INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Predictors of the Effect of Tolvaptan on the Prognosis of Cirrhosis

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Abstract

Objective Tolvaptan was first approved for use for cirrhosis in Japan in September 2013. The aim of the study was to examine the effect of tolvaptan, a vasopressin V2 receptor antagonist, on the prognosis of cirrhosis.

Methods The effect of tolvaptan was evaluated in 26 patients with cirrhosis treated at our hospital from September 2013 to April 2015.

Results The primary disease was hepatitis C in 20 patients, hepatitis B in 2, nonalcoholic steatohepatitis in 2 and others in 2; and 12 had hepatocellular carcinoma. The Child-Pugh score was 9.7±1.6 and the serum albumin level was 2.53±0.44 g/dL. Body weight decreased from 55.5±11.8 kg before administration to 52.1±14.7 kg after 7 days of tolvaptan treatment. After 7 days, patients with weight loss ≥2 kg (n=16, mean decrease of 4.3±2.3 kg) had significantly lower blood urea nitrogen (24.2±14.4 vs. 36.1±11.4 mg/dL) and serum creatinine (1.1±0.5 vs. 1.5±0.7 mg/dL) levels and decreased urine osmolality 4 h after the administration of tolvaptan (236±96 vs. 364±122 mOsm/kg) compared with patients with weight loss <2 kg (n=10, mean increase of +0.7±2.1 kg) (all $p<0.05$). The prognosis was significantly better in the group with weight loss ≥2 kg.

Conclusion The effect of tolvaptan on the renal function is likely to improve the prognosis of patients with cirrhosis if the drug is started at a stage in which the renal function is maintained.

Key words: tolvaptan, cirrhosis, ascites, hepatocellular carcinoma

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Introduction

Ascites is a major complication associated with portal hypertension in decompensated cirrhotic patients (1, 2) and is commonly treated with aldosterone antagonists and loop diuretics (3). However, patients with cirrhosis have decreased serum sodium and hypoalbuminemia (4), which reduce the effects of diuretics (4). This requires an dosage adjustment, resulting in limitations in treatment (5, 6) due to concerns of exacerbating hyponatremia and nephropathy by high-dose diuretics (7, 8).

Tolvaptan is an oral vasopressin V2 receptor antagonist that was approved for the indications of fluid retention associated with cirrhosis in September 2013. Tolvaptan has a mechanism of action that differs completely from other diuretics (9) and eliminates excess water without increased electrolyte excretion. Therefore, tolvaptan may be an innovative therapy for ascites that is resistant to treatment with existing diuretics in patients with hepatic edema.

Tolvaptan is a diuretic drug that functions independently of liver functions, particularly the level of serum albumin. Clinical trial data in Japan showed that tolvaptan is effective for ascites complicated with decompensated cirrhosis with decreased albumin synthesis (10-12). The efficacy of tolvaptan has been found to be about 60% (13), but in clinical practice some patients with cirrhosis experienced earlier relief and improved quality of life (QOL), whereas other patients have a delayed response or are nonresponsive to tolvaptan and require other treatment. Therefore, in the cur-

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Table 1. Baseline Characteristics of the Patients.

Variable	Value
Age (years)	72.2 (53-84)
Sex (male)	12 (46%)
Body weight (kg)	55.5 ± 11.8
Height (cm)	154.5 ± 8.6
Etiology (HCV/HBV/Other)	20/2/4
Child class (A/B/C)	0/9/9
Child-Pugh score	9.7 ± 1.6
Serum albumin (g/dL)	2.53 ± 0.44
Serum creatinine (mg/dL)	1.22 ± 0.59
Serum sodium (mEq/L)	135.9 ± 4.4
Urine osmolality (mOsm/kg)	473.7 ± 150.4
Loop diuretic dose (mg)	43.8 ± 33.2
Spironolactone dose (mg)	37.5 ± 17.6
HCC (with/without)	17/9
HCC stage (I/II/III//IV)	0/2/10/5
Vp (0/1/2/3/4)	14/0/1/0/2

Data are shown as median (range), number (%) or mean ± SD

rent study we compared patients with cirrhosis who did and did not show an early response to tolvaptan, with the goal of identifying predictors of the effect of tolvaptan that would allow another therapeutic intervention to be used as soon as possible in non-responders.

