【 ORIGINAL ARTICLE 】

The Outcome of Cirrhotic Patients with Ascites Is Improved by the Normalization of the Serum Sodium Level by Tolvaptan

Tomomi Kogiso, Mutsuki Kobayashi, Kuniko Yamamoto, Yuichi Ikarashi, Kazuhisa Kodama,
Makiko Taniai, Nobuyuki Torii, Etsuko Hashimoto and Katsutoshi Tokushige

Abstract:
Objective Hyponatremia is frequently observed in patients with decompensated liver cirrhosis and it is also related to a poor prognosis. The vasopressin V2-receptor antagonist tolvaptan is used to treat cirrhotic patients with ascites and increases the serum sodium (Na) level. In this study, we investigated (i) whether or not correction of the Na level improves the prognosis of cirrhotic patients with ascites and (ii) predictors of normalization of the serum Na level after tolvaptan therapy.
Methods This was a single-center retrospective study. A total of 95 Japanese cirrhotic patients (60 men, median age 63 years) were enrolled and received tolvaptan orally after hospitalization for ascites treatment. The serum Na level was monitored during the period of tolvaptan treatment. The laboratory data and survival rates of patients who achieved serum Na levels of <135 and ≥135 mEq/L after 1 week were compared.
Results Patients showed serum Na levels of 136 (121-145) mEq/L, and 42.1% had a serum Na level of < 135 mEq/L. Among patients with an initial serum Na level <135 mEq/L, 60.0% achieved a normal level after 1 week, and the survival rate was significantly higher in patients with a normalized serum Na level (p<0.01). The pretreatment brain natriuretic peptide (BNP) level was predictive of achieving a serum Na level of ≥135 mEq/L (odds ratio: 0.87, 95% confidence interval: 0.316-0.987, p<0.05).
Conclusion Normalization of the Na level after one week was associated with a favorable outcome of tolvaptan therapy, and Na correction improved the prognosis.

Key words: tolvaptan, liver cirrhosis, brain natriuretic peptide (BNP), hyponatremia

Introduction

Hyponatremia is commonly observed in decompensated liver cirrhotic patients and is a marker of the advanced stage of cirrhosis (1, 2). Patients with hyponatremia can also experience ascites, hepatic encephalopathy, and hepato-renal syndrome. Ascites treatment for liver cirrhosis patients has been improved dramatically using the vasopressin V2-receptor antagonist tolvaptan. The Japanese Society of Gastroenterology published evidence-based clinical practice guidelines in 2015 (3), in which tolvaptan was recommended as a useful add-on therapy in patients with decompensated liver cirrhosis with ascites prior to albumin administration or ascites drainage.

Hyponatremia in liver cirrhosis is caused by an increase in arginine vasopressin (AVP) release due to arterial splanchnic vasodilation and arterial underfilling (4, 5). AVP leads to renin-angiotensin-aldosterone system (RAAS) activation following the development of hypo-osmotic pressure and portal hypertension. The hyperactivated RAAS increases the reabsorption of water in collecting tubules, leading to a dilutionally low serum sodium (Na) level. Although conventional diuretics, particularly furosemide, decrease the serum level of Na, tolvaptan increases free water excretion without introducing major systemic electrolyte loss. Instead, the se-

rum Na concentration increases dose-dependently (6).

Around 70% of tolvaptan-treated patients exhibit increased urination and achieve body weight reduction (7-9). We have reported candidate predictors of a response to tolvaptan treatment by urination: the combination of an initial blood urea nitrogen (BUN)/creatinine (Cr) ratio <17.5 and a urine Na/potassium (K) ratio ≥3.09 was predictive of a urination response to tolvaptan (10). Hyponatremia is associated with a poor prognosis in cirrhosis patients; however, whether or not tolvaptan corrects the serum Na level in cirrhosis patients and its effect on their prognosis remain unknown. In addition, no predictor of normalization of the serum Na level by tolvaptan therapy has been reported.

We therefore evaluated the serum Na level after tolvaptan therapy according to age, underlying liver diseases, the liver and renal function, and hyponatremia severity in cirrhosis patients. We also evaluated the effect on the prognosis of Na correction after tolvaptan therapy.

Materials and Methods

Patients and study design

This was a single-center, retrospective, observational study conducted between September 2013 and July 2016. The median observation period was 203 (1-1,290) days. A total of 95 cirrhotic Japanese patients (60 men, 63.2%) complicated with ascites who received tolvaptan at 3.75 mg once per day (Samsca™; Otsuka Pharmaceutical, Tokyo, Japan) after hospitalization (including 4 retreatment patients) were enrolled. They were treated with conventional diuretics including 0-80 mg/day furosemide and/or 0-400 mg/day spironolactone, and a salt/water-restricted diet. The pretreatment Na level was evaluated in 95 patients. In 12 patients, the serum Na level could not be measured after 1 week of treatment due to hospital transfer or withdrawal. Thus, 83 patients with available serum Na level data were divided into those who reached a serum Na level <135 and those who reached a serum Na level ≥135 mEq/L after 1 week of treatment. We investigated the urine volume and body weight reduction after 1 week of treatment and laboratory test results, including the renal and liver function, at pretreatment and after 1 day (n=87), 1 week (n=83), and 1 month of treatment (n=73). Furthermore, in patients with an initial serum Na level of <135 mEq/L, the survival rates were compared between those who achieved serum Na levels of <135 and those who achieved serum Na levels of ≥135 mEq/L after 1 week of treatment. Tolvaptan was not used in patients with severe renal dysfunction [estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m^2 or a serum creatinine level >3.5 mg/dL] and patients with a hepatic encephalopathy scale score > II.

