: a 2020 update

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Since the publication in 2016 of the recommendations on the appropriate use of albumin in patients with liver cirrhosis endorsed by the Italian Association for the Study of the Liver (AISF) and the Italian Association of Transfusion Medicine and Immunohematology (SIMTI)[1,2], a considerable amount of pathophysiological and clinical data have been collected on the long-term administration of human albumin in decompensated cirrhosis. Considering the potential impact of these novel results on daily clinical practice, which will likely lead to an increase in the demand for human albumin, and taking into account the limited availability of this blood product, the two scientific associations nominated a panel of experts to review the available clinical literature and produce new practical clinical recommendations for the long-term use of human albumin in patients with decompensated cirrhosis.
The level of evidence and strength of recommendation were judged according to the Grading of Recommendations Assessment Development and Evaluation (GRADE) system[3]. The strength of the evidence has been classified into three levels: high, moderate, and low quality, while that of the recommendation has been divided into two: strong and weak. Where there is no clear evidence, the recommendations are based on the consensus advice of the writing committee and the expert opinion(s) reported in the literature.

BACKGROUND AND RATIONALE

The current medical management of decompensated cirrhosis is based on the sum of therapies used to prevent or treat each specific complication of the disease. Thus, there is an unmet need for a more comprehensive therapeutic strategy able to modify the natural history of the disease by preventing the development of additional complications, organ dysfunction and acute-on-chronic liver failure (ACLF), thus reducing hospital admissions and health care costs, and improving quality of life and survival.
The use of mechanistic treatments able to interrupt the pathophysiological cascade responsible for the clinical manifestations of decompensated cirrhosis represents an ambitious approach. In the complex network of many interacting and redundant pathophysiological pathways that underly decompensated cirrhosis[4], a mechanistic treatment could only be effective if it were able to silence a "core" mechanism, usually located upstream in the cascade of events, or to antagonise multiple steps, usually located further downstream, by acting alone or in combination with other agents[5].
Based on its oncotic and non-oncotic properties, besides promoting plasma volume expansion, human albumin could simultaneously antagonise several other

pathophysiological alterations of decompensated cirrhosis by binding damaging molecules, modulating inflammation and immune responses, exerting anti-oxidation, improving cardiac function, and restoring endothelial integrity[6]. Therefore, in a pathophysiological perspective, prolonged human albumin administration has been proposed as a multi-target disease-modifying treatment for the management of patients with decompensated cirrhosis[5].

CLINICAL EVIDENCE

Long-term human albumin administration to patients with decompensated cirrhosis and ascites has been a subject of debate for decades. Ascites is the most frequent decompensating event in cirrhosis; 5-10% of compensated patients develop this complication every year[7]. The occurrence of clinically manifest (grades 2 and 3) ascites impairs patients' working and social lives, and requires chronic treatment and recurrent hospitalisations, since it is also a direct or indirect cause of further complications, such as spontaneous bacterial peritonitis (SBP), renal failure, malnutrition, abdominal hernias, and restrictive ventilatory dysfunction. As a result, the presence of ascites implies a heavy economic burden to health care systems. Finally, the onset of ascites leads to a dramatic worsening of prognosis, as the 1-, 2- and 5-year mortality rates are approximately 30%, 50%, and 70%, respectively[7,8].

Until recently, only two randomised clinical trials assessing the potential efficacy of long-term albumin administration to patients with cirrhosis and ascites had been published. The first study[9] enrolled 126 hospitalised patients with cirrhosis and ascites who were also followed for 2 years after being discharged. Patients were randomised to receive standard diuretic treatment or standard diuretic treatment associated with albumin administration (25 g every week for 1 year and 25 g every 2 weeks thereafter). An improved rate of response to diuretics during hospitalisation, and a significant reduction both in the probability of developing ascites and in the number of hospital readmissions during follow-up, were reported; however, no effect on survival was seen. An improved transplant-free survival was instead reported by the second study from the same group[10], in which the follow-up of 100 patients was extended to a median of 84 months. Despite these encouraging results, the relatively small sample size meant that no firm conclusions could be made, and international guidelines did not include this type of treatment approach[11,12].