Materials and Methods

The subjects included 26 patients with cirrhosis who were treated with tolvaptan in our hospital from September 2013 to April 2015. Tolvaptan was administered to liver cirrhosis patients who had ascites despite treatment with combination therapy of a loop diuretic and an anti-aldosterone agent. The details of the subjects are shown in Table 1. Tolvaptan was initially administered at a dose of 3.75 mg and increased to 7.5 mg if the effect was insufficient on administration day 3.

Height, body weight, urine volume, blood test and urinalysis data were collected and are presented as the mean ± standard deviation (SD). Statistical analyses were conducted using the JMP9 software program (SAS Institute, Cary, USA). A chi-square test or Fisher's exact test was used to evaluate differences between two groups. Changes from baseline in the sample data from the same group were evaluated by the *t*-test. Missing data were excluded from analyses. Cut-off values were determined by receiver operating characteristic (ROC) analyses to build categorical valuables from consecutive data. Kaplan-Meier survival curves were evaluated by the log-rank test. All tests were two-tailed and $p<0.05$ was considered to indicate significance. The study was performed according to the Declaration of Helsinki and the clinical research guidelines in Japan and approved by the Institutional Review Board at Yamaguchi University Hospital (No. H27-096). Written informed consent was obtained from all patients.

Results

Tolvaptan was initially administered to all patients at a dose of 3.75 mg and increased to 7.5 mg if the effect was insufficient on administration day 3. The mean dosing period was 27.5 days. Body weight decreased significantly from 55.5±11.8 kg before treatment to 52.1±10.5 kg after 1 week of treatment. Urine osmolality significantly decreased from 488±170.4 to 355.5±138.6 mOsm/kg after 1 week of treatment; however, serum albumin, creatinine and sodium concentrations were not significantly changed after 1 week (Table 2). Body weight decreased by approximately 2.4 and 3.5 kg after 1 and 2 weeks of treatment, respectively, with respective reductions of 6.2% and 8.0% from baseline (Fig. 1).

Data were compared between patients with weight loss ≥2 kg (early responders, group R) and <2 kg (early non-responders, group N) after 1 week of treatment with tolvaptan (Fig. 2). Four patients in group N subsequently had a decrease in body weight of ≥2 kg after reduction of loop diuretics (2 patients), fluid replacement (1 patient) and ascites removal (1 patient), leading to remission and hospital discharge. There were no significant differences in age, height, body weight, sex, Child-Pugh score, hepatic function including albumin, Model for End-Stage Liver Disease (MELD) score, MELD-Na score, rate of complication with hepatocellular carcinoma (HCC), or dose of diuretics between groups R and N. However, blood urea nitrogen (BUN) and serum creatinine were significantly lower and the renal function was better maintained in group R, suggesting that these conditions were requirements for an early effect of tolvaptan (Table 3).

After initiating treatment with tolvaptan, urine osmolality 4 h after oral administration was significantly lower (236±96 vs. 364±122 mOsm/kg, $p<0.05$) and the % decrease in osmolality from baseline was significantly higher (48.0±23.3% vs. 15.4±17.3%, $p<0.01$) in group R. The patients in group R also had higher serum sodium and lower brain natriuretic peptide (BNP) levels, however, the levels were not significantly difference from that of group N (Table 3).

Treatment outcomes for HCC were compared between the two groups using the Response Evaluation Criteria in Solid Tumors (RECIST). There were no significant differences in the rate of complication with HCC, clinical stage, or cancer treatment between groups R and N (Table 3). The presence of HCC did not affect the prognosis (Fig. 3), and the complete response (CR) + partial response (PR) rate did not differ significantly between groups R and N (40.0% vs. 14.3%, $p=0.28$) (Fig. 4). The prognosis in group R was better due to a significant increase in the Kaplan-Meier survival curve ($p<0.05$) (Fig. 5).

Discussion

The treatment of 26 patients in our hospital with tolvap-

Table 2. Changes in Parameters from before Treatment to after One Week of Tolvaptan Administration.

