Predictors of the Effect of Tolvaptan on the Prognosis of Cirrhosis

Takuya Iwamoto, Masaki Maeda, Takuro Hisanaga, Issei Saeki, Koichi Fujisawa, Toshihiko Matsumoto, Isao Hidaka, Tsuyoshi Ishikawa, Taro Takami and Isao Sakaida

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

(Intern Med 55: 2911-2916, 2016)  
(DOI: 10.2169/internalmedicine.55.6819)

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-
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. 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 different 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 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

---

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).
had achieved a weight loss response rate of 61.5%. Within 1 week, 16 of these patients tan at a dose of 3.75 mg for 1 week resulted in an overall 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 cutoff 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

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

| Parameter                        | 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/1.73m²)             | 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 51.1 ± 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).
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/1.73m²)     | 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-TAL 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-
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.

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

Financial Support
This work was supported by JSPS KAKENHI Grant Number 15K19330.

## References

1. El-Bokl MA, Senoufy BE, El-Karmouty KZ, et al. Spot urinary sodium for assessing dietary sodium restriction in cirrhotic ascites. World J Gastroenterol 15: 3631-3635, 2009.
2. Moore KP, Wong F, Gines P, et al. The management of ascites in cirrhