

Effectiveness of tolvaptan and long-term prognosis in patients with liver cirrhosis

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ABSTRACT

Subjects: Spironolactone and furosemide are commonly used for treatment of hepatic ascites, but the vasopressin V2 receptor inhibitor tolvaptan may also be added in cases that are treatment-resistant. The present study was conducted to clarify the factors affecting the therapeutic effectiveness of tolvaptan.

Methods: We studied 65 patients who were admitted to our hospital between September 2013 and September 2018. Patients whose weight decreased by 1.5 kg or more one week after tolvaptan administration were defined as responders (R), and compared with non-responders (NR).

Results: The two groups were compared in terms of age, cause of liver cirrhosis, presence of esophageal varices, presence of hepatocellular carcinoma, dose of furosemide, dose of spironolactone, albumin, T-bilirubin, PT%, and creatinine. Serum Na levels were significantly higher in R patients with significantly lower BUN. R patients survived significantly longer than NR patients. There was significant difference in survival rate between patients with a Na level of 138 mEq/L or less than for those with a Na level of 139 mEq/L or more. The main factor related to good treatment responsiveness in patients receiving tolvaptan was absence of any decrease in serum Na and a stable BUN level.

Conclusion: The factors related to the effectiveness of tolvaptan for treatment of ascites are a decrease in Na and an increase in BUN.

Keywords: Tolvaptan, hepatic ascites, sodium (Na)

Introduction

Decompensated cirrhosis has a poor prognosis once hepatic ascites has developed¹⁾.

Such patients are usually treated orally with the diuretics furosemide and spironolactone, together with administration of albumin, ascites puncture drainage, and cell-free concentrated ascites reinfusion therapy (CART)^{2), 3)}.

In poor responders, the prognosis is generally poor, and many suffer concomitant renal failure and death. The vasopressin V2 receptor inhibitor tolvaptan is

known to be more effective for improving ascites in view of its strong diuretic effect⁴⁾, and in recent years it has been used in combination for cases resistant to spironolactone and furosemide⁵⁾.

Tolvaptan exerts its diuretic effect by suppressing both the expression of aquaporin-2 (a water channel) and the reabsorption of water through vasopressin V2-receptor antagonism in the collecting duct of the kidney. Thus, it exerts a stronger effect than other diuretics⁵⁾⁻⁸⁾. However, the diuretic effect of tolvaptan is known to vary from case to case, and some patients thus treated still show a poor prognosis⁹⁾. Kogiso et al. have also reported

Table 1. Characteristics of patients with cirrhosis and ascites, grouped according to treatment response to tolvaptan

The two groups were compared in terms of age, sex ratio, cause of liver cirrhosis, presence or absence of esophageal varices, presence or absence of liver cancer, dose of furosemide, dose of spironolactone, albumin, T-bilirubin, prothrombin time %, and creatinine.

Characteristics		Total (n=65)	Responders (n=37)	Non-responders (n=28)	P-value
Age, years		69.4±7.9	68.7±8.2	70.2±7.5	NS
Sex(male/female)		40/25	23/14	17/11	NS
HCV/Alcohol/NASH/ PBC/Others		38/12/5/4/6	21/8/4/2/2	17/4/1/2/4	NS
HCC(Yes/No)		29/36	15/22	14/14	NS
Child-Pugh score(A/B/C)		6/56/3	2/25/1	4/31/2	NS
Varices(Yes/No)		42/23	24/13	18/10	NS
Body weight	kg	59.3±13.3	61.9±15.2	55.9±9.4	NS
Dose of furosemide before treatment	mg	45.2±31.5	43.9±30.9	46.8±32.7	NS
Dose of Spironolactone before treatment	mg	36.7±20.4	37.8±22.5	35.2±17.3	NS
Alb	g/dl	2.68±0.50	2.69±0.54	2.66±0.45	NS
T-bil	mg/dL	1.97±2.07	1.61±1.26	2.43±2.76	NS
PT%	%	72.4±21.8	72.8±24.6	71.9±17.9	NS
BUN	mg/dL	24.5±15.4	20.5±10.5	29.7±19.1	P<0.05
Cre	mg/dL	1.00±0.61	0.90±0.42	1.14±0.79	NS
Serum Na	mEq/L	137.6±4.0	138.8±3.6	136.1±4.0	P<0.01

NASH : Nonalcoholic steatohepatitis

PBC : Primary biliary cholangitis

HCC : Hepatocellular carcinoma

that the response to tolvaptan is dependent of the serum levels of BUN and Na¹⁰⁾. However, the factors associated with long-term prognosis in patients with cirrhosis receiving tolvaptan have remained unclear. Here we investigated these factors and examined the prognosis of patients thus treated.

Material and Methods

This was retrospective observation study undertaken in single hospital. The subjects were 65 patients with hepatic ascites (40 males and 25 females, aged 69.4±7.9 years) who were admitted to our department between September 2013 and September 2018. All were administered tolvaptan at 7.5mg/day for 1 week or more. Prior to administration, furosemide at 45.2±31.5mg/day and spironolactone at 36.7±20.4mg/day had been administered. Patients whose body weight

decreased by 1.5kg or more one week after the start of administration were defined as responders (R), and the rest were defined as non-responders (NR)¹¹⁾. These two groups were compared for related factors and prognosis. They were also divided and compared on the basis of creatinine and serum sodium values. Student's *t* test and χ^2 test were used for statistical analysis, and the R and NR groups were subjected to multivariate analysis.

Results

There were 37 R patients and 28 NR patients. The two groups were compared in terms of age, sex ratio, cause of liver cirrhosis, presence or absence of esophageal varices, presence or absence of liver cancer, dose of furosemide, dose of spironolactone, albumin, T-bilirubin, prothrombin time %, and creatinine (Table 1). In R patients BUN was

The factors related to the effectiveness of tolvaptan

Table 2. Logistic analysis for response to treatment with tolvaptan at 7.5 mg/day for 7 days in liver cirrhosis patients with ascites

Only the serum Na level was shown to be significant by multivariate analysis.

Factor	95%CI	Hazard ratio	P-Value
Dose of furosemide before treatment	0.9796-1.0281	1.0035	0.7747
Dose of Spironolactone before treatment	0.9877-1.0596	0.9877	0.2034
Alb before treatment	0.2531-3.1373	0.2531	0.8575
T-bil before treatment	0.4632-1.2056	0.4632	0.2326
PT% before treatment	0.9643-1.0299	0.9643	0.8371
BUN before treatment	0.8777-1.0359	0.8777	0.2601
Cre before treatment	0.2008-9.1108	0.2008	0.7564
Serum Na before treatment	1.0114-1.4539	1.2126	0.0373*
Body Weight before treatment	0.9696-1.0765	1.0217	0.4213

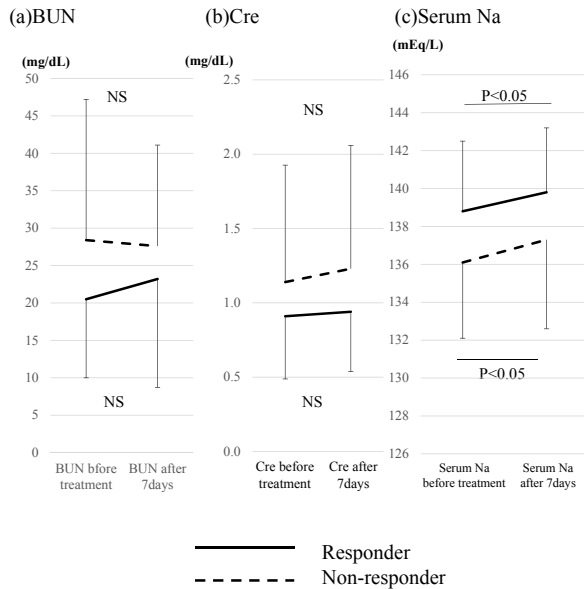


Figure 1. There were no significant differences between BUN and creatinine at 7 days after tolvaptan administration, but serum Na levels were significantly elevated in both the R and NR groups.

significantly lower (20.5 ± 10.5 vs. 29.7 ± 19.1 mg/dL, $p < 0.05$) whereas the Na level was significantly higher (138.8 ± 3.7 vs. 136.1 ± 4.0 mEq/L, $p < 0.01$). Only the serum Na level was shown to be significant by multivariate analysis (Table 2). There were no significant differences between BUN and creatinine at 7 days after tolvaptan administration, but serum Na levels were significantly elevated in both the R and NR groups (Figure 1). Albumin showed a tendency to increase in R patients one week after tolvaptan administration, T-bilirubin decreased significantly,

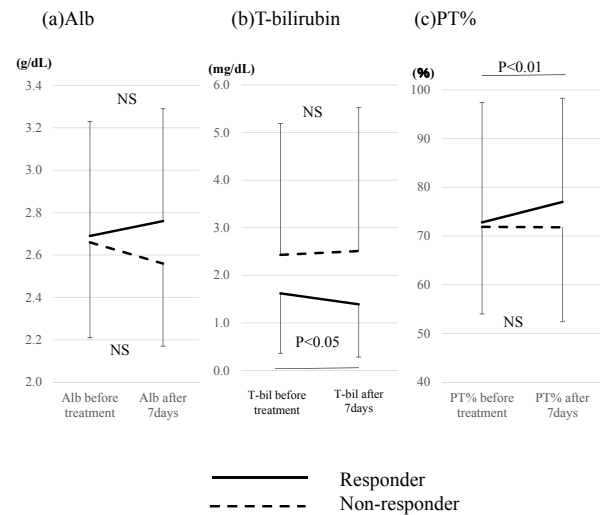


Figure 2. Albumin showed a tendency to increase in R patients one week after tolvaptan administration, T-bilirubin decreased significantly, and prothrombin time increased significantly.

and prothrombin time increased significantly (Figure 2). Survival was significantly longer in R patients than in NR patients (50.3 vs. 9.0 months, $p < 0.01$: log rank test) (Figure 3). There was no significant difference in survival rate between patients with a creatinine level of 0.9 mg/dL or less and those with a creatinine level of 1.0 mg/dL or more, but survival rate was significantly better in patients with a serum Na level of 139 mEq/L than in those with a serum Na level of 138 mEq/L or less (Figures 4, 5).

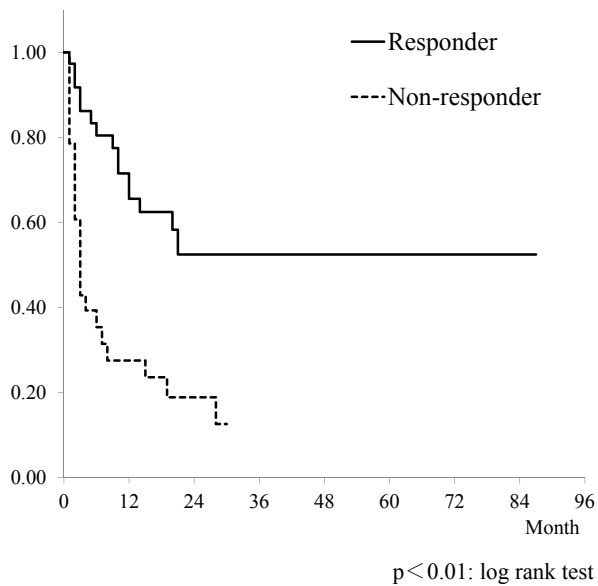


Figure 3. Survival was significantly longer in R patients than in NR patients (50.3 vs 9.0 months, $p < 0.01$; log rank test).

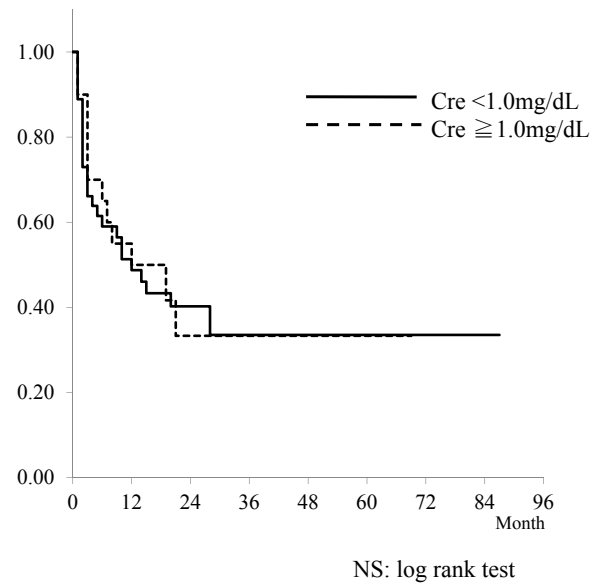


Figure 4. There was no significant difference in survival rate between patients with a pretreatment creatinine level of 0.9 mg/dL or less and those with a creatinine level of 1.0 mg/dL or more.

