Correction and Prevention of Hyponatremia in Patients With Cirrhosis and Ascites: *Post Hoc* Analysis of the ANSWER Study Database

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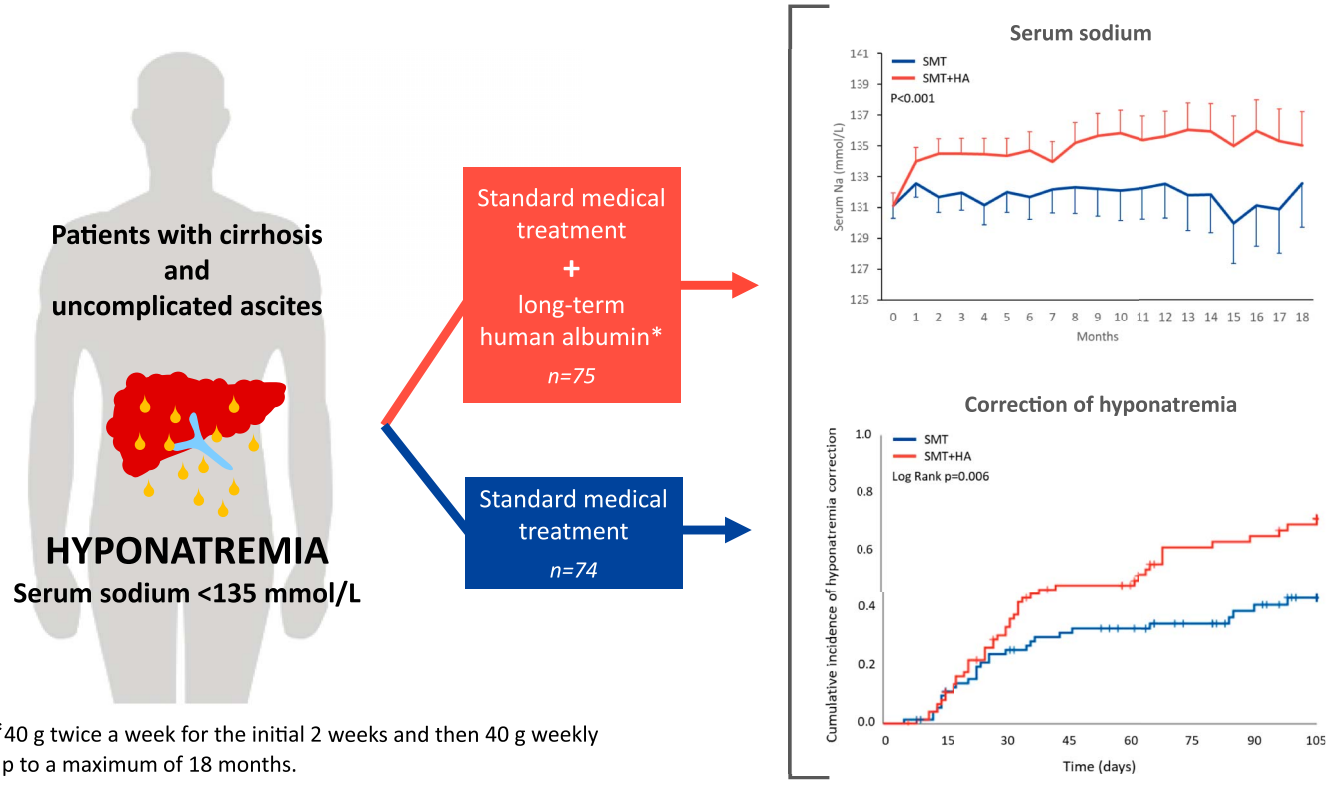
INTRODUCTION: **We assessed the impact of long-term albumin administration to hyponatremic patients with ascites enrolled in the ANSWER trial.**



*40 g twice a week for the initial 2 weeks and then 40 g weekly up to a maximum of 18 months.

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METHODS: **The normalization rate of baseline hyponatremia and the 18-month incidence rate of at least moderate hyponatremia were evaluated.**

RESULTS: **The hyponatremia normalization rate was higher with albumin than with standard medical treatment (45% vs 28%, $P = 0.042$ at 1 month). Long-term albumin ensured a lower incidence of at least moderate hyponatremia than standard medical treatment (incidence rate ratio: 0.245 [CI 0.167–0.359], $P < 0.001$).**

DISCUSSION: **Long-term albumin administration improves hyponatremia and reduces episodes of at least moderate hyponatremia in outpatients with cirrhosis and ascites.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/C679

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INTRODUCTION

Hyponatremia is the most common electrolyte disorder in patients with cirrhosis. Its prevalence ranges from 21% to 50% based on the cutoff serum sodium (130 or 135 mmol/L) used to define hyponatremia and increases in parallel with the severity of cirrhosis (1). It associates with severe complications of cirrhosis and elevated mortality (1,2), so it possesses a high prognostic power (2,3). Hyponatremia favors or aggravates hepatic encephalopathy by enhancing ammonia-induced astroglial cell swelling (4). Finally, the rapid correction of severe hyponatremia can induce irreversible brain damage and even death, as reported in patients undergoing liver transplantation (5) or general surgery (6).

Human albumin is frequently used to correct hyponatremia in cirrhosis (7,8). However, no controlled clinical trials assessing this form of treatment are available. An anecdotal study showed that HA administration improved spontaneous or diuretic-induced hyponatremia (9). A retrospective observational study suggested that hospitalized hyponatremic patients normalized serum sodium more often if they received HA (10). Finally, a recent study reported that intravenous HA slightly increased serum sodium without influencing the outcome in hospitalized patients with acutely decompensated cirrhosis (11).

The ANSWER trial assessed the effects of long-term albumin administration to patients with cirrhosis and uncomplicated ascites (12). HA treatment was associated with better survival and a lower incidence of complications, including moderate-to-severe hyponatremia. The present *post hoc* analysis of the ANSWER study database evaluated the impact of long-term HA administration to hyponatremic patients with cirrhosis and ascites.

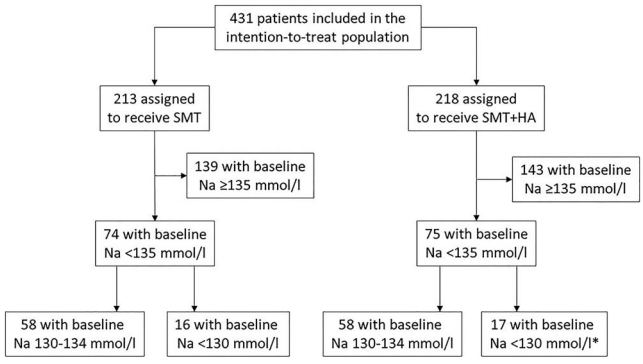

Figure 1. Patient disposition. *Two patients had serum sodium <125 mmol/L. HA, human albumin; Na, serum sodium; SMT, standard medical treatment.

METHODS

The ANSWER study is an investigator-initiated, multicenter, randomized, open-label, pragmatic clinical trial including adult patients with liver cirrhosis and uncomplicated ascites, requiring diuretic treatment (12). Patients were randomized to receive standard medical treatment (SMT) or SMT plus HA (20% HA in 50-mL vials: 40 g twice a week for 2 weeks and then, 40 g weekly) and followed monthly. The duration of follow-up was up to a maximum of 18 months or until death, liver transplantation, need of 3 large paracenteses in a month, or transjugular intrahepatic porto-systemic shunt insertion. Further details on the study protocol have been reported in the Supplementary Digital Content (see Supplementary Appendix, http://links.lww.com/AJG/C679). The principal results of the trial have been published elsewhere (12).

In this *post hoc* analysis we assessed whether long-term HA administration influenced (i) the rate of normalization of serum sodium defined as the first occurrence of a serum sodium level of >135 mmol/L in patients with hyponatremia and (ii) the prevention of episodes of at least moderate hyponatremia in patients with either normonatremia or hyponatremia at baseline. The cutoff values of serum sodium used in this study were as follows: ≥135 mmol/L: normonatremia; <135 and ≥130 mmol/L: mild hyponatremia; <130 and ≥125 mmol/L: moderate hyponatremia; and <125 mmol/L: severe hyponatremia. Further details on statistical methods are presented in the Supplementary Digital Content (see Supplementary Appendix, http://links.lww.com/AJG/C679).

RESULTS

The ANSWER trial enrolled 431 patients (213 randomized to SMT and 218 to SMT + HA), 149 of whom presented hyponatremia at inclusion: 116 had mild hyponatremia (58 in either arm of the study) and 33 had at least moderate hyponatremia (16 allocated to SMT and 17 to SMT + HA) (Figure 1). Among these, 54 patients (73%) in the SMT group and 60 patients (80%) in the SMT plus HA group completed the study according to protocol. The median follow-up estimated according to the reverse Kaplan-Meier method was significantly lower in the SMT group as

Table 1. Baseline characteristics of patients with normal natremia (≥135 mmol/L) or with mild (<135 and ≥130 mmol/L) or at least moderate (<130 mmol/L) hyponatremia at the inclusion in the ANSWER study

	Normal natremia (n = 282)	Mild hyponatraemia (n = 116)	At least moderate hyponatraemia (n = 33)	*P* value
SMT arm	139	58	16	—
SMT + HA arm	143	58	17	—
Demographic data				
Age (yr)	62 (52–69)	62 (55–70)	60 (55–66)	0.756
Male sex	196 (70%)	78 (67%)	22 (67%)	0.877
Etiology of cirrhosis				
Viral	92 (33)	45 (38)	10 (30)	0.463
Alcohol	91 (32)	34 (29)	7 (21)	
NASH	15 (5)	4 (3)	1 (3)	
Viral and alcohol	33 (12)	19 (16)	7 (21)	
Viral and NASH	13 (5)	3 (3)	1 (3)	
Other	38 (14)	11 (10)	7 (21)	
Clinical features				
Body mass index (kg/m^2)	26 (24–28)	25 (23–27)	24 (21–28)	0.028
Systolic arterial pressure (mm Hg)	110 (110–120)	110 (105–125)	110 (97–115)	0.002
Diastolic arterial pressure (mm Hg)	70 (65–80)	70 (60–80)	65 (60–70)	0.001
Mean arterial pressure (mm Hg)	83 (80–90)	83 (78–93)	77 (73–85)	<0.001
Heart rate (beats per minute)	70 (64–76)	72 (65–80)	76 (68–80)	0.009
Ascites				
Grade 2	235 (83)	97 (84)	26 (79)	0.791
Grade 3	47 (17)	19 (16)	7 (21)	
Hepatic encephalopathy grade I/II	25 (9)	12 (10)	2 (6)	0.738
Hematologic and biochemical data				
White blood cells (10^3/mm^3)	4.8 (3.6–6.2)	5.6 (4.4–7)	5.1 (3.7–6.6)	0.006
Hemoglobin (g/dL)	11.7 (10.5–13)	11.7 (10.3–12.9)	11 (9.4–12.4)	0.129
Platelets (10^3/mm^3)	90 (62–129)	102 (78–140)	76 (56–113)	0.006
Serum creatinine (mg/dL)	0.93 (0.78–1.13)	0.96 (0.82–1.17)	0.96 (0.8–1.14)	0.505
Serum sodium (mmol/L)	138 (136–139)	133 (131–134)	127 (126–128)	<0.001
Serum potassium (mmol/L)	4.3 (3.93–4.67)	4.5 (4.1–4.7)	4.5 (4.1–4.8)	0.012
Serum bilirubin (mg/dL)	1.72 (1.11–2.66)	1.99 (1.19–3.38)	3.22 (1.6–4.2)	0.004
Serum albumin (g/dL)	3.16 (2.8–3.5)	2.97 (2.6–3.25)	2.9 (2.7–3.3)	0.001
International normalized ratio	1.32 (1.19–1.47)	1.39 (1.21–1.52)	1.4 (1.21–1.64)	0.080
Prognostic scores				
Child-Pugh class				
Class A	49 (17)	12 (10)	3 (9)	0.008
Class B	188 (67)	77 (66)	17 (52)	
Class C	45 (16)	27 (23)	13 (39)	
Child-Pugh score	8 (7–9)	8 (7–9)	9 (7–10)	0.005
MELD score	12 (10–15)	13 (10–17)	15 (11–19)	0.018

Data are presented as n (%), median (inter-quartile range), or mean (SD).
HA, human albumin; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; NASH, nonalcoholic steatohepatitis; SMT, standard medical treatment.

Table 2. Baseline characteristics of patients with hyponatremia at inclusion in the ANSWER study, comparing subjects in the SMT and SMT + HA arms

	SMT (n = 74)	SMT + HA (n = 75)	*P* value
Demographic data			
Age (yr)	61 ± 11	61 ± 11	0.991
Male sex	52 (70)	48 (64%)	0.486
Etiology of cirrhosis			
Viral	30 (41)	25 (33)	0.568
Alcohol	23 (31)	18 (24)	
NASH	2 (3)	3 (4)	
Viral and alcohol	11 (15)	15 (20)	
Viral and NASH	2(3)	2 (3)	
Other	6 (8)	12 (16)	
Clinical features			
Body mass index (kg/m^2)	25 (23–27)	25 (22–27)	0.827
Systolic arterial pressure (mm Hg)	110 (100–120)	110 (105–125)	0.095
Diastolic arterial pressure (mm Hg)	70 (60–75)	70 (60–79)	0.729
Mean arterial pressure (mm Hg)	83 (77–88)	83 (77–93)	0.285
Heart rate (beats per min)	72 (65–80)	72 (66–80)	0.438
Ascites			
Grade 2	60 (81)	63 (84)	0.671
Grade 3	14 (19)	12 (16)	
Hepatic encephalopathy grade I/II	5 (7)	9 (12)	0.401
Hematologic and biochemical data			
White blood cells (10^3/mm^3)	5.82 ± 2.60	5.70 ± 2.03	0.754
Hemoglobin (g/dL)	11.37 ± 1.82	11.74 ± 2.08	0.257
Platelets (10^3/mm^3)	89 (57–130)	108 (75–137.5)	0.101
Serum creatinine (mg/dL)	0.99 ± 0.25	0.97 ± 0.23	0.517
Serum sodium (mmol/L)	131 (130–133)	132 (130–133)	0.694
Serum potassium (mmol/L)	4.47 ± 0.52	4.46 ± 0.55	0.844
Serum bilirubin (mg/dL)	1.95 (1.34–3.43)	2.1 (1.26–4.1)	0.460
Serum albumin (g/dL)	2.9 (2.7–3.2)	3 (2.6–3.36)	0.406
International normalized ratio	1.41 (1.22–1.59)	1.35 (1.2–1.52)	0.241
Prognostic scores			
Child-Pugh class			
Class A	4 (5)	11 (15)	0.094
Class B	52 (70)	42 (56)	
Class C	18 (24)	22 (29)	
Child-Pugh score	8 (7–9)	8 (7–10)	0.729
MELD score	14 (11–17)	14 (10–17)	0.761

Data are presented as n (%), median (IQR), or mean (SD).
HA, human albumin; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; NASH, nonalcoholic steatohepatitis; SMT, standard medical treatment.

compared with the SMT plus HA group (8.2 [2.7–17.5] vs 16.1 [6.8–17.9] months, log rank *P* value 0.001). Median age, sex, and etiology of cirrhosis did not differ between patients with or without hyponatremia. Hyponatremic patients showed a more severe liver disease because they presented lower mean arterial pressure, higher serum bilirubin, lower serum albumin, and higher Child-Turcotte-Pugh and model for end-stage liver disease scores (Table 1). There were no differences in serum

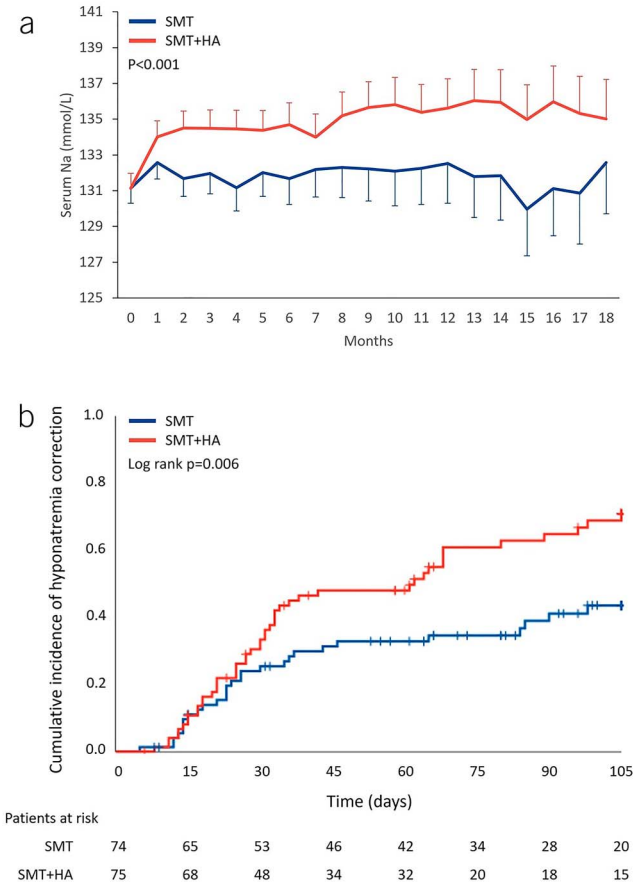

Figure 2. (**a**) Serum sodium level during the study period in patients with baseline hyponatremia (serum sodium level <135 mmol/L). (**b**) Correction of hyponatremia (achievement of a serum sodium level of ≥135 mmol/L) within 3 months. According to the study protocol, monthly visits were performed with a tolerance of ±15 days. HA, human albumin; SMT, standard medical treatment.

creatinine levels (Table 1). Comparing hyponatremic patients randomized to either SMT or SMT + HA, no differences in baseline clinical or laboratory parameters were observed (Table 2). Moreover, no differences in the same parameters were found when normonatremic patients were compared (see Supplementary Table 1, http://links.lww.com/AJG/C679).

Serum sodium concentration increased significantly in hyponatremic patients receiving HA as compared with those in the SMT group. Random coefficient linear regression showed that treatment with HA was associated with an average increase of 2.6 (95% CI 1.3–4.0) mmol/L of Na ($P = 0.0001$) (Figure 2a).

After 1 month of treatment, serum sodium normalized in 34 patients (45%) in the SMT + HA arm and 21 (28%) in the SMT arm ($P = 0.042$). This finding strengthened during the following 2 months because the cumulative correction rate of hyponatremia after 3 months was 71% vs 44% in the SMT + HA and SMT groups, respectively ($P = 0.006$) (Figure 2b). Interestingly, there were no significant differences in the daily dosage of diuretics administered to hyponatremic patients receiving albumin or not (see Supplementary Table 2, http://links.lww.com/AJG/C679).

During the trial follow-up, HA-treated patients with either baseline hyponatremia or normonatremia had a lower incidence of at least moderate hyponatremia as compared with those who received SMT. The incidence rate ratios were 0.245 (95% CI 0.167–0.359) ($P < 0.001$) in hyponatremic and 0.539 (95% CI 0.338–0.859) ($P = 0.008$) in normonatremic patients. Further details are reported in Table 3.

DISCUSSION

This study, based on data gathered from a prospective controlled clinical trial, shows that HA administration to hyponatremic patients with cirrhosis and ascites is associated with serum sodium normalization in a time frame of 3 months in a higher number of patients compared with SMT. A recent report study also described an increase in serum sodium after targeted HA administration (11). However, the extent of serum sodium increase was modest, and the number of patients resolving hyponatremia was unknown. There are differences in patient populations and study design between the 2 trials that warrant discussion to clarify the potential translation of their results into clinical practice. The ANSWER study enrolled outpatients with uncomplicated ascites (12) while the ATTIRE study enrolled patients with low serum albumin (<3.0 g/dL) hospitalized because of acute decompensation of cirrhosis (11). Furthermore, in the active arms of these studies, HA administration consisted of either a fixed long-term schedule (up to 18 months) or short-term infusions (up to 2 weeks) targeted to raise serum albumin above 30 g/L. Finally, the cutoff serum sodium concentration used to define hyponatremia (<135 or 130 mmol/dL) differed between the 2 studies.

What we describe and support here is not the therapeutic approach to severe acute hyponatremia but the way of correcting a sustained, prognostically relevant sodium imbalance. In this respect, the other finding of this study is also relevant. The ANSWER study had shown that long-term HA was associated with a lower incidence of moderate-to-severe hyponatremia (12). This study showed that this also occurred in the patient subset with baseline hyponatremia and was even more marked than in normonatremic patients.

Table 3. IR and IRR of episodes of moderate hyponatremia (Na <130 mmol/L) in patients with baseline mild and moderate hyponatremia (Na <135 mmol/L; n = 74 SMT and 75 SMT + HA) or normonatremia (Na ≥135 mmol/L; n = 139 SMT and 143 SMT + HA) randomized in the SMT or SMT + HA arms

	SMT IR (95% CI)	SMT + HA IR (95% CI)	SMT + HA/SMT IRR (95% CI)	*P* value
Baseline Na <135 mmol/L	2.262 (1.839–2.754)	0.554 (0.389–0.767)	0.245 (0.167–0.359)	<0.001
Baseline Na ≥135 mmol/L	0.376 (0.272–0.506)	0.203 (0.137–0.289)	0.539 (0.338–0.859)	0.008

The number of hyponatremic episodes were expressed as IR (number of events per person per year) and compared by IRR using SMT as the reference category.
IR, incidence rate; IRR, incidence rate ratio; SMT, standard medical treatment; SMT + HA, standard medical treatment plus human albumin.

Our results differ from those of the MACHT study, a placebo-controlled randomized trial, reporting no effect of long-term albumin plus midodrine on the incidence of complications, including hyponatremia, in patients with cirrhosis and ascites awaiting a liver transplantation (13). This variance is likely the consequence of the lower amount of albumin administered and the much shorter duration of albumin treatment so that no impact on serum albumin concentration was observed in the MACHT trial in contrast to what occurred in the ANSWER trial (14).

Post hoc analyses have well-known limitations, but the heterogeneity of the treatment effect can only be explored by this approach (15). Our findings offer the rationale for further investigations and randomized clinical trials assessing the effect of long-term albumin administration in hyponatremic patients with decompensated cirrhosis. The settings of liver transplantation waitlist or elective general surgery would merit particular attention because severe hyponatremia at the time of surgery can favor neurological damage secondary to rapid correction (16).

CONFLICTS OF INTEREST

Guarantors of the article: Mauro Bernardi, MD, and Paolo Caraceni, MD.

Specific author contributions: The original concept of the study was developed by Mauro Bernardi and P.C. This study was designed and planned by G.Z., Mauro Bernardi, M. Baldassarre, and P.C. The chief investigators were Mauro Bernardi and P.C. Acquisition of the data was done by G.Z., M.T., S. Nardelli, S.P., C.A., S. Neri, and F.G.F. Statistical analysis was done by M. Baldassarre and G.B. Data analysis and interpretation was done by G.Z., Mauro Bernardi, M. Baldassarre, M.T., M.D., and P.C. The manuscript was drafted by G.Z., M. Baldassarre, Mauro Bernardi, and P.C. Images were processed by G.Z. and M. Baldassarre. All authors critically reviewed the manuscript and approved the final draft for submission.

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Potential competing interests: G.Z. is part of the speakers' bureau for Grifols SA and Octapharma AG, outside the submitted work. M. Baldassarre is part of the speakers' bureau for Octapharma AG, outside the submitted work. M.T. is part of the speakers' bureau for Grifols SA and Octapharma AG, outside the submitted work. M. Bernardi is part of the speakers' bureau for Grifols SA, Octapharma AG, Takeda, CSL Behring GmbH, and PPTA and is a consultant for CLS Behring GmbH, Grifols SA, and Takeda, outside the submitted work. S.P. is a consultant for Mallinckrodt, outside the submitted work. C.A. is a consultant for Alfasigma, outside the submitted work. P.C. is part of the speakers' bureau for Grifols SA, Kedrion Biopharma SpA, and Sobi SA and reports research grants from Grifols SA and Octapharma SA, outside the submitted work. S. Nardelli, S. Neri, F.G.F., and F.L. declare no potential competing interests.

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