Almost 15 years after these two pivotal studies, three clinical trials evaluating the effects of long-term albumin administration to patients with decompensated cirrhosis were published in 2018[13-15]. In the ANSWER study[13], a non-profit, multicentre, randomised, open-label, pragmatic trial, 431 patients with persisting non-complicated grade 2 or 3 ascites requiring the administration of at least 200 mg of anti-mineralocorticoids and 25 mg of furosemide per day were randomised to either standard medical treatment (SMT) or SMT plus 40 g of albumin twice a week for the initial two weeks and then 40 g once a week. A significantly longer 18-month overall survival was seen in patients receiving albumin, with a 38% reduction in the hazard ratio for mortality. The multivariable risk analysis for 18-month all-cause mortality considering TIPS placement or liver transplantation as competing events showed that albumin treatment was the sole variable associated with survival. Albumin administration clearly facilitated the management of ascites, as the need for paracentesis and the incidence of refractory ascites were halved by around 50%. Furthermore, the cumulative incidence of complications of cirrhosis, including spontaneous bacterial peritonitis (SBP), non-SBP bacterial infections, episodes of renal dysfunction (as defined by serum creatinine >1.5 mg/dL) hepatorenal syndrome type 1 and severe hepatic encephalopathy grade III or IV, as well as potential diuretic-induced side effects, such as hyponatremia and hyperkalemia, were significantly reduced by 30-67% in the albumin group. As a result, patients enrolled in the albumin arm had a significantly lower number of either liver-related hospitalisations or days spent in hospital, the incidence rate ratios for which were reduced by 35% and 45% respectively. Finally, albumin treatment also proved to be cost-effective based on the reimbursement figures available from the Italian National Health Service.

The core results of the ANSWER trial have been very recently confirmed by a prospective, non-randomised clinical trial performed in Padua, which enrolled 70 patients with cirrhosis and refractory ascites[14]. Patients who received SMT + albumin (20 g twice a week) had a significantly lower 24-month mortality than the 25 patients receiving the SMT. Treatment with albumin was the sole

independent protective factor against death and it was associated to a significantly lower cumulative incidence of re-hospitalisations due to hepatic encephalopathy, accumulation of ascites, and bacterial infections.

The study on midodrine-albumin in cirrhotic patients awaiting liver transplantation (MACHT study) challenges these results[15]. In this placebo controlled clinical trial, 173 patients with ascites awaiting a liver transplant were randomised to receive SMT plus 40 g of albumin every 15 days and the α_1-receptor agonist midodrine (from 15 to 30 mg/day according to their pressor response) or SMT plus placebos. Despite a mild improvement in effective volaemia, as witnessed by a decrease in plasma renin activity and plasma aldosterone, and noradrenaline concentrations, no differences were seen in either the probability of developing complications or death during the 12 months of follow-up.

A comparison of the characteristics of these studies can provide some important lessons on how to interpret the apparently divergent results between the ANSWER and MACHT trials. They differ in terms of sample size, design, and length of follow-up, which largely exceeded one year in the ANSWER study, compared with around two months in the MACHT trial due to the high rate of liver transplantation. Furthermore, patients at baseline present a more advanced liver disease in the MACHT study (Model for End-stage Liver Disease [MELD] score: 17/18) as compared to those enrolled in the ANSWER trial (MELD score: 12/13). However, far more importantly, the amount of albumin administered in the MACHT trial was about half that administered in the other two studies and a loading dose was only used in the ANSWER study. This difference likely accounted for the fact that no effect on serum albumin concentration was seen in the MACHT study, while a significant and sustained increase of 0.6-0.8 g/L to a median value close to 4 g/dL was observed in the ANSWER study from about the first month onwards. Interestingly, a recent post-hoc analysis of the ANSWER database demonstrated that serum albumin concentration reached after 1 month of treatment is correlated with the probability of 18-month overall survival, which was greater than 90% in patients presenting with ≥4 g/dL. Furthermore, baseline serum albumin and MELD levels independently predicted the achievement of this threshold, so that the efficacy of treatment appears to be strongly influenced by the patient's starting serum albumin concentration and the severity of the underlying cirrhosis. Finally, even those patients who failed to increase 1-month on-treatment serum albumin levels up to the normal range (3.5 g/dL) received a benefit from long-term albumin administration in terms of longer survival and fewer complications[16].

The importance of increasing the serum albumin levels to beyond a certain level in order to obtain the maximal effect of albumin treatment was further highlighted by the pilot-PRECIOSA study[9], which showed that a steady suppression of plasma renin activity and a significant reduction in systemic inflammation was achieved in patients with decompensated cirrhosis receiving high doses (1.5 g/kg b.w. every week) but not low doses (1 g/kg b.w. every 10 days) of albumin for 12 weeks. Interestingly, only high doses of albumin were able to normalise serum albumin concentration, reaching a median value of 3.92 g/dL[17].

Taken together, all these data indicate that the serum albumin concentration can be used to guide treatment, since on-treatment levels predict clinical outcomes.

IMPACT OF THIS NEW INDICATION ON THE GLOBAL ALBUMIN CONSUMPTION

The consumption of human albumin in Italy is one of the highest in the world. The latest available data show that in Italy the total standardised demand for human albumin for the 5-year period 2011-2014 was 598 g *per* 1,000 inhabitants[18], a very slight decrease compared to demand for the years 2007 (620 g) and 2011 (601 g)[19-21]. Moreover, Italy has positioned itself well above the average consumption of albumin of other European countries with a comparable level of health care, such as France (238 g), Germany (148 g), and the United Kingdom (82 g)[22].