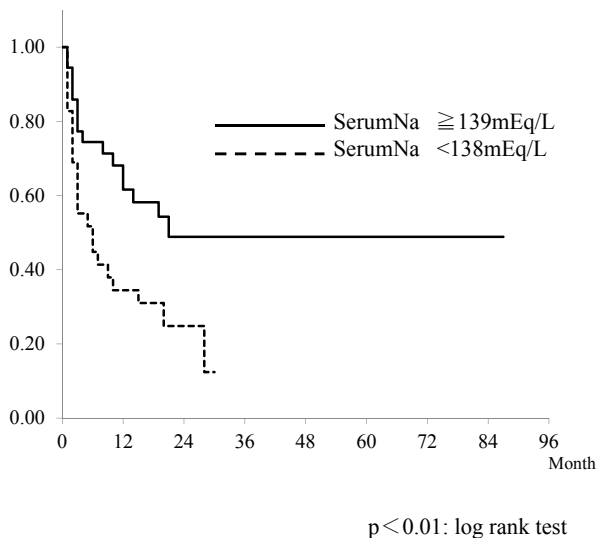


Figure 5. Survival rate was significantly better in patients with a pretreatment serum Na level of 139 mEq/L than in those with a serum Na level of 138 mEq/L or less. ($p < 0.01$; log rank test).

Discussion

Tolvaptan selectively inhibits the vasopressin V2 receptor in renal collecting ducts¹²⁾. Patients with hepatic ascites are administered spironolactone as a first-line drug, followed by administration of furosemide^{13), 14)}. Tolvaptan is used in combination

with these existing diuretics if there is no improvement in the ascites¹⁵⁾. In our present series, the NR group had significantly lower serum Na levels. As production of ascites worsens, activities of daily living (ADL) and nutritional conditions deteriorate, and the prognosis becomes poor. Various reports have documented the effectiveness of tolvaptan in patients with ascites^{16), 17)}. In this study, serum Na was significantly higher in the R group, whereas BUN was significantly lower, and the effect of initially administered diuretics appeared to be less marked.

Similar observations have been reported elsewhere, and our findings are consistent with a previous reports.^{18)–21)}. The reduction in serum Na is attributable of the effects of preceding diuretics, especially furosemide, whereas the high BUN level thought to be due to dehydration of blood vessels and a decrease in renal blood flow. These conditions are evident in NR patients and account for their poor prognosis. R patients showed an elevated albumin level and a decreased bilirubin level, indicating a significant improvement of liver reserve and nutritional status through increased food intake and decreased production of ascites. There was also a

significant increase in the serum Na level, consistent with a previous report¹⁸⁾. Furthermore, the survival rate was significantly better in R patients and in patients without a reduction in the Na level. Similar reports have indicated that R patients have a better prognosis^{22), 23)}. However, few previous studies have examined the long-term prognosis of such patients, and the present study appears to be the first to have done so. Although the dose of tolvaptan administered to such patients has been controversial, all of the present patients received 7.5mg. In some cases, a urine volume of 1000ml/day or more was achieved, and there were also cases in which a small amount was considered to be acceptable. In one study, a dose of 3.75mg was reported to be effective, but further investigation of this issue will be necessary²⁴⁾. The main factor related to good treatment responsiveness in patients receiving tolvaptan was absence of any decrease in serum Na and a stable BUN level.

Conclusion

Our present report is the first to indicate that tolvaptan has a favorable impact on the prognosis of patients with liver cirrhosis. In particular, for patients with a decreased serum Na level that can adversely affect prognosis, it is important to administer tolvaptan before such a decrease becomes apparent.

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