	Before treatment	After one week	p value
Body weight (kg)	55.5 ± 11.8	52.1 ± 14.7	<0.01
Serum albumin (g/dL)	2.53 ± 0.44	2.69 ±0.47	0.21
BUN (mg/dL)	27.6 ± 14.3	26.7 ± 15.8	0.67
Serum creatinine (mg/dL)	1.24 ± 0.66	1.29 ± 0.72	0.78
eGFR (mL/min/1.73m^2)	51.9 ± 25.2	49.7 ± 22.5	0.25
Serum sodium (mEq/L)	135.9 ± 4.4	137.0 ± 5.4	0.06
Urine osmolality (mOsm/kg)	488.0 ± 170.4	355.5 ± 138.6	<0.01

Data are shown as mean ± SD

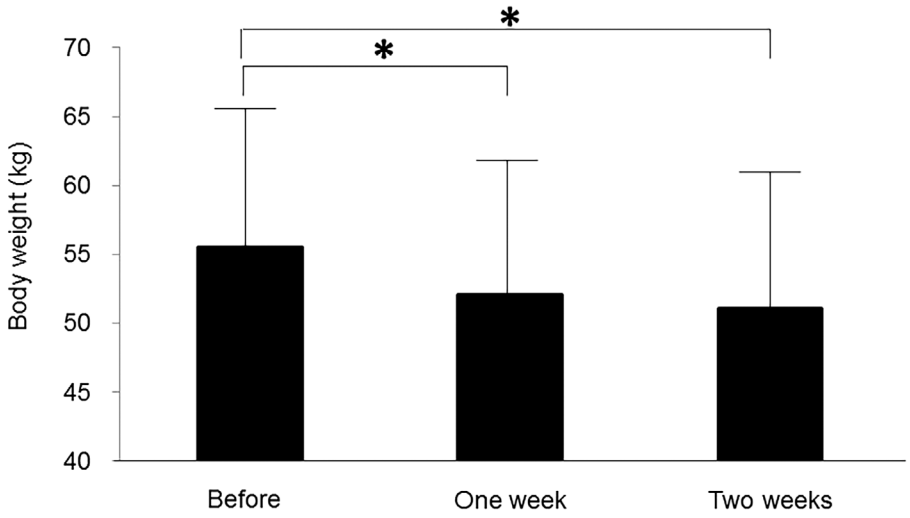

Figure 1. Changes in body weight after the administration of tolvaptan. Body weight significantly decreased from 55.5 ± 11.8 kg before treatment to 52.1 ± 10.5 and 5.1 ± 11.7 kg after 1 and 2 weeks of treatment (p<0.001). The respective body weight decreases of approximately 2.4 ± 3.3 and 3.5 ± 4.7 kg after 1 and 2 weeks represented reductions of 6.2% and 8.0%, respectively, from baseline. Data are shown as the mean ± standard deviation (SD).

tan at a dose of 3.75 mg for 1 week resulted in an overall response rate of 61.5%. Within 1 week, 16 of these patients had achieved a weight loss ≥2 kg. Therefore, the results of this study were similar to or better than those in a previous clinical trial that showed an efficacy of 55% at a dose of 7.5 mg (13). There was no significant difference in the hepatic reserve between responders and non-responders in the current study; however, the renal function in early responders was better than that in early non-responders. Diuretics cause renal impairment (14-16) and the effect of tolvaptan is poor in patients with heart failure, an increased BUN/Cre ratio and decreased estimated glomerular filtration rate (eGFR) (15-18). Because the renal function is involved in the prognosis of hepatic cirrhosis, it is important to maintain the renal function and control diuretics (19-22). However, the non-responder group may have included many patients with potential renal insufficiency. Therefore, further prospective studies are needed to evaluate whether the efficacy of tolvaptan improves by early administration.

In the current study, non-responders were likely to have higher BNP levels, however, none had clinical heart failure. Non-responders were found to have significantly poorer renal functions and there was a correlation between the renal function and BNP level (18, 19). Therefore, the BNP level in non-responders may be increased by renal impairment. In responders, urine osmolality 4 h after tolvaptan administration was significantly lower and the rate of reduction of urine osmolality was high. This suggests that tolvaptan increased the urine volume, resulting in diluted urine. The cut-off values determined by the ROC analysis to achieve a weight loss ≥2 kg were BUN ≤29 mg/dL, serum creatinine ≤ 1.35 mg/dL, and decreased urine osmolality 4 h after administration ≤34.7%.