The out-of-hospital prescription of human albumin is regulated nationally by Note 15 of the Italian Medicine Agency (AIFA), which limits the reimbursement for its administration to patients with liver cirrhosis presenting *"severe retention of sodium and water not responding to an appropriate diuretic treatment, particularly when associated with hypoalbuminaemia and clinical features of hypovolaemia"*. However, additional restrictions to prescription, often quite arbitrary and not based on scientific evidence, are

imposed by local healthcare authorities, resulting in a rather heterogeneous access to this treatment across Italy for patients with decompensated cirrhosis.

The ANSWER study provides solid scientific evidence supporting the long-term use of human albumin for the management of patients with decompensated cirrhosis and ascites. Beyond the general indication given by the current AIFA Note 15, the results of the ANSWER trial indicate that patients with persisting grades 2 and 3 ascites despite a moderate dose of diuretics are eligible for treatment, and define the dosage and schedule of albumin administration. As a result, it is hoped that a more homogeneous access to this treatment can be expected.

However, the long-term treatment of decompensated cirrhosis will certainly lead to a significant increase in the use of human albumin, and the possible serious consequences on the availability of this blood product (at least of that produced by toll fractionation) must not be underestimated. Indeed, according to the schedule of administration used in the ANSWER trial, for each patient treated, 2,160 g of human albumin (equal to 216 10-g bottles) are needed each year.

As reported by several studies worldwide, including from Italy[23-30], a great number of albumin prescriptions, from 50% up to 90%, are not supported by clinical evidence, guidelines or recommendations. The use of human albumin for nutritional reasons or for the correction of hypoalbuminaemia not accompanied by hypovolaemia, are examples of inappropriate use in various settings (general surgery, internal medicine, geriatrics, oncology), as it has been shown that the use of albumin is not associated with a real benefit for the patient. Other conditions in which the use of albumin is not supported by solid evidence of efficacy are nephrotic syndrome, pancreatitis, abdominal surgery, respiratory distress syndrome, cerebral ischaemia, and enteric pathologies.

Action is needed to avoid the use of human albumin for these inappropriate indications and it is, therefore, necessary to promote effective policies to control the appropriateness of prescription, also acting on drug distribution systems[20-22], in order to ensure the availability of this strategic therapy for those conditions for which a real effectiveness and a benefit for the patient have been demonstrated, such as the long-term treatment of patients with decompensated cirrhosis and ascites.

FUTURE RESEARCH

A major goal of future research is to introduce criteria for personalising treatment at the individual or at least subgroup patient level in terms of stratification of the probability of response, selection of dose and frequency of albumin administration, and identification of parameters and criteria for the temporary or permanent discontinuation of treatment. In this context, it will be important to confirm that the changes in serum albumin concentration over time could be used as a guide to maximise the beneficial effects of the treatment and optimise albumin utilisation. In addition, it will be important to consider the impact of this new indication on indirect health-related costs and quality of life, considering that patients will need to visit hospital or other local health-care facilities more frequently for intravenous albumin administration. Finally, since these recommendations are expected to increase the demand for albumin, strategies to reduce inappropriate use and maintain a national self-sufficiency in the supply chain need to be developed.

RECOMMENDATIONS

- **Long-term albumin treatment should be included among the medical treatment options of patients with ascites.**
  Quality of evidence: ***high***
  Strength of recommendation: ***strong***
- **Patients with at least grade 2 non-complicated ascites not responding to moderate doses of diuretics (at least 200 mg/day of an anti-mineralcorticoid drug and 25 mg/day of furosemide) are candidates for long-term albumin administration. A dose of 40 g twice a week for the first 2 weeks and then once a week is currently recommended.**
  Quality of evidence: ***high***
  Strength of recommendation: ***strong***
- **Patients with refractory ascites can also benefit from long-term albumin administration.**
  Quality of evidence: ***moderate***
  Strength of recommendation: ***strong***
- **The duration of long-term albumin treatment should be adapted to the individual patient.**
  Quality of evidence: ***moderate***
  Strength of recommendation: ***strong***

- **Long-term albumin treatment in patients with ascites and hepatocellular carcinoma should be considered according to each individual patient, taking into account the tumour-related prognosis and the potential feasibility of tumour treatment.**
  Quality of evidence: ***low***
  Strength of recommendation: ***weak***

DISCLOSURE OF CONFLICTS OF INTEREST

PC has been speaker about this issue in symposia or webinars sponsored by Grifols SA, Octapharma SA and Kedrion Biopharma SpA and is collaborating with Octapharma SA industry for research in the field. PA has been a member of Sequana Medical AG Advisory Board and Ferring Advisory Board, and speaker in symposia sponsored by Kedrion Biopharma SpA. MB has been consultant and speaker for CSL Behring GmbH, Takeda, Grifols SA, and speaker in symposia sponsored by PPTA and Octapharma AG. No conflict of interest for all other Authors.

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