This study was conducted in accordance with the principles of the Declaration of Helsinki and the ethics rules of Tokyo Women's Medical University Hospital (TWMU, Tokyo, Japan). The TWMU Institutional Review Board (IRB) approved the study protocol.

Clinical parameters

The following baseline characteristics of patients were assessed: age, sex, clinical history, body weight, urine volume, underlying hepatic diseases, complications of cirrhosis (i.e. varices, hepatocellular carcinoma, and hepatic encephalopathy), administration of diuretics, branched-chain amino acids (BCAAs), albumin, and ascites drainage. Blood samples for biochemistry and hematological data were collected at the time that tolvaptan was administered. Laboratory tests assessed the serum concentrations of albumin, total bilirubin, aspartate aminotransferase, alanine transaminase, γ-glutamyltransferase, platelet counts, prothrombin time, ammonia, alpha-fetoprotein, des-gamma-carboxy prothrombin, and brain natriuretic peptide (BNP). For urinary tests, the levels of BUN and urine urea nitrogen (UUN), Cr, liver-type fatty-acid-binding protein (L-FABP), eGFR, serum and urine Na, potassium, and osmolarity were assessed. The 24-hour Cr clearance (24-hour Ccr) was calculated by estimating the renal function based on the serum and urine Cr levels (11). Chronic kidney disease (CKD) stage according to the eGFR was assessed using the guidelines of the Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (12). Plasma renin activity, aldosterone, and AVP were determined to evaluate RAAS activation. The Child-Pugh (CP) (13) and model for end-stage liver disease (MELD) scores (14) were used for the evaluation of the liver function.

Follow-up and outcomes

The patients were hospitalized and administered tolvaptan for 1-2 weeks following salt-/water-restricted diet-induced body weight reduction. After discharge, patients were followed every 1-2 months at the outpatient clinic. The prognosis was evaluated in terms of the survival time until death or liver transplantation after tolvaptan treatment. The observation periods were from the date of initiation of tolvaptan to death, liver transplantation, and the time of censoring (July 2016).

Statistical analyses

The data are presented as medians with minimum and maximum values. Changes in the Na level are shown as means and standard deviations. Significant differences between the two groups were assessed using the Mann-Whitney U-test and χ^2 test with the SPSS statistical software package (SPSS, Chicago, USA). Statistical significance was considered at $p<0.05$. A multivariate logistic regression analysis was performed with the likelihood ratio test to assess the fit of serum Na improvement to a normal range. The survival rates were subjected to a Kaplan-Meier analysis. Differences between groups were analyzed by the log-rank test.

Results

Baseline characteristics of patients pretreated with tolvaptan

The median age of the 95 patients receiving tolvaptan treatment was 63 (range, 22-90) years, and 63.2% were men (Table 1). The underlying liver diseases included viral hepatitis (35.8%), metabolic liver disease (40.0%), and primary biliary cholangitis (PBC; 9.5%). Regarding complications of liver cirrhosis, varices (63.2%), hepatocellular carcinoma (HCC; 34.7%), and hepatic encephalopathy (20.0%) were observed.

The patients showed a serum Na level of 136 (121-145) mEq/L. Of the patients, 20.0% showed a serum Na level of <130 mEq/L, 22.1% a level of 130-134 mEq/L, and 57.9% a serum sodium level of ≥135 mEq/L.

Change in Na level after tolvaptan treatment

The median increase in the urine volume was 675 (-530 to +3,490) mL and the median total urine volume was 1,630 (195-6,630) mL. The body weight change was -1.4 (-17.2 to +6.2) kg after 1 week of treatment. The serum Na level was monitored for 1 month after tolvaptan treatment. The serum Na level peaked at 1 week after treatment (Fig. 1a). In total, 78.3% of patients reached a normal serum Na level (≥135 mEq/L) after 1 week, and 74.0% did so after 1 month. In patients with an initial Na level of <135 mEq/L, 60.0% achieved a normal Na level at 1 week, and 50.0% did so after 1 month (Table 2). In contrast, about 90% of patients with an initially normal Na level retained a serum Na level of ≥135 mEq/L after 1 month. In the analysis of the Na level over time based on the initial Na level, the age, underlying liver disease, CP class, and renal level were assessed (Fig. 1). Patients with an initial Na level of <135 mEq/L exhibited an increased Na level after 1 week of treatment (Fig. 1a). Patients aged <72 years showed a lower Na level than those aged ≥72 years (Fig. 1b). Patients with hepatitis C virus (HCV)-related cirrhosis showed a lower Na level than those with liver disease of other causes (Fig. 1c). Patients with CP class C showed a lower Na level than those of class B (Fig. 1d). The serum Na level did not differ significantly according to renal stage (Fig. 1e). Thus, CKD stage based on the eGFR did not significantly affect the serum Na level.

Initial serum Na and the change in the Na level after 1 week of tolvaptan treatment

In patients with an initial serum Na level of <135 mEq/L, the mean Na level increased by 6.3±6.6 mEq/L, and those with a normalized Na level exhibited a 12.3±3.6 mEq/L increase after 1 week of treatment. In contrast, patients who did not have a normalized Na level showed a 2.3±4.8 mEq/L increase (Table 3, p<0.01). In patients with an initial serum Na level of 130-134 mEq/L, the mean increase in Na

level was 4.3±2.2 mEq/L. Patients that did not have a normalized Na level had a 2.6±4.0 mEq/L decrease (p<0.05). In patients with an initial Na level ≥135 mEq/L, the change in the Na level was not significantly different between patients who did and did not have a normalized Na level after tolvaptan treatment.

Comparison of the survival rate between patients with a serum Na level <135 and ≥135 mEq/L

Patients with a pretreatment serum Na level of <135 mEq/L showed a poor prognosis as determined by a Kaplan-Meier analysis (Fig. 2a). In addition, regarding the exclusion of patients who could not be followed up for 1 week, patients with a normalized serum Na level after 1 week of tolvaptan treatment showed significantly higher survival rates than those without a normalized level at that time (Fig. 2b, p<0.05).

Among the patients with an initial serum Na level of <135 mEq/L (n=35), those with Na levels of <135 mEq/L and ≥135 mEq/L after 1 week (Fig. 3a) and 1 month (Fig. 3b) of tolvaptan treatment were compared. The survival rate was significantly higher in patients with a normalized serum Na level after tolvaptan therapy than in patients with non-normalized Na levels (p<0.01, Fig. 3a). The survival rate was not significantly different but tended to be higher in patients with a normalized serum Na level after a month of tolvaptan therapy (Fig. 3b). Normalization of the Na level at 1 week affected the survival rate; therefore, a further study of patients who achieved a serum Na level of ≥ 135 mEq/L after 1 week of treatment was conducted.

An analysis of the factors associated with a normalized serum Na level after 1 week of treatment

The patients who achieved serum Na levels of <135 and ≥ 135 mEq/L after 1 week of treatment were compared in a univariate analysis (Table 1). Patients with a serum Na level of ≥135 mEq/L had a higher post-treatment urine volume, PT%, L-FABP, and serum Na than those with a serum Na level of <135 mEq/L. In contrast, BNP, UUN, urine Cr, plasma renin activity, and aldosterone were lower in patients with a normal Na level. The rates of cirrhosis-related complications and other ascites therapy (including diuretic use, administration of BCAA, and drainage of ascites) were not significantly different. The administration of albumin was higher in patients with a serum Na level of <135 mEq/L, albeit not significantly so. The BUN/Cr and urine Na/K ratios were not markedly different according to normalization of the Na level.

We next evaluated the factors predictive of normalization of the Na level after 1 week of treatment in a multivariate analysis. The parameters included were age, post-urine volume, PT%, BNP, L-FABP, serum Na, UUN, urine Cr, plasma renin activity, aldosterone, and CP score (Table 4). The serum BNP level [odds ratio: 0.87, 95% confidence interval (CI): 0.316-0.987, p<0.05] was a predictor of achievement of a serum Na level of ≥135 mEq/L after 1 week of

Table 1. Baseline Characteristics of Patients.

		Serum Na level at 1 week		p value
	Total (n=95)	<135 mEq/L (n=18)	≥135 mEq/L (n=65)	Na<135 vs. ≥135 mEq/L
Age (years)	63 (22-90)	61 (31-84)	64 (22-90)	0.42
Sex (% men)	61.5	73.7	55.2	0.14
Body weight (kg)	61.4 (35.1-143.6)	61.0 (50.0-98.9)	60.2 (35.1-143.6)	0.17
Urine volume (mL)	1,030 (135-3,970)	870 (280-2,600)	1,080 (135-3,970)	0.09
Underlying hepatitis (%) (Viral/metabolic/PBC)	35.8/40.0/9.5	52.6/36.8/5.3	35.8/34.3/11.9	0.51
Complications (%) (Varices/HCC/hepatic encephalopathy)	63.2/34.7/20.0	72.2/33.3/21.1	68.8/34.3/16.4	0.90
Diuretics				
Furosemide dose (mg/day)	20 (0-80)	20 (0-80)	20 (0-80)	0.48
Spironolactone dose (mg/day)	50 (0-400)	25 (0-400)	38 (0-100)	0.24
Branched-chain amino acid (%)	88.0	93.3	85.4	0.86
Administration of albumin (%)	55.8	77.8	54.1	0.07
CART or drainage (%)	37.9	50.0	32.2	0.17
Laboratory data at the initiation of tolvaptan				
Albumin (g/dL)	2.5 (1.5-4.2)	2.4 (1.8-3.2)	2.5 (1.9-4.2)	0.85
Total bilirubin (mg/dL)	1.8 (0.3-52.4)	3.0 (0.6-26.1)	1.5 (0.3-33.0)	0.21
Aspartate aminotransferase (U/L)	48 (13-551)	57 (20-551)	43 (13-233)	0.25
Alanine aminotransferase (U/L)	28 (3-381)	31 (11-381)	26 (3-144)	0.24
γ-Glutamyl transpeptidase (U/L)	48 (9-269)	26 (12-168)	48 (13-269)	0.69
Platelet counts (×10^4/μL)	8.6 (1.5-42.4)	9.3 (4.1-19.8)	8.2 (2.1-42.2)	0.65
Prothrombin time (%)	54.5 (16.3-90.3)	48.6 (19.5-76.0)	57.1 (16.3-90.3)	<0.05
Ammonia (μg/dL)	75 (24-269)	58 (31-167)	77 (24-174)	0.57
α-Fetoprotein (ng/mL)	4 (1-29,292)	3 (1-75)	5 (1-4,510)	0.11
Des-gamma-carboxy prothrombin (mAU/mL)	65 (3-4,994)	98 (13-2,982)	65 (3-1,788)	0.38
Brain natriuretic peptide (BNP, pg/mL)	74. 2 (7.9-1,002.3)	80.6 (8.1-176.4)	72.5 (7.9-1,002.3)	0.05
Blood urea nitrogen (BUN, mg/dL)	23.3 (5.5-125.3)	22.5 (5.8-64.3)	23.1 (5.5-78.7)	0.80
Creatinine (Cr, mg/dL)	1.06 (0.20-3.30)	1.05 (0.53-2.12)	1.07 (0.20-3.30)	0.33
L-FABP adjusted by Cr (μg/g·Cr)	9.0 (2.2-122.3)	7.8 (2.4-20.1)	10.6 (2.2-122.3)	<0.05
eGFR (mL/min/1.73 m^2)	50.3 (14.9-250.6)	51.5 (24.2-128.0)	49.7 (16.8-250.6)	0.39
Serum sodium (Na, mEq/L)	136 (121-145)	130 (122-142)	137 (121-145)	<0.01
<130, n (%)	19 (20.0%)	9 (50.0%)	6 (9.2%)	<0.01
130-134, n (%)	21 (22.1%)	5 (27.8%)	14 (21.5%)	0.58
≥135, n (%)	55 (57.9%)	4 (22.2%)	45 (69.2%)	<0.01
Serum potassium (K, mEq/L)	4.2 (2.8-6.1)	4.2 (3.1-6.1)	4.2 (2.8-5.3)	0.45
Serum osmolarity (mOsm/L)	281 (100-317)	278 (259-281)	283 (100-317)	0.28
Urine osmolarity (mOsm/L)	409 (116-938)	464 (277-938)	404 (116-747)	0.10
Urine urea nitrogen (mg/dL)	466 (54-1,375)	577 (332-1,311)	405 (54-1,375)	0.05
Urine Cr (mg/dL)	74 (7-246)	108 (40-246)	65 (7-229)	<0.05
Urine Na (mEq/L)	61 (7-256)	39 (7-256)	64 (7-155)	0.62
Urinary K (mEq/L)	21 (6-72)	24 (10-54)	21 (6-58)	0.48
24-h Cr clearance (mL/min)	51.9 (7.6-128.5)	43.9 (20.2-124.0)	53.0 (7.6-128.5)	0.80
Plasma renin activity (ng/mL/h)	4.9 (0.2-85.0)	15.5 (0.7-85.0)	3.4 (0.2-45.0)	<0.05
Aldosterone (pg/mL)	156 (10-2,920)	703 (10-2,920)	120 (10-1,110)	<0.05
Arginine vasopressin (AVP)	2.05 (0.4-5.0)	2.25 (0.4-4.8)	2.1 (0.4-5.0)	0.66
Child-Pugh (CP) score	10 (7-14)	11 (8-13)	10 (7-14)	0.08
MELD score	14 (7-31)	17 (10-31)	14 (8-30)	0.15
BUN/Cr ratio	6.44 (2.61-28.65)	6.37 (3.77-11.00)	6.72 (2.61-28.65)	0.47
Urine Na/K ratio	2.68 (0.22-25.60)	2.24 (0.22-25.60)	3.01 (0.29-8.06)	0.90

Na: sodium, PBC: primary biliary cholangitis, HCC: hepatocellular carcinoma, CART: cell-free and concentrated ascites reinfusion therapy, L-FABP: liver-type fatty acid binding protein, eGFR: estimated glomerular filtration rate, n: number of patients, MELD: model for end-stage liver disease, vs.: versus
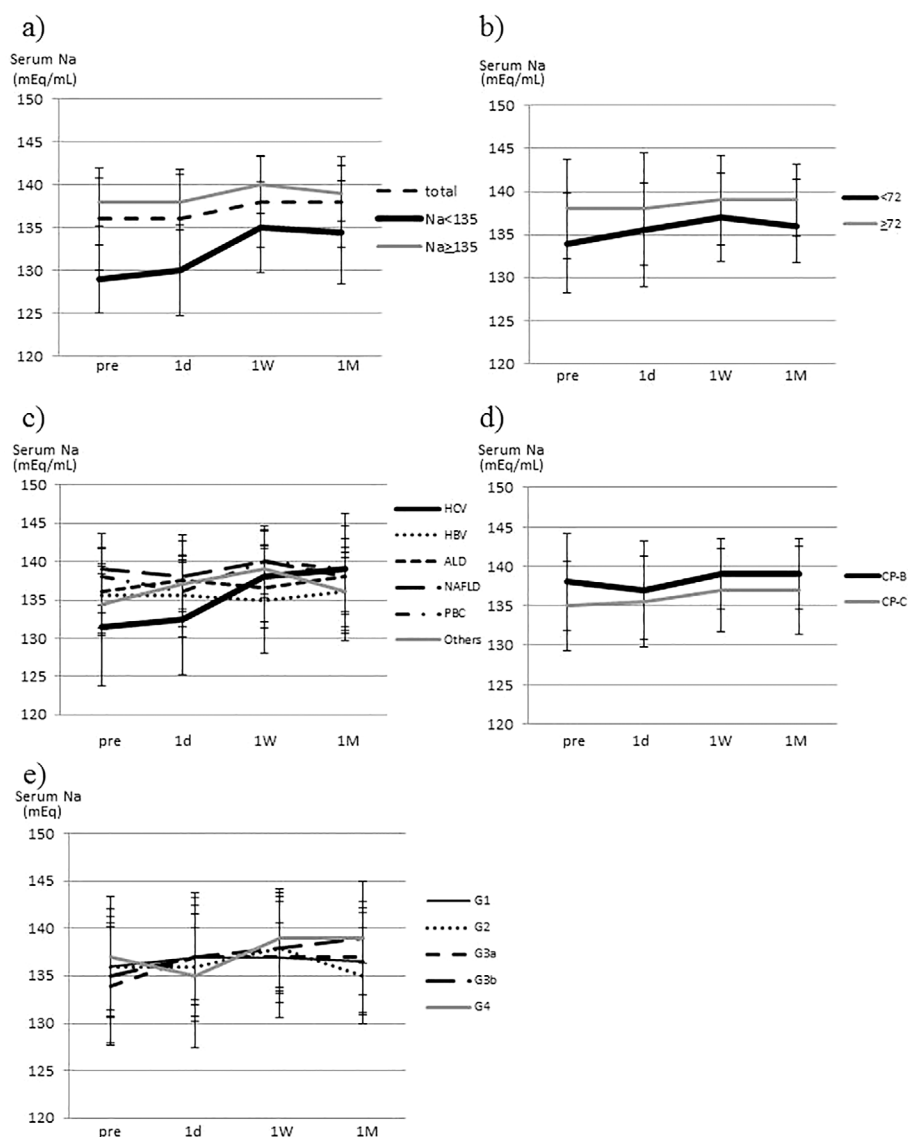
Figure 1. Responses to tolvaptan treatment in terms of the serum sodium (Na) level at 1 day, 1 week, and 1 month after treatment. a) Initial serum Na level, b) age, c) underlying hepatic diseases, d) Child-Pugh (CP) class, and e) renal stage. Patients with an initial serum Na level of <135 mEq/L showed a higher serum Na level increase than those with an initial serum Na level ≥ 135 mEq/L after 1 week of treatment (a). Patients aged <72 years showed a lower Na level than those aged ≥ 72 years (b). Patients with HCV showed a lower Na level than those without HCV (c). Patients with CP class C showed a lower Na level than those with CP class B (d). The serum Na level did not differ significantly according to renal stage (e). Na: sodium, Pre: pretreatment, 1d: 1 day of treatment, 1W: 1 week of treatment, 1M: 1 month of treatment, HCV: hepatitis C virus, HBV: hepatitis B virus, ALD: alcoholic liver disease, NAFLD: non-alcoholic fatty-liver disease, PBC: primary biliary cholangitis, CP: Child-Pugh, G: grade

**Table 2.** Rates of Normalization of Serum Na Level after Tolvaptan Treatment.

Duration	Total	Initial serum Na <135 mEq/L	Initial serum Na ≥135 mEq/L	p value Na<135 vs. ≥135 mEq/L
Normalization rate of serum Na (%)				
1 week (n=83)	65/83 (78.3%)	20/34 (58.8%)	45/49 (91.8%)	<0.01
1 month (n=73)	54/73 (74.0%)	14/28 (50.0%)	40/45 (88.9%)	<0.01

Na: sodium, vs.: versus

Table 3. Initial Serum Na Level and the Mean Change in Serum Na Level after 1 Week of Tolvaptan Treatment.

	Total (n=83)	Serum Na level at 1 week		p value
		<135 mEq/L (n=18)	≥135 mEq/L (n=65)	Na<135 vs. ≥135 mEq/L
Initial serum Na (mEq/L)	Change in the Na level			
<130	6.3±6.6 (n=15)	2.3±4.8 (n=9)	12.3±3.6 (n=6)	<0.01
130-134	2.5±4.1 (n=19)	-2.6±4.0 (n=5)	4.3±2.2 (n=14)	<0.05
≥135	0.7±2.8 (n=49)	-3.5±3.8 (n=4)	1.0±2.4 (n=45)	n.s.

Na: sodium, vs.: versus, n.s.: not significant
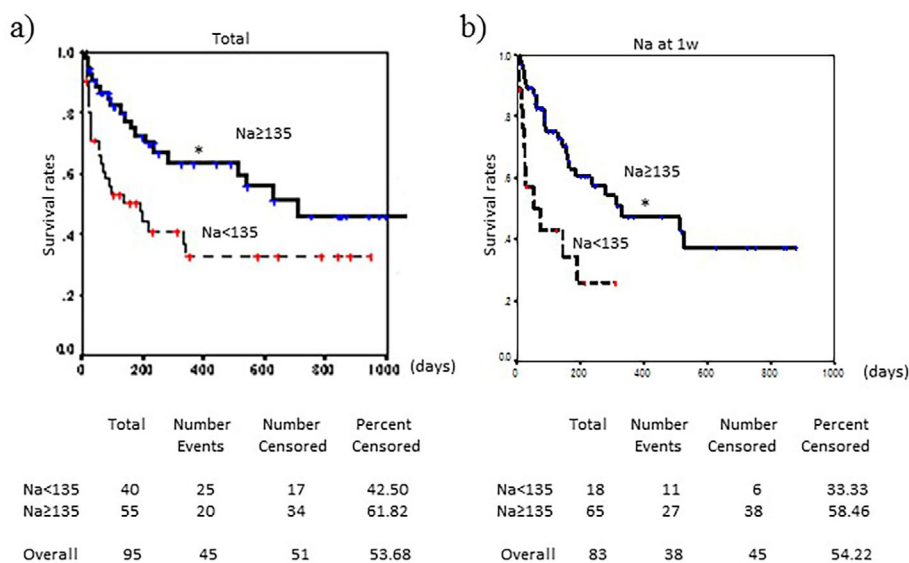
Figure 2. The survival rates according to the initial serum Na level and after 1 week of tolvaptan treatment. a) Patients with a serum Na level of <135 mEq/L showed significantly lower survival rates than those with a serum Na level of ≥ 135 mEq/L by a Kaplan-Meier analysis. b) The survival rates of patients who achieved serum Na levels of <135 and ≥ 135 mEq/L after 1 week of tolvaptan treatment by a Kaplan-Meier analysis. Patients with a serum Na level of ≥ 135 mEq/L showed a higher survival rate after 1 week than those with a serum Na level of <135 mEq/L. Na: sodium, 1W: 1 week of treatment, *p<0.05

tolvaptan treatment. Age (odds ratio: 1.46, 95% CI: 0.986-34.906, p=0.07), urine Cr (odds ratio: 1.07, 95% CI: 1.000-1.823, p=0.05), and CP score (odds ratio: 82.19, 95% CI: 0.884-1.9e+16, p=0.06) were also associated with the achievement of a serum Na level of ≥135 mEq/L.

Discussion

We demonstrated that normalization of the serum Na levels (≥135 mEq/L) after 1 week of tolvaptan treatment is associated with a favorable outcome in liver cirrhosis with ascites, even in the patients with an initial serum Na level of < 135 mEq/L. Normalization of the Na level might improve the prognosis of cirrhosis patients and can be predicted based on the pretreatment serum BNP level.

Hyponatremia in cirrhosis has been linked to a clinically urgent condition with symptoms of unconsciousness and hepatic encephalopathy and is associated with an impaired quality of life and a poor prognosis (15, 16). Regarding treatment of hyponatremia, the administration of a hypertonic saline bolus is not always recommended (17) because additional expansion of the extracellular fluid worsens edema and ascites. Furthermore, a too-rapid increase in the serum Na level may result in osmotic demyelination syndrome and injury to the cerebral vascular system (18).

The clinical efficacy and safety of tolvaptan for hypervolume hyponatremia (chronic heart failure and liver cirrhosis) and envolemic hyponatremia (the syndrome of inappropriate antidiuretic hormone (ADH) secretion: SIADH) have been reported (19). The Study of Ascending Levels of Tolvaptan in Hyponatremia (SALT) trials showed that tolvaptan treatment rapidly and effectively resolved hyponatremia in cirrhosis (20). Recently, it was also applied to the treatment of cancer patients with hyponatremia (21). Tolvaptan excludes only free water without accompanying Na elimination, resulting in an increase in the serum Na level.
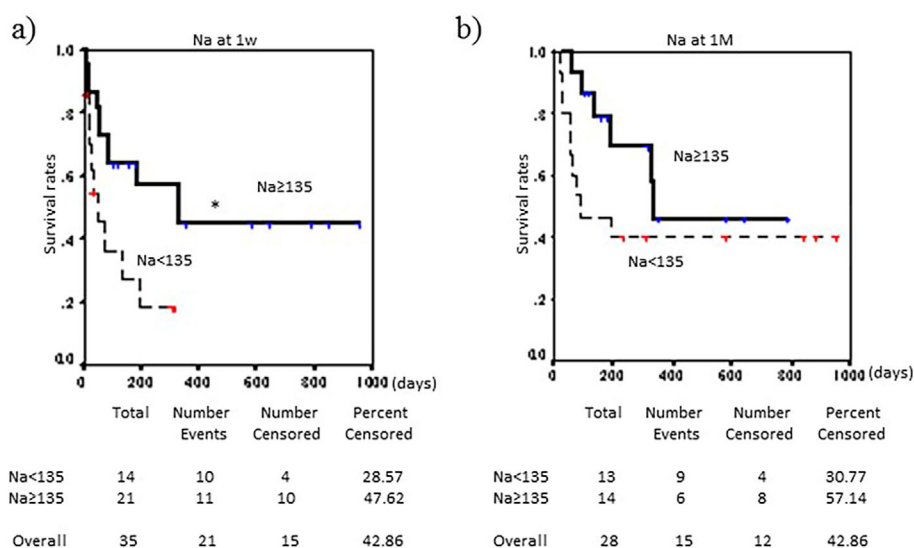
Figure 3. The survival rates of patients with an initial serum Na level of <135 mEq/L. Among patients with an initial serum Na level of <135 mEq/L, those with Na levels of <135 and ≥ 135 mEq/L a) after 1 week and b) after 1 month of tolvaptan treatment were compared by a Kaplan-Meier analysis. In patients with low Na levels (<135 mEq/L, n=35), the survival rates were significantly improved by normalization of the Na level after 1 week of treatment (a, p<0.05). The survival rate was not significantly different but tended to be higher in patients with a normalized serum Na level after a month of tolvaptan therapy than in those who did not achieve normalization (b). Na: sodium, 1W: 1 week of treatment, 1M: 1 month of treatment, *p<0.05

Table 4. Predictors of a Serum Na Level of ≥ 135 MEq/L after 1 Week of Tolvaptan Treatment by a Multivariate Analysis (n=83).

	Odds ratio	95% CI	p value
Age (years)	1.46	0.986-34.906	0.07
Post urine volume (mL/day)	1.00	0.991-1.000	0.12
Prothrombin time (%)	1.12	0.891-2.983	0.37
Brain natriuretic peptide (BNP) (pg/mL)	0.87	0.316-0.987	<0.05
L-FABP adjusted by Cr (μg/g·Cr)	1.06	0.891-1.968	0.44
Serum sodium (mEq/L)	0.40	4.79e-6-2.128	0.34
Urine urea nitrogen (mg/dL)	1.00	0.994-1.053	0.49
Urine creatinine (mg/dL)	1.07	1.000-1.823	0.05
Plasma renin activity (ng/mL/h)	1.15	0.962-3.349	0.14
Aldosterone (pg/mL)	1.01	0.994-1.028	0.48
Child-Pugh score	82.19	0.884-1.9e+16	0.06

Na: sodium, L-FABP: liver-type fatty acid binding protein, Cr: creatinine, CI: confidence interval

The Na level should be monitored for 8 hours or 1 day after treatment.

The change in the Na level is correlated with the serum Na level prior to receiving tolvaptan (22, 23). In 2016, Hirai et al. evaluated the risk of hypernatremia; a baseline Na level of ≥140 mEq/L, initial tolvaptan ≥7.5 mg/day, and a serum BUN/Cr ratio of ≥20 were independent risk factors for early-onset hypernatremia, particularly in elderly patients (24). In the present study, a younger age, higher CP score, and HCV-related cirrhosis were associated with a lower Na level, and patients with an initial low Na level tended to show an increased Na level after treatment. How-

ever, no cases experienced hypernatremia. This was probably because we administered tolvaptan at a half dose and used it with a diuretic, which inhibited Na reabsorption. In contrast, Imamura reported that the serum Na level remained unchanged after tolvaptan treatment while urinary Na excretion increased over 24 hours in heart failure patients (25). In our series, patients with an initial serum Na level of <130 mEq/L exhibited a 6.3±6.6-mEq/L increase in Na level; in contrast, patients with a serum Na level of ≥135 mEq/L showed only a slight increase of 0.7±2.8 mEq/L.

The serum level of Na was associated with mortality, and a low serum Na level was related to a poor prognosis (26)

(Fig. 2a). In our study, 78.3% of patients showed a normalized serum Na level after 1 week and 74.0% after 1 month. Although the degree of change in the Na level was not correlated with the survival rate, the achievement of a normal serum Na level (≥135 mEq/L) was associated with a favorable outcome (Fig. 2b). In a study by Boyer et al., the survival time did not differ markedly between patients that received and did not receive tolvaptan treatment; however, the treatment period was only 30 days in that study (27). Dahl et al. and Yan et al. conducted a meta-analysis and found that vaptan treatment led to an increase in the serum Na level but had no effect on the mortality (28, 29). However, the sample size of patients who received tolvaptan treatment was very small, and the treatment period was too short to evaluate the prognosis. Furthermore, the tolvaptan dose was too high (60 mg/day). In contrast, tolvaptan has been reported to decrease the rate of hospital death and prolong the survival time (10, 30, 31). In this study, patients with a serum Na level ≥135 mEq/L maintained their Na level within normal limits. Only 4 patients at 1 week and 5 patients at 1 month showed a serum Na level <135 mEq/L. In these cases, furosemide was increased or the intake was decreased. Based on these conditions, the Na level decreased despite tolvaptan therapy, and the patients showed a poor prognosis. Serum Na correction was also shown to improve the cognition, quality of life, and brain edema in cirrhosis patients (32). A normal serum Na level is associated with consciousness; therefore, an increase in the Na level may improve the performance status of patients. In the current study, the risks of severe ascites, spontaneous bacterial peritonitis, and hepatic encephalopathy were increased in patients with hyponatremia (33). This leads to portal hypertension, which increases the concentration of nitric oxide (NO) and is associated with vasodilatory processes in animal models (34). Serum Na correction may be associated with an improved survival through a reduction in NO production and complications; however, the physiological effect of serum Na requires further study. In addition, we previously reported that the BUN/Cr and the urine Na/K ratios were predictors of a tolvaptan response in terms of urination (10). Building on this earlier work, the present study focused on the Na level after tolvaptan therapy, and the BUN/Cr and urine Na/K ratios were not significantly associated with normalization of the Na level. Such normalization may prolong the life expectancy and was an independent and simple predictor of the prognosis. However, our study was also associated with some limitations. For instance, HCC affects the mortality rate of cirrhosis patients; therefore, HCC cases had to be excluded from the prognostic analyses. A prospective study is needed to confirm the effect of tolvaptan on the prognosis of cirrhosis patients without HCC.

An Na level of 135 mEq/L is at the lower range of normal in cirrhosis patients (26). Umemura et al. determined the optimum serum Na level in cirrhosis by means of an receiver operating characteristics (ROC) curve (35). A cut-off of 139 mEq/L predicted the survival (AUC 0.64, sensitivity

68.8%, and specificity 56.0%). In our study, 28.4% of patients had a serum Na level of ≥139 mEq/L compared with 34.9% after 1 week of treatment. Further prospective studies should assess (i) whether or not tolvaptan improves the mortality and (ii) the optimum Na level in cirrhotic patients.

BNP is a ringed peptide that consists of 32 amino acids and is secreted predominantly from the heart ventricles to enhance the volume expansion and pressure overload in order to regulate the blood pressure and fluid balance (36). BNP counteracts the RAAS in arterial pressure regulation and has both natriuretic and diuretic properties. Because BNP inhibits the RAAS, a low BNP level may lead to a high RAA level, and tolvaptan may be used to increase the Na level. BNP is predictive of a response to tolvaptan, along with the urinary Na/Cr ratio, in patients with heart failure (37). A higher BNP level was independently associated with failure of tolvaptan treatment. In our study, the BNP level was lower in patients with a serum Na level of ≥135 mEq/L and was an independent predictor of normalization of the Na level after 1 week of tolvaptan therapy (odds ratio: 0.87; 95% CI 0.316-0.987, p<0.05). The association of tolvaptan and BNP with the serum Na level should be further investigated, as it has been shown that other factors, such as age, urine Cr level, and CP score, are associated with normalization of the Na level.

In conclusion, tolvaptan may reduce the mortality rates by correcting the Na level to within the normal range. The serum BNP level may be predictive of achievement of a serum Na level of ≥135 mEq/L after 1 week of treatment. Normalization of the serum Na level after 1 week by tolvaptan treatment may therefore be predictive of the survival in cirrhotic patients with hyponatremia and ascites.

The authors state that they have no Conflict of Interest (COI).

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