Tolvaptan was approved in 2010 for treatment of heart failure. A clinical study showed that tolvaptan was effective in patients with urine osmolality >352 Osm/L before administration and decreased urine osmolality of >26% at 4 to 6 h after administration (19, 20). For patients with hepatic cirrhosis, the change in urine osmolality after administration is an indicator of efficacy in early administration. Determination of urine osmolality 4 h after the administration of tolvaptan can predict the subsequent efficacy and appropriate dosage of tolvaptan. If tolvaptan is effective, the QOL is improved due to reduced ascites and edema; however, such a

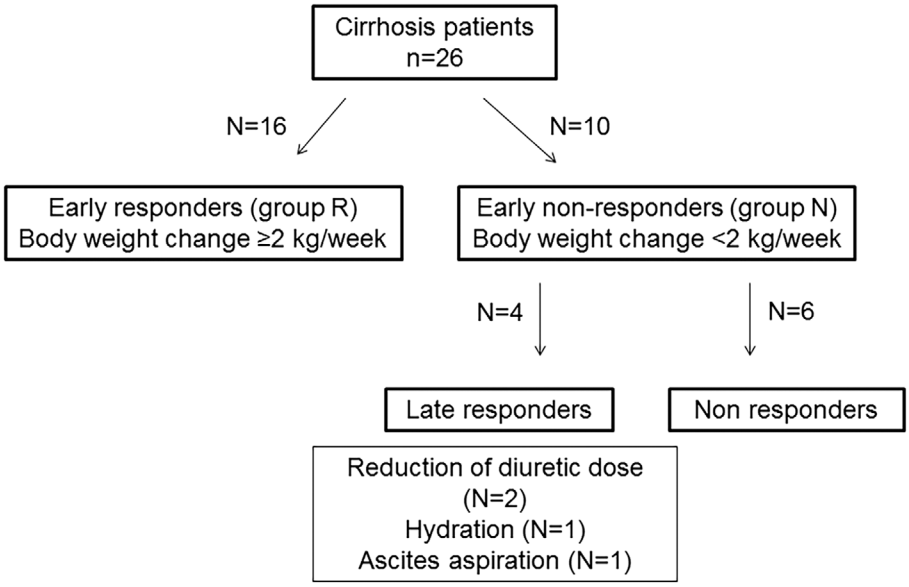

Figure 2. **Therapeutic effects of tolvaptan in the 26 patients in the study.**

Table 3. **Characteristics of Early Responders and Early Non-responders to Tolvaptan.**

	Responders	Non-responders	p value
Age (year)	71.6 ± 9.0	71.9 ± 6.2	0.93
Height (cm)	153.7 ± 9.7	154.9 ± 8.3	0.73
Body weight (kg)	57.4 ± 12.2	51.5 ± 10.3	0.25
Sex (male: female)	8 : 9	4 : 5	0.90
Child-Pugh score	9.8 ± 1.9	9.7 ± 1.1	0.89
MELD score	13.3 ± 3.2	12.7 ± 3.3	0.61
MELD-Na score	15.6 ± 4.2	16.3 ± 5.1	0.69
Serum albumin (g/dL)	2.6 ± 0.5	2.5 ± 0.4	0.54
BUN (mg/dL)	24.2 ± 14.4	36.1 ± 11.4	<0.05
Serum creatinine (mg/dL)	1.1 ± 0.5	1.5 ± 0.7	<0.05
eGFR (mL/min/1.73m^2)	54.9 ± 22.5	42.6 ± 30.3	0.25
Patient with HCC (%)	64.7	66.7	0.92
Clinical stage of HCC (I or II/ III or IV)	1/4	0/6	0.45
Treatment for HCC (RFA/ Lip-TAI, TACE)	1/4	0/6	0.45
Etiology (HCV/HBV/NASH/Others)	15/0/2/0	5/2/0/2	
Diuretic dose [loop / spironolactone (mg)]	50.0 ± 38.6/ 35.3 ± 15.5	32.2 ± 15.6/ 41.7 ± 21.7	0.20/ 0.39
Body weight change (kg/week)	-4.3 ± 2.3	0.7 ± 2.1	<0.01
Body weight change (%)	-9.1 ± 5.3	1.0 ± 5.1	<0.01
Urine osmolality (mOsm/kg)	495 ± 163	436 ± 129	0.42
Urine osmolality (after 4 h) (mOsm/kg)	236 ± 96	364 ± 122	<0.05
Reduction of urine osmolality (%)	48.0 ± 23.3	15.4 ± 17.3	<0.01
Serum sodium (mmol/L)	136.6 ± 3.6	134.4 ± 5.7	0.23
Serum sodium (after 4 h) (mmol/L)	136.4 ± 3.4	133.6 ± 6.8	0.17
Serum sodium (after 7 days) (mmol/L)	138.0 ± 4.2	135.1 ± 7.1	0.20
ADH (pg/dL)	2.4 ± 2.1	3.0 ± 2.4	0.55
BNP (pg/dL)	104.7 ± 74.5	254.7 ± 85.1	0.05
Cause of death (Liver failure/HCC)	2/2	3/3	0.41

Data are shown as mean ± SD

prognosis has not been shown in patients with hepatic cirrhosis. Some cardiovascular studies have shown an improved prognosis in responders, whereas others have indicated that the prognosis is not improved (21-24).

