Chapter 7

Predictors of the Response to Tolvaptan Therapy and Its Effect on Prognosis in Cirrhotic Patients with Ascites

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

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Abstract

Aims: The vasopressin V2 receptor antagonist, tolvaptan, has been reported to be effective in cirrhotic patients with ascites. Here, we evaluated predictors of the response to tolvaptan. *Methods*: A total of 97 patients with cirrhosis (60 males; median age, 63 years) who had been treated for ascites with oral tolvaptan were enrolled. Tolvaptan efficacy was defined as urine volume increase of ≥500 mL or a urine volume ≥2000 mL/day on the day following treatment. Normalization of the serum sodium (Na) level after 1 week of treatment and the posttreatment survival rate was analyzed. *Results*: Tolvaptan therapy resulted in effective urination in 67% of patients. A multivariate analysis revealed that the blood urea nitrogen/creatinine (BUN/Cr) ratio and urinary Na/potassium (Na/K) ratio were predictive of the tolvaptan response ($p < 0.05$). The serum Na level was 135 (121–145) mEq/L, and normal levels were recovered in 50.0% of the patients with an initial Na level of <135 mEq/L. The posttreatment survival rate was significantly higher in patients who responded to tolvaptan therapy ($p < 0.05$). *Conclusions*: The combination of the initial BUN/Cr and urine Na/K ratios and a normalized serum Na level after 1 week was predictive of a favorable outcome to tolvaptan therapy.

Keywords: vasopressin V2 receptor antagonist, tolvaptan, blood urea nitrogen/creatinine ratio, urine sodium/potassium ratio, serum sodium

1. Introduction

Ascites accumulation is commonly observed in decompensated liver cirrhosis [1]. The symptoms of ascites lead to a poor quality of life and prognosis [2]. Recently, the vasopressin V2 receptor

antagonist tolvaptan has been used for ascites treatment of cirrhosis in addition to spironolactone ± furosemide [3, 4]. The Japanese Society of Gastroenterology published evidence-based clinical practice guidelines in 2015 [5]. Tolvaptan is recommended for use before ascites drainage or administration of albumin because of its high efficacy irrespective of the serum albumin level [6]. While the serum sodium (Na) level is low in cirrhosis, it is increased in tolvaptan-treated patients because of free water clearance without accompanying Na elimination. In contrast, conventional diuretics promote hyponatremia and impair renal function. Thus, tolvaptan has benefits for the treatment of cirrhosis.

The mechanism underlying refractory ascites caused by liver cirrhosis has been hypothesized as one or more of the following [7, 8]: (1) hypo-osmotic pressure due to hypoalbuminemia; (2) a response to mesenteric and systemic vasodilation, accompanied by development of portal hypertension, which decreases the effective circulatory volume and depletes renal flow, leading to increased arginine vasopressin (AVP) release; increased AVP results in an increase in renin-angiotensin-aldosterone system activity; and (3) postsinusoidal obstruction and lymphatic edema. These multiple causative factors are associated with ascites accumulation.

Approximately 70% of tolvaptan-treated patients exhibit increased urination and achieve a reduction in body weight within 7–14 days [9, 10]. In addition to this short-term efficacy, tolvaptan also exerts long-term effects [11]. However, factors that predict the response to tolvaptan and its effect on prognosis are unclear. In this study, we focused on predictors of the tolvaptan response and the outcome of tolvaptan therapy.

2. Patients and methods

2.1. Patients

This was a single-center, retrospective observational study performed between September 2013 and March 2016. We enrolled a total of 97 Japanese cirrhotic patients (60 males, 62%) who received tolvaptan 3.75–7.5 mg/day (Samsca™; Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan) after hospitalization for ascites treatment. They were treated with conventional diuretics.

2.2. Method

The patients were classified as responders or nonresponders to tolvaptan therapy. Tolvaptan efficacy was defined as a urine volume increase of ≥500 mL or a urine volume ≥2000 mL/day on the day following tolvaptan treatment, as described by Ohki et al. with slight modifications [12]. The baseline characteristics of patients, including age, sex, medications, and laboratory parameters, were evaluated. We investigated the changes in body weight and the serum Na level after 1 week of treatment and evaluated laboratory parameters. Tolvaptan

was not used in patients with severe renal dysfunction (estimated glomerular filtration rate <15 mL/min/1.73 m^2 or a serum creatinine [Cr] level >3.5 mg/dL) or a hepatic coma scale score >II.

This study was conducted according to the principles of the Declaration of Helsinki, and the Institutional Review Board of Tokyo Women's Medical University Hospital (Tokyo, Japan) approved the study protocol (no. 3258-R). The results of this study, including figures and tables, were published in Hepatology Research [13] and were transferred with permission.

2.3. Statistical analysis

Data are presented as medians with minimum and maximum values. Significant differences between the two groups were assessed using the Mann–Whitney U-test and χ^2 test. The Statistical Package for the Social Sciences software (SPSS Institute, 11.01.J, Chicago, IL, USA) was used for the statistical analyses. Statistical significance was considered at $p < 0.05$.

3. Results

3.1. Response to tolvaptan according to urination and body weight parameters

The median age of the 97 patients (62% male) receiving tolvaptan treatment was 63 years (range, 22–90 years; **Table 1**). The underlying liver diseases and frequency of other ascites treatments did not differ significantly. The median increase in urine volume on the day after treatment was 690 mL (range: −530 to +3490 mL), while the median urine volume was 1675 mL/day (range: 195–6630 mL/day). The distributions of urination and body weight changes and their correlations with the tolvaptan response are shown in **Figure 1(a)**. The change in body weight after 1 week of treatment was −1.5 kg (−17.2 to +6.2 kg). A total urine volume ≥2000 mL was achieved in 40% of cases and an increase in the urine volume in ~50% of cases (**Figure 1b**). Approximately 40% of cases achieved a ≥2.0 kg body weight reduction after 1 week of treatment. Overall, 67% of the cases achieved the desired level of urination. In cases who responded to tolvaptan, the platelet count, urine Na level, and urine Na/potassium (K) ratio were higher, and the blood urea nitrogen (BUN)/Cr ratio was lower (**Table 2**). The serum Na level was 135 (121–145) mEq/L, and 39.2% of cases had an Na level of <135 mEq/L.

3.2. Urination-based predictors of the response to tolvaptan

Multivariate analysis revealed that the BUN/Cr ratio (odds ratio [OR], 1.08; 95% confidence interval [CI], 1.006–1.174; $p < 0.05$) and urine Na/K ratio (OR, 0.59; 95% CI, 0.366–0.855; $p < 0.01$) were predictors of the tolvaptan response (**Table 3**). In particular, patients who satisfied both

	Total (n = 97)	Responder (n = 65)	Nonresponder (n = 32)	p-value
Age (years)	63 (22–90)	62 (22–90)	63 (37–84)	0.21
Sex (% of males)	62	66	53	0.21
Underlying hepatitis (%) (viral/metabolic/ PBC)	37/39/9	32/43/11	47/31/6	0.29
Complication (%) (varices/HCC/hepatic encephalopathy)	67/35/23	71/35/18	59/34/31	0.37
Diuretics				
Furosemide dose (mg/ day)	20 (0–160)	20 (0–160)	20 (0–80)	0.96
Spironolactone dose (mg/day)	50 (0–400)	50 (0–400)	50 (0–400)	0.97
BCAA (%)	90	89	91	0.11
Administration of albumin (%)	62	63	59	0.65
CART or drainage (%)	41	38	47	0.43
Prognosis; death or transplantation (%)	45	37	63	0.03

Notes: PBC, primary biliary cholangitis; HCC, hepatocellular carcinoma; BCAA, branched-chain amino acid; CART, cell-free and concentrated ascites reinfusion therapy.

Table 1. Baseline characteristics of the patients.

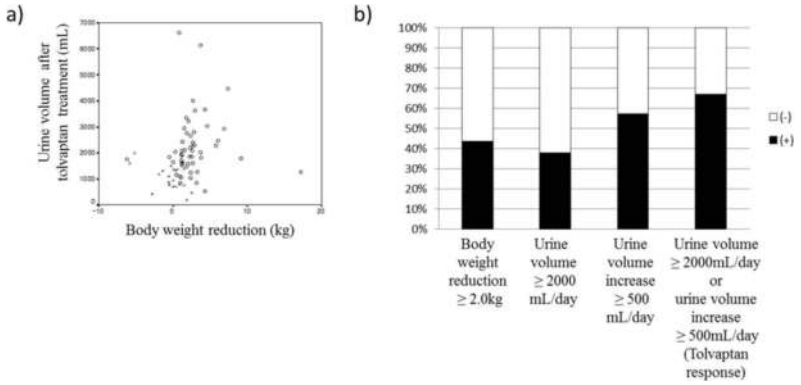

Figure 1. Urine volume and body weight response after tolvaptan treatment. (a) Distributions of urine volume after 1 day, and change in body weight after 1 week, of tolvaptan treatment. Circle, responder; cross, nonresponder. (b) The percentage of urination and body weight reduction responded to a tolvaptan therapy. Urine volume 1 day after, and change in body weight 1 week after, tolvaptan treatment was correlated with the tolvaptan response (a). A body weight reduction of ≥2.0 kg was found in 40% of cases, and a urine volume ≥2000 mL and a urine volume increase ≥500 mL were found in 67% of patients in response to tolvaptan therapy (b).

	Total (n = 97)	Responder (n = 65)	Nonresponder (n = 32)	p value
Albumin (g/dL)	2.5 (1.5–4.2)	2.5 (1.5–4.2)	2.4 (1.9–3.5)	0.88
Total bilirubin (mg/dL)	1.8 (0.3–52.4)	1.5 (0.5–33.0)	2.2 (0.3–52.4)	0.73
Platelet count ($\times 10^4$ μL^{-1})	8.6 (1.5–42.4)	9.0 (1.5–42.4)	6.4 (2.1–23.9)	0.05
Prothrombin time (%)	54.5 (16.3–90.3)	54.5 (16.3–90.3)	52.6 (22.6–89.0)	0.70
Ammonia (mg/dL)	69 (25–269)	70 (25–269)	63 (29–212)	0.97
α-Fetoprotein (ng/mL)	4 (1–29,292)	4 (1–4510)	6.5 (1–29,292)	0.36
DCP (mAU/mL)	75 (3–4994)	42 (3–4994)	324 (10–1788)	0.61
BUN (mg/dL)	23.4 (5.5–125.3)	21 (5.5–63.3)	27 (12.0–125.3)	0.02
Creatinine (mg/dL)	1.07 (0.20–3.30)	1.00 (0.42–2.12)	1.17 (0.50–3.30)	0.13
eGFR (mL/min/1.73 m^2)	50.0 (15.0–250.6)	50.3 (18–250.6)	46.2 (15.0–108.6)	0.15
Serum Na (mEq/L)	135 (121–145)	136 (122–145)	133 (121–144)	0.06
Serum K (mEq/L)	4.2 (2.8–6.1)	3.9 (2.8–5.3)	4.3 (3.1–6.1)	0.06
Serum osmolarity (mOsm/L)	281 (100–317)	283 (100–317)	279 (256–299)	0.68
Urine osmolarity (mOsm/L)	404 (116–938)	405 (116–938)	388 (233–715)	0.63
Urinary Na (mEq/L)	61 (7–256)	69.5 (10–256)	39 (7–108)	<0.01
Urinary K (mEq/L)	21 (6–72)	20 (6–72)	22 (13–48)	0.72
24 h creatinine clearance (mL/min)	51.2 (7.6–124.0)	52.8 (12.4–124.0)	44.1 (7.6–92.9)	0.12
BUN/creatinine ratio	22.5 (6.83–138.5)	21 (5.5–138.5)	23.7 (14.4–48.3)	0.01
Urine Na/K ratio	2.53 (0.22–25.6)	3.31 (0.35–25.6)	2.01 (0.22–5.13)	<0.01
Child-pugh score	10 (7–14)	10 (7–13)	10 (8–14)	0.23
Model for end-stage liver disease score	14 (7–31)	14 (7–31)	16 (8–31)	0.37

Notes. DCP; des-γ-carboxy prothrombin, BUN; blood urea nitrogen; eGFR, estimated glomerular filtration rate; Na/K; sodium/potassium.

Table 2. Laboratory data at initiation of tolvaptan treatment.

Parameter	Odds ratio	95% confidence interval	p-value
BUN/Cr ratio	1.08	1.006–1.174	<0.05
Urine Na/K ratio	0.59	0.366–0.855	<0.01
Serum K	1.41	0.537–3.893	n.s
Serum Na	0.96	0.854–1.080	n.s
Platelet count	0.95	0.839–1.051	n.s

Notes. Na/K, sodium/potassium; n.s, not significant.

Table 3. Multivariate analysis of parameters predicting a urination response to tolvaptan therapy.

		Urine Na/K ratio	
		<3.09 (n= 47)	≥3.09 (n = 30)
BUN/Cr ratio	<17.5 (n = 23)	10/12 (83.3%)	8/8 (100.0%)
	≥17.5 (n = 64)	13/33 (39.4%)	19/22 (86.3%)

Notes. BUN/Cr, blood urea nitrogen/creatinine; Na/K, sodium/potassium.

Table 4. Response to tolvaptan according to BUN/Cr and urine Na/K ratios.

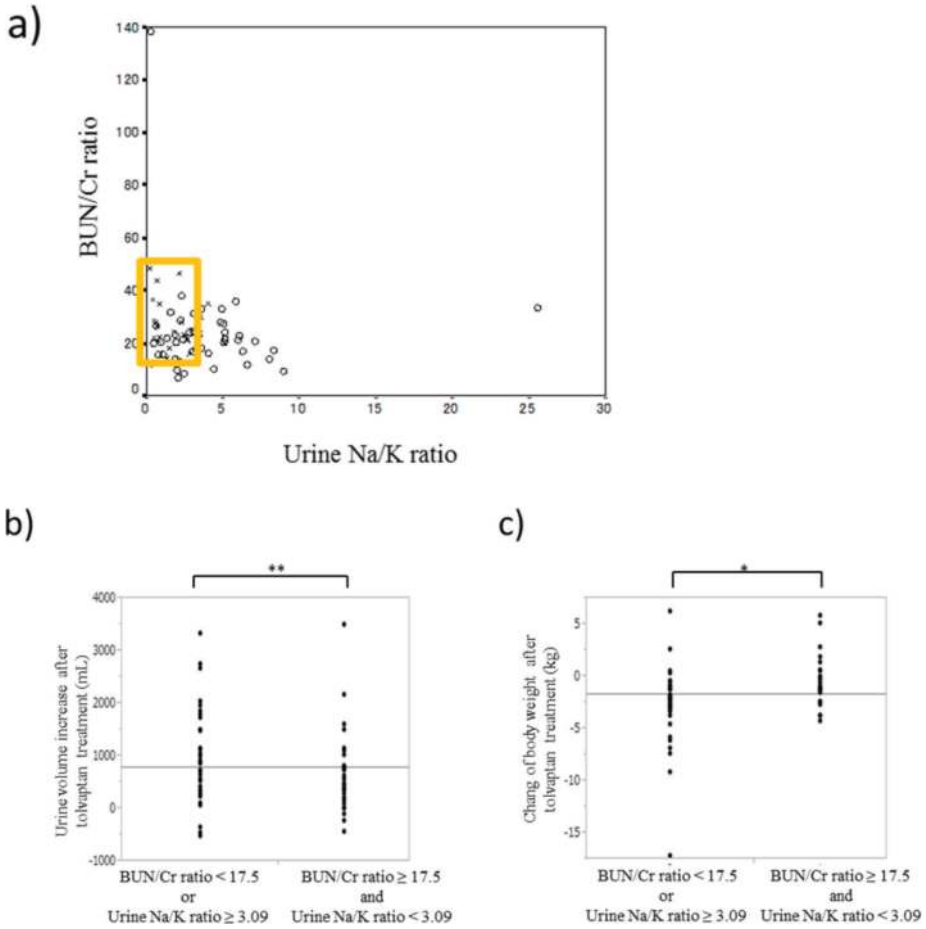

Figure 2. Distributions of the BUN/Cr ratio and urinary Na/K ratio and changes in urine volume and body weight. (a) Distributions of the BUN/Cr ratio and urinary Na/K ratio according to the tolvaptan response. Circle, responder, cross, nonresponder; framed square, BUN/Cr ratio ≥17.5, and urine Na/K ratio <3.09. Changes in (b) urine volume and (c) body weight in patients with and those without a BUN/Cr ratio ≥17.5 and urine Na/K ratio <3.09. Patients without a BUN/Cr ratio ≥17.5 and urine Na/K ratio <3.09 showed greater reductions in urine volume after 1 day (b) and in body weight after 1 week of treatment (c). BUN/Cr, blood urea nitrogen/creatinine; Na/K, sodium/potassium, *$p < 0.01$, **$p < 0.05$.

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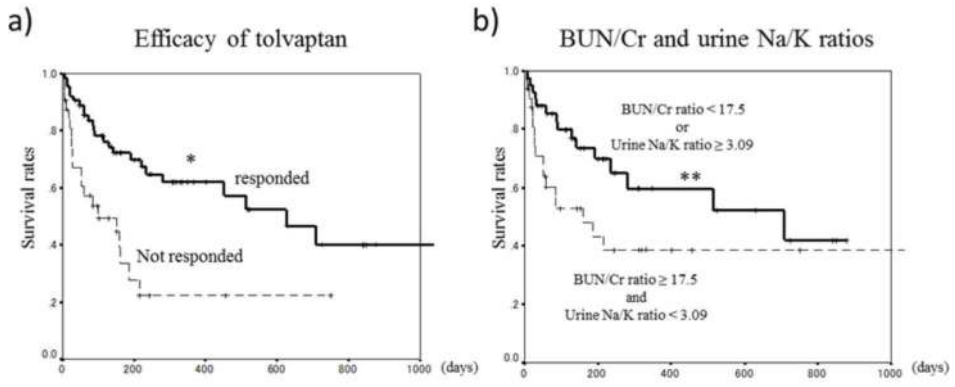

	Total	Number of events	Number censored	Percent censored
———	65	24	41	63.1
- - - - -	32	20	12	37.5
Overall	97	44	53	54.6

	Total	Number of events	Number censored	Percent censored
———	42	15	27	64.3
- - - - -	33	17	16	48.5
Overall	75	32	43	57.3

Figure 3. Survival rate of patients with and without a response to tolvaptan and the BUN/Cr and urine Na/K ratios. Patients who responded to tolvaptan therapy (a) and who did not have a BUN/Cr ratio ≥17.5 or urine Na/K ratio <3.09 (b) showed a significantly higher survival rate compared with nonresponders. BUN/Cr, blood urea nitrogen/creatinine; Na/K, sodium/potassium, *$p < 0.01$, **$p < 0.05$.

criteria of a BUN/Cr ratio <17.5 and urine Na/K ratio ≥3.09 achieved high tolvaptan response rates ($n = 8$, 100%; **Table 4**). In contrast, patients with a BUN/Cr ratio ≥17.5 and urine Na/K ratio <3.09 exhibited an extremely poor response (**Figure 2a**, framed area). In those patients who did not meet these criteria, urination and body weight reductions were observed (**Figure 2b** and **c**).

3.3. Prognosis after tolvaptan treatment

Regarding the mortality rate, 44 subjects died (45.4%). The survival rate was higher in patients who responded to tolvaptan therapy, as estimated by the Kaplan–Meier analysis (**Figure 3a**, $p < 0.01$). Patients with a BUN/Cr ratio <17.5 or urine Na/K ratio ≥3.09 showed a significantly higher survival rate than that of those who did not meet these criteria (**Figure 3b**, $p < 0.05$).

After 1 week of treatment, 70.1% of the patients achieved a normal serum Na level. These patients showed a significantly higher survival rate ($p < 0.05$). Among the patients with an initial Na level of <135 mEq/L ($n = 38$), 50.0% achieved a normal Na level after tolvaptan therapy and showed a significantly higher survival rate than that of patients without normalized Na levels ($p < 0.05$).

4. Discussion

The results suggest that the initial BUN/Cr and urine Na/K ratios and a normalized serum Na level after 1 week of treatment is predictive of a tolvaptan response in cirrhosis patients. The

patients showing a response to tolvaptan in terms of increased urination or serum Na level had prolonged survival and a better prognosis.

Representative factors predicting a response to tolvaptan are shown in **Table 5**. Free water clearance [14], aquaporin-2/AVP [15], and urinary Na excretion [16] were reported to be predictors of a tolvaptan response in patients with cirrhosis. The combination of BUN/Cr and urine Na/K ratios was the first reported predictor of a tolvaptan response.

Regarding prognosis, tolvaptan reduced the rate of inhospital mortality [17] and evidenced longer mortality same as other diuretics in heart failure patients [18], although no study has assessed these parameters in cirrhotic patients. In our study, patients with a BUN/Cr <17.5 or urine Na/K ≥3.09 showed high response rates. Approximately 50.0% of tolvaptan-treated patients reached a normal serum Na level after 1 week of tolvaptan therapy. Patients who responded to tolvaptan exhibited prolonged survival compared with those who did not. Tolvaptan may improve the prognosis.

Tolvaptan has been reported to delay the onset of end-stage renal disease and to be associated with a low rate of renal function deterioration [19, 20]. Therefore, early initiation of tolvaptan is recommended to protect renal function and improve prognosis.

However, our study had limitations because hepatocellular carcinoma (HCC) affects the mortality rate of patients with cirrhosis. Therefore, HCC cases must be excluded from prognostic analyses.

Author	Journal	Year	Predictor	Disease
Imamura et al. [21]	Circ J.	2013	Urine osmolality and percentage decrease in urine osmolarity	Heart failure
Imamura et al. [22]	Circ J.	2014	Urine aquaporin-2 (AQP2)/plasma arginine vasopressin	Heart failure
Okayama et al. [23]	Am J Cardiovasc Drugs	2015	Blood urea nitrogen/ creatinine (BUN/Cr) ratio	Heart failure
Shimizu et al. [24]	Nephrology (Carlton)	2015	Urine urea nitrogen/BUN ratio	Heart failure
Iwatani et al. [25]	Nephron	2015	Urine osmolarity	Chronic kidney disease
Miyaaki et al. [14]	Biomed Rep.	2015	Free water clearance	Liver cirrhosis
Nakanishi et al. [15]	J Gastroenterol.	2016	Urinary AQP2/Cr ratio	Liver cirrhosis
Chishina et al. [26]	Dig Dis.	2016	Serum BUN and serum Cr	Liver cirrhosis
Imamura et al. [27]	Int J Mol Sci.	2016	Urine AQP2	Heart failure
Kogiso et al. [13]	Hepatol Res.	2016	Serum BUN/Cr and urine sodium/potassium ratios	Liver cirrhosis

Table 5. Representative predictors of the response to tolvaptan therapy.

5. Conclusion

In addition to the combination of an initial BUN/Cr ratio <17.5 and urine Na/K ratio ≥3.09, a normalized serum Na level after 1 week of tolvaptan therapy was predictive of a favorable outcome in cirrhotic patients with hyponatremia and ascites treated with tolvaptan.

Author details

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

*Address all correspondence to: kogiso.ige@twmu.ac.jp

Department of Internal Medicine, Institute of Gastroenterology, Tokyo Women's, Medical University, Shinjuku-ku, Tokyo, Japan

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