The role and indications of albumin in advanced liver disease

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Abstract

Low serum albumin is common in cirrhosis and is associated with a reduced survival. Moreover, in this setting, the native isoform of albumin can be severely reduced due to several post-transcriptional changes that impair the non-oncotic properties of the molecule.

Due to its oncotic power, albumin acts as a powerful plasma expander. As such, it can antagonize the consequences of effective hypovolemia deriving from the systemic hemodynamics abnormalities that characterize advanced cirrhosis. Indeed, the current established indications to the use of albumin in this context pertain to conditions deriving from an acute drop of effective volemia.

Recent advances have shown that the pathophysiological background of decompensated cirrhosis is characterized by a sustained systemic inflammatory and pro-oxidant state deriving by an abnormal bacterial translocation from the gut. These abnormalities ultimately lead to the multiorgan dysfunction. In this cascade of events, long-term albumin administration could act against several pathogenic factors through its non-oncotic properties, thus representing a potential multi-target mechanistic treatment.

Over the last year, two randomized clinical trials on this topic were published. The ANSWER Trial demonstrated that the long-term albumin administration in patients with decompensated cirrhosis improves overall survival, reduces the incidence of complications and the need of hospitalizations and ameliorates the quality of life, being cost-effective. The MACHT trial challenged these results, but the differences between the two studies (sample size, baseline severity of cirrhosis, length of follow-up and amount of albumin administered) could explain its variant results, providing the basis for further insights into this matter. (Acta gastroenterol. belg., **2019**, 82, **301-308**).

Key words : decompensated cirrhosis, human albumin, post-transcriptional abnormalities of albumin, effective hypovolemia, systemic inflammation.

Introduction

Reduced serum albumin concentration is a common feature in patients with cirrhosis and holds an adverse prognostic meaning, being associated with a reduced survival (1). Indeed, hypoalbuminemia results from both a decreased synthesis by the liver and various events closely related to the progression of the disease (2). For example, both renal sodium and water retention, which lead to plasma volume expansion and dilution of extracellular fluid protein content, and the increased trans-capillary escape rate of albumin towards the extravascular space contribute to lower serum albumin concentration.

Hypoalbuminemia is traditionally thought to play an important role in ascites formation by disrupting Starling forces equilibrium through the reduction of plasma colloid-osmotic pressure. However, the net trans-capillary fluid exchange is governed from the hydrostatic and oncotic pressure gradients between intravascular and interstitial compartments, rather than by their intravascular absolute values. Post-sinusoidal portal hypertension enhances the hydrostatic pressure gradient between the sinusoid and the space of Disse, where the lymphatic system drains the excess fluid to the thoracic duct, thus maintaining an elevated transcapillary gradient. This favors a net fluid flow towards the interstitium. Once the lymphatic system drainage capacity is exceeded, hepatic lymph pours in the peritoneal cavity through the Glissonian capsule leading to ascites formation.

This is not the case for the colloid-osmotic pressure, as albumin concentrations roughly decline in parallel in both compartments leaving the oncotic pressure gradient between intra- and extravascular spaces substantially constant (3). Thus, reduced albumin concentration does not play a pre-eminent role in ascites formation and the enhancement of plasma colloid-osmotic pressure should not represent, *per se*, a reason for albumin administration in patients with cirrhosis.

Albumin as a plasma-expander

Due to its colloid-osmotic effect, albumin is the main modulator of fluid distribution in the various compartments of the body, accounting for about 70-75% of the total plasma oncotic pressure. Moreover, the negative charges of the protein lead water to move from interstitium to the intravascular compartment due to the binding of cations such as sodium, exerting the indirect osmotic function defined “Gibbs-Donnan effect” (4). Because of this physiological background, the administration of human albumin represents a powerful tool to expand total plasma volume.

For decades, the pathophysiological background underlying decompensated cirrhosis has been seen as the expression of arterial vasodilation, which mainly occurs in the splanchnic circulatory area, whose extent is such that it reduces effective volemia (5). This

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evokes homeostatic compensatory responses such as the increase in cardiac output, thus leading to the picture of hyperdynamic circulatory syndrome, and the activation of neuro-humoral systems such as the renin-angiotensin-aldosterone axis, the sympathetic nervous system and arginine-vasopressin, leading to the renal retention of sodium and water. The following plasma volume expansion favors ascites formation as portal hypertension compartmentalizes the excess fluid into the peritoneal cavity (5). Despite these compensatory responses, effective hypovolemia can persist, especially in the most advanced stages of the disease, where cardiac dysfunction does not allow the cardiac output to increase enough to cope the needs of systemic circulation (6). As a result, renal perfusion declines, ultimately leading to complications as dilutional hyponatremia and hepatorenal syndrome (5,6).

Based on peripheral arterial vasodilation hypothesis (5), most treatments to prevent or treat complications of cirrhosis traditionally aim at restoring effective volemia. Indeed, the current, well established indications to the use of human albumin in patients with cirrhosis pertain to conditions characterized by an acute worsening of effective hypovolemia, such as paracentesis-induced circulatory dysfunction, renal dysfunction secondary to spontaneous bacterial peritonitis, and hepatorenal syndrome, as indicated by the international guidelines on the management of decompensated cirrhosis (7) (Table 1).

Albumin: beyond plasma expansion

The albumin molecule, besides its oncotic power, possesses functional domains with important properties, such as the free cysteine residue in position 34 (Cys-34), which exerts potent anti-oxidant and scavenging activities, the aminoterminal residue that binds and removes highly toxic reactive metal species, and other domains binding a variety of endogenous and exogenous substances, including bilirubin, bile salts, endotoxin, and many drugs. At last, albumin has immune-modulatory functions, protects capillary integrity, and influences acid-base balance and hemostasis (8).

The beneficial effects deriving from albumin administration to patients with cirrhosis have been traditionally attributed to an improvement in effective volemia. However, considering the pleiotropic properties of albumin described above a question emerges: were these effects exclusively due to plasma volume expansion? Indeed, evidence that non-oncotic properties of albumin also play a role is already available for years. In patients with spontaneous bacterial peritonitis, the administration of albumin, but not hydroxyethyl starch, improved stroke work index and peripheral vascular resistance (9,10). These changes were associated with the reduction of Von Willebrand-related antigen plasma levels and the prevention of serum nitrates and nitrites burst seen in patients treated with hydroxyethyl starch, suggesting an effect of albumin on endothelial function. In rats with carbon tetrachloride-induced cirrhosis and ascites the administration of albumin, but not starch or saline, was able to restore an impaired cardiac contractility (11). This inotropic effect of albumin was mediated by opposing the negative effects of oxidative stress- and TNF-α-induced activation of NF-κB-iNOS pathway, and the oxidative stress-induced alteration of β-receptor signaling. In patients with cirrhosis, increased circulating free prostaglandin E2 (PGE2) endangers macrophage function, thus contributing to the cirrhosis-associated immune dysfunction (12). Albumin administration improves immune competence by binding PGE2 (12). Interestingly, the improvement in PGE2 binding capacity following albumin administration is not solely due to an increase in serum albumin concentration. In fact, post-treatment plasma bounds significantly more PGE2 than pretreatment plasma even when both are diluted to the same albumin concentration, suggesting an improvement in binding capacity (13). Finally, albumin is widely used as toxin absorbent in several extracorporeal liver-assist devices (14).

Albumin molecular abnormalities in cirrhosis

During the last few years, it has become clear that in patients with cirrhosis the albumin molecule undergoes

Table 1. — **Current established indications for albumin use in patients with cirrhosis (7)**

CLINICAL CONDITION		DOSE AND SCHEDULE OF ADMINISTRATION
PREVENTION OF PICD	Paracentesis >5 l: mandatory	8 g/l of ascites tapped
	Paracentesis <5 l: preferred	
PREVENTION OF RENAL DYSFUNCTION INDUCED BY SBP		1.5 g/kg bw at diagnosis + 1 g/kg bw at day 3
DIAGNOSIS OF HRS-AKI		1 g/kg bw for 2 days
TREATMENT OF HRS-AKI		20-40 g/day (associated with vasoconstrictors)

PICD : paracentesis-induced circulatory dysfunction. SBP : spontaneous bacterial peritonitis. BW : body weight. HRS : hepatorenal syndrome. AKI : acute kidney injury.

functional and structural changes that can impair its non-oncotic properties. Oxidation of the Cys-34 residue leading to the reversibly (human non-mercaptalbumin-1; HNA-1) and irreversibly (HNA-2) oxidized isoforms of albumin has been described (15). These abnormalities were associated with an impaired binding capacity for dansyl-sarcosine. Moreover, the plasma level of HNA-2 was closely related to patient survival.

Oxidation of the Cys-34 residue is not the sole molecular abnormality of circulating albumin in patients with cirrhosis. High-performance liquid chromatography/electrospray ionization mass spectrometry (HPLC/ESI-MS) technique allows the simultaneous assessment of the relative abundance of different serum albumin isoforms, such as the native, structurally and functionally intact albumin and its cysteinilated, sulphydrilated, glycosilated, and truncated isoforms. By using this technique, we found that substantial alterations in the molecular structure of albumin occur in patients with cirrhosis (16). As a result, the relative abundance of intact albumin is greatly reduced. These abnormalities increase in parallel with the severity of cirrhosis, as the relative abundance of native albumin steadily decreases with respect to healthy controls in outpatients with stable cirrhosis and patients hospitalized because of an acute decompensation of the disease (16). Interestingly, the prognostic power in term of survival of total serum albumin concentration is enhanced when patients are stratified according to the relative abundance of native serum albumin, with a best cut-off value of about 44% (16). Another albumin abnormality recently described in cirrhosis consists with the enhanced development of homodimers resulting from the covalent or non-covalent interactions between both native and truncated isoforms (17,18).

Specific structural changes of albumin appear to be associated with specific clinical contexts and complications of cirrhosis. As an example, serum ischemia-modified albumin (IMA), resulting from the aminoterminal truncation that hampers the capacity to bind cobalt and other metal species (19), is increased and associated with a poor survival in patients with alcoholic cirrhosis who develop acute-on-chronic liver failure (ACLF) (20). Moreover, we found that increased IMA serum levels in patients with cirrhosis of mixed etiology do not correlate with disease severity scores but are specifically associated with the occurrence of bacterial infections with a discriminating performance similar to C-Reactive Protein (21).

As a whole, these results clearly show that patients with cirrhosis present not only a reduced total serum albumin concentration, but also, to an even greater extent, a reduction in its native, functionally intact isoform due to several molecular abnormalities that endanger the non-oncotic properties of the molecule (Figure 1). Thus, the attention of clinicians should be also devoted to the serum "effective" albumin concentration (8) and methods assessing albumin integrity in clinical practice would be warranted.

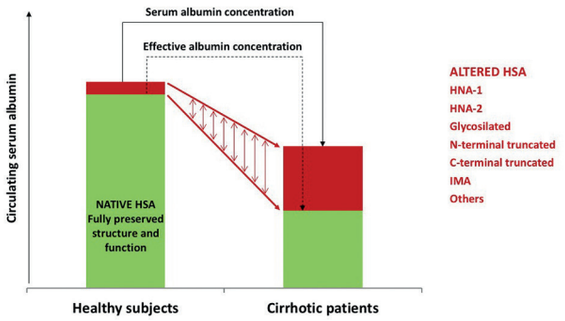

Figure 1. — The concept of effective serum albumin concentration. In patients with cirrhosis serum albumin does not only undergoes quantitative changes (total serum albumin concentration), but also develops several qualitative abnormalities listed on the right (in red) that endanger non-oncotic properties of the molecule. As a result, the concentration of functionally intact albumin (effective albumin; in green) is reduced to an even greater extent.
HNA-1 : non-mercaptalbumin-1 ; HNA-2 : non-mercaptalbumin-2 ; IMA : ischemia-modified albumin

Advances in the knowledge of the pathophysiology of decompensated cirrhosis

The peripheral vasodilation hypothesis (5) accounted for the development of many clinical manifestations of decompensated cirrhosis. However, other aspects, namely the multiorgan dysfunction that characterizes this stage of cirrhosis, could not be solely attributed to hemodynamic abnormalities. Furthermore, the efferent molecular mechanisms leading to arterial vasodilation, consisting with an enhanced endothelial production of vasodilating substances such as nitric oxide, carbon monoxide, prostacyclin and endocannabinoids (22) were identified. However, the primary cause of these abnormalities long remained undefined until it became clear that the internal milieu of patients with decompensated cirrhosis is characterized by a sustained pro-inflammatory and pro-oxidant state (23). Indeed, it is now rather clear that the systemic spread of pathogen-associated molecular patterns (PAMPs), due to abnormal translocation from the gut, and damage associated molecular patterns (DAMPs), released by the diseased liver where inflammation, apoptosis and necrosis take place, activate immune cells through binding with innate recognition receptors. Activated immune cells produce pro-inflammatory cytokines and chemokines, along with reactive oxygen and nitrogen species. This cascade of events contributes to the development of circulatory dysfunction and, along with it, favors the development of multiorgan dysfunction and, ultimately, failure. The extent of these abnormalities intensifies in parallel with the severity of the underlying liver disease. Indeed, the serum concentration of pro-oxidant cytokines such as TNF-a, interleukin-6 (IL-6) and IL-8 progressively increases in patients hospitalized because of an acute

decompensation of cirrhosis and in those who developed acute-on-chronic liver failure (24).

The sustained systemic inflammatory and pro-oxidant state that characterizes patients with decompensated cirrhosis likely represent the most relevant factor inducing the structural changes of albumin molecule described above. In fact, the proportion of HNA-1 and HNA-2 in the serum of patients with cirrhosis increase in parallel with the serum concentration of pro-inflammatory cytokines (24). Moreover, the relative abundance of albumin homodimers in the plasma of healthy subjects is progressively enhanced by its exposure to increasing concentrations of tert-butyl hydroperoxide, suggesting that oxidation likely represents a main mechanism also leading to albumin dimerization in patients with cirrhosis (18).

Interestingly, inflammation- and oxidation-induced molecular abnormalities in cirrhosis do not act as innocent bystanders but contribute in turn to inflammation. Indeed, the inflammatory response of peripheral blood mononuclear cells, assessed by measuring the *in vitro* production of IL-6 and TNF-a is greatly enhanced by a challenge with HNA-1 (25).

New perspectives for the use of albumin in patients with cirrhosis

The current strategies for the management of patients with decompensated cirrhosis rely on targeted measures aiming to address each complication. Indeed, they attempt at attenuating or correcting effective hypovolemia (7), reducing portal hypertension by means of non-selective β-blockers (NSBBs) and terlipressin (26) or the insertion of a trans-jugular intrahepatic portosystemic shunt (TIPS) (27), and finally, antagonizing intestinal dysbiosis and bacterial overgrowth to reduce ammonia production and bacterial translocation (28).

However, besides improving the already well-established treatments, we should aim to a more comprehensive management of the disease. Such an approach, if successful, could modify the natural history of the disease, preventing organ failure and ACLF, reducing hospitalizations and the burden on healthcare, and improving patient survival and quality of life.

A rather obvious response to these needs is represented by etiologic treatments. Indeed, the removal of the cause of cirrhosis is expected to halt the progression of the disease, thus preventing complications and improving patient survival. However, etiological treatments achieve their optimal results when are applied in the compensated stages of cirrhosis. However, taking as example the use of direct-acting antiviral drugs (DAA) able to eradicated HCV-infection, cirrhosis does not improve or even worsen in about a half of patients despite the removal of the etiologic factor once the decompensated stage has been reached (29). In the setting of patients awaiting liver transplantation, only one-third of waitlisted patients with decompensated cirrhosis can be withdrawn from the list because of an improvement. More than 40% need to be transplanted and about fifteen percent still die or become too sick to undergo liver transplantation in the waitlist (30).

Therefore, alternative treatments such as mechanistic pathophysiological therapies are warranted. Of course, this strategy would need to be aware of the pathophysiological background underlying decompensated cirrhosis. In the light of the current knowledge (23), pathophysiological treatments would need to counteract one or possibly more mechanisms, such as bacterial translocation, chronic systemic inflammation, cardiocirculatory dysfunction and cirrhosis-associated immune dysfunction. On this respect, it should be recalled that we are facing a complex pathophysiological network with interacting and redundant pathways. Thus, single target interventions can only be expected to be effective if they are sufficiently upstream to act on a "core" mechanism, such as portal hypertension or bacterial translocation. Instead, downstream interventions could only be successful if they are able to hit several factors alone or combining different agents. Among the potential targets of this approach, systemic inflammation, circulatory dysfunction, oxidative stress and immune dysfunction represent the most relevant ones. There is a number of treatments that can be at least theoretically employed against upstream core events and/or downstream events (31). Interestingly, most of them are already in use for years in patients with cirrhosis. However, the studies that have specifically addressed the issue of modifying the course of decompensated cirrhosis are relatively few and most of them have assessed the effect of human albumin administration (32-34).

In this pathophysiological network, besides promoting plasma volume expansion, albumin could simultaneously act on several abnormalities, by binding offending molecules, modulating immune responses, exerting anti-oxidation, improving cardiac function, attenuating immune dysfunction and restoring endothelial integrity. Therefore, prolonged albumin administration may represent, at least potentially, an effective multi-target treatment (Figure 2).

Long-term albumin administration to patients with decompensated cirrhosis

Despite the potential efficacy of long-term albumin administration to patients with cirrhosis and ascites has long been debated, only two randomised clinical trials assessing this form of treatment were published until recently. The first study (35) enrolled 126 hospitalized patients with cirrhosis and ascites who were also followed after discharge for 2 years. Patients were randomized to receive standard diuretic treatment or standard diuretic treatment associated with albumin administration (25g every week for 1 year and 25g every 2 weeks thereafter). An improved rate of response to diuretics during hospitalization as well as a significant reduction in

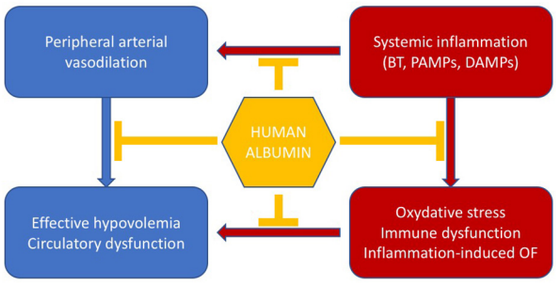

Figure 2. — Potential effects of albumin administration to patients with decompensated cirrhosis. In addition to plasma volume expansion, albumin can exert a multitarget effect on several pathophysiological mechanism related to systemic inflammation, pro-oxidant state and end-organ integrity.
OF : organ failure.

the probability of developing ascites and hospital readmissions during the 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 (36), in which the follow-up of 100 patients was extended to a median of 84 months. Unfortunately, the relatively small sample size precluded a firm conclusion, so that current guidelines do not support such a treatment (7). Despite this, a recent survey on the use of albumin in patients with cirrhosis reported that about one-fourth of European hepatologists prescribe long-term albumin administration to patients with cirrhosis and ascites, at least in selected cases (37).
Over last year, three controlled clinical trials evaluating the effects of long-term albumin administration to patients with decompensated cirrhosis have been published. The first one, the ANSWER study (32), is a non-profit, multicenter, randomized, open-label, pragmatic clinical trial that enrolled patients with cirrhosis and persisting non complicated ascites requiring the administration of at least 200 mg of anti-mineralocorticoids and 25 mg of furosemide per day. After stratification according to the need of paracentesis in the month preceding the enrolment and serum sodium concentration, patients were randomized 1:1 to either standard medical treatment (SMT; 213 patients), which included albumin administration for well-established indications, or SMT plus 40 g of albumin (HA) twice a week for the initial two weeks and then 40 g once a week (218 patients). Patients were followed-up for 18 months or to liver transplantation, TIPS insertion or to a severity of ascites refractoriness requiring three or more paracentesis per month, which represents an indication to TIPS. The primary end point was overall survival. The secondary end-points and the management of ascites, the incidence of complications of cirrhosis, admissions to hospital, quality of life and cost-effectiveness analysis.

The primary end-point was reached, as a significantly better overall survival was seen in the albumin arm, with a 38% reduction of the hazard ratio for mortality. The competing risks analyses for 18-month all-cause mortality considering TIPS placement or liver transplantation as competing events showed that age, viral cause of cirrhosis, Child-Pugh and MELD-Na score were independent predictors of mortality, whereas albumin treatment was the sole variable associated with survival.

As far as the secondary end-points were concerned, up to two third of patients in SMT arm needed at least one paracentesis during their follow-up. Such a percentage was significantly reduced to 38% in the SMT+HA arm. The cumulative incidence rate of paracentesis in the SMT arm was 3.5 per patient per year and dropped by 54% in the SMT+HA arm. Notably, the amount of ascites tapped per paracentesis did not differ between the two arms. The incidence of refractory ascites was also significantly lower in the SMT+HA arm, with a hazard ratio reduced by 46%. The cumulative incidence of complications of cirrhosis was also reduced by albumin administration. These included spontaneous bacterial peritonitis, non-SBP bacterial infections, episodes of renal dysfunction, as defined by serum creatinine above 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. Bleedings from gastroesophageal varices and other portal hypertensive bleedings, such as congestive gastropathy or hemorrhoids, did not significantly differ between the two arms of the trial.

Quality of life evaluation, as assessed by EQ-5D utility index and visual analogue scale, showed that values remained substantially steady in SMT+HA arm, whereas they declined in SMT arm, with a difference that reached full statistical significance at 3, 6 and 12 months, a result that sounds relevant in such severely ill patients. Finally, patients enrolled in the albumin arm had a significantly lower number of either liver-related hospitalizations or days spent in hospital, whose incidence rate ratios were reduced by 35 and 45% respectively. The cost-effectiveness of albumin treatment was based on costs reimbursed for liver and non-liver related hospitalizations, paracentesis, hospital accesses for per protocol albumin infusion and per protocol albumin administration. Despite the reimbursement rates from the Italian National Health Service are much lower than in other Western Countries, the calculated incremental cost-effectiveness ratio (€ 24,888 per QALY gained/year) was well below the threshold adopted by that the UK National Institute for Health and Clinical Excellence (€ 35,000 per QALY gained/year) to consider a treatment cost-effective.

The core results of the ANSWER trial have been very recently confirmed by a prospective, non-randomized clinical trial performed in Padua, which enrolled patients with cirrhosis and refractory ascites (34). Indeed, the 45 patients who received albumin (20 g twice a week) up to 24 months had a significantly lower mortality than the 25 patients receiving the standard of care. Furthermore, while age and baseline MELD were the independent predictors

of mortality at multivariate analysis, the treatment with albumin was the sole protective factor. Similar to what was found in the ANSWER study, the cumulative incidence of re-hospitalizations due to complications of cirrhosis such as hepatic encephalopathy, accumulation of ascites and bacterial infections was significantly lower in patients treated with albumin. A decline in the occurrence of hepatorenal syndrome was also seen, but it did not reach the statistical significance.

The midodrine and albumin in cirrhotic patients awaiting liver transplantation (MACHT) study, also published in 2018, challenges these results (33). This randomized, placebo controlled clinical trial enrolled patients listed for liver transplantation: 87 received 40 g of albumin every 15 days plus the α_1-receptor agonist midodrine (from 15 to 30 mg/day according to their pressor response) and 86 received SMT and placebos for a planned follow up of 12 months. Despite a mild improvement in effective volemia, 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, including renal failure, bacterial infections, hyponatremia, hepatic encephalopathy or gastrointestinal bleeding, which was the primary end-point of the study, nor in the time to develop the first complication. This negative result pertained to both the assessment of complications as a whole and the incidence of each complication individually, even though the episodes of hyponatremia and renal failure were more severe in patients from the placebo group compared to those also receiving albumin and midodrine. At last, the probability of survival did not differ between the two groups of patients.

The comparison of the characteristics of these studies can provide some relevant lessons (Table 2). They differ in terms of sample size, design, and baseline severity of cirrhosis, as assessed by MELD score that was 12/13 in the ANSWER study, 15 in the Di Pascoli's study and 17/18 in the MACTH study. However, far more important is the fact that the median or mean duration of albumin administration largely exceeded one year in the ANSWER and Di Pascoli's studies, while was about two months in the MACHT trial due to high rate of liver transplantation (68% in the active arm of the study). Furthermore, the amount of albumin administered in the MACHT trial was about half with respect to the other two studies and a loading dose was only used in the ANSWER study. This difference likely accounted of the fact that no effect on serum albumin concentration was seen in the MACHT study, while a significant and sustained increase by 0.6-0.8 g/L occurred in the ANSWER study from about the second month onwards.

Conclusions and perspectives

The use of albumin in patients with cirrhosis and ascites has long been established in the specific settings to prevent or treat specific complications. However, based on the advancements in the knowledge of the pathophysiological background underlying decompensated cirrhosis, new perspectives for albumin administration have recently arisen. The pleiotropic, non-oncotic properties of this molecule, able to modulate immune responses, exert a potent antioxidant and scavenging activity, protect endothelia integrity, bind and transport several endogenous and exogenous substances represent the rationale for its long-term use in patients with decompensated cirrhosis and make it a promising candidate for a mechanistic pathophysiological treatment. Indeed, available evidence suggests that long-term albumin administration in this context, in addition to ease the management of ascites, improves survival, reduces the incidence of severe life-threatening complications and ameliorates the quality of life. Moreover, it reduces the number of hospitalizations, being cost-effective. Based on these results, long-term albumin administration to patients with decompensated cirrhosis can be seen as a disease-modifying treatment and may become a novel indication for the use of albumin in this context. However, recent studies suggest that these results can be expected provided that the dose of albumin administered succeeds in steadily increasing serum albumin concentration to a significant extent and the treatment lasts for a sufficient time to exert its effects (38).

Of course, several issues still need to be ascertained and should be sought for in future studies. First, whether there are patient sub-populations who would benefit most from long-term albumin administration; second, whether there are baseline factors that influence the outcome of long-term albumin administration; third, whether there

Table 2. — **Main characteristics of the two largest randomized controlled trials (32,33) assessing the effects of long-term albumin administration in decompensated cirrhosis**

The ANSWER Trial [32]		The MACHT Trial [33]
431 (218 HA / 213 SMT)	Patients	173 (87 HA / 86 SMT)
Randomized open-label	Design	Randomized placebo-controlled
12 / 13	Baseline MELD score	17 / 18
14.5 months	Median duration of albumin administration	63 days
40 g twice a week for 2 weeks then 40 g once a week	Dosage and timing of Albumin administration	40 g every 15 days (no loading dose)
Steady and significant increase in HA arm (0.6-0.8 g/dl)	Effect on serum albumin concentration	No changes in both groups

HA : human albumin. SMT : standard medical treatment. MELD : model for end-stage liver disease.

are target levels of serum albumin concentration to be reached to obtain favorable results; fourth, whether there are factors that influence the amount of albumin to be administered to reach such target levels; fifth, it would be important to identify the optimal duration of treatment, as well as the optimal dosage and administration schedule of albumin. We hope that our ongoing post-hoc analysis of the ANSWER database will enable us to shed light, at least in part, on these aspects.

Conflict of interest statement:

GZ is part of the speakers' bureau for Octapharma AG and received travel grants from Kedrion Biopharma and Alfasigma. MB is part of the speakers' bureau for Grifols SA, Octapharma AG, Baxalta, CLS Behring GmbH, Takeda and PPTA, and is a consultant for Baxalta, CLS Behring GmbH Grifols SA and Martin Pharmaceuticals.

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