In this study, there was no significant difference in the treatment outcome of HCC between responders and non-responders and no significant difference in the prognosis between patients with and without HCC. However, the progno-

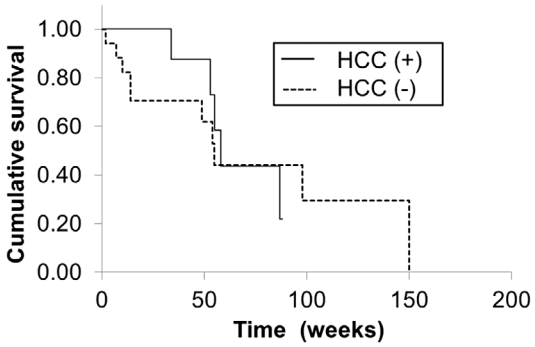

Figure 3. **Kaplan-Meier curves for patients with HCC (solid line) and without HCC (dotted line). Significant differences were analyzed by the log-rank test (Cochran-Mantel-Haenszel).**

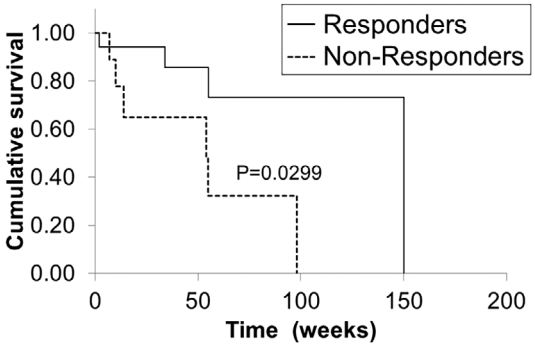

Figure 5. **Kaplan-Meier curves for early responders (solid line) and early non-responders (dotted line) to tolvaptan. Significant differences were analyzed by the log-rank test (Cochran-Mantel-Haenszel).**

sis of responders was significantly improved in comparison with that of non-responders. This result suggests that tolvaptan can improve the prognosis in patients with hepatic cirrhosis; however, the responder group included many subjects with good renal functions. Consequently, it is possible that their prognosis was already good before the administration of tolvaptan. Because of the small numbers of patients in the multivariate analysis, there were no significant differences; however, the prognosis tended to improve in the effective group (data not shown). A potential limitation associated with this study is the small number of patients. Therefore, prospective randomized comparative trial (RCT) studies are needed in more subjects without complication of HCC and in those with relatively well-maintained hepatic functions.

Conclusion

Indicators for an early response to tolvaptan were identified in this study. Tolvaptan is effective for diuretics-resistant ascites regardless of the hepatic function and albumin level and may improve the prognosis. An accumulation of cases for prospective RCT studies including multivariate analyses is needed to evaluate the long-term safety and efficacy of tolvaptan, the effect on prognosis, and the appropriate administration period.

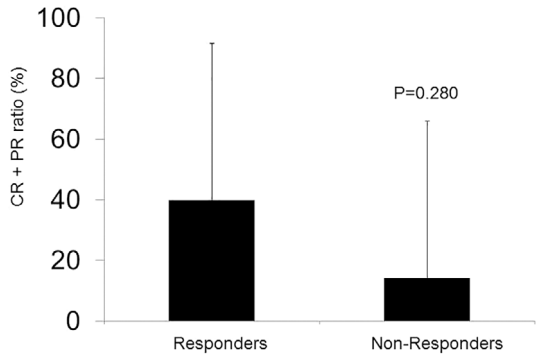

Figure 4. **Association between therapeutic effects of tolvaptan on ascites and the response evaluation criteria in hepatocellular carcinoma. The results were evaluated using the Response Evaluation Criteria in Solid Tumors Solid Tumors (RECIST). The y-axis indicates the complete response (CR)+partial response (PR) rates (%) for HCC. These rates were 40.0% in responders and 14.3% in non-responders. There was no significant differences between responders and non-responders (p=0.280). Data are shown as the mean ± standard deviation (SD).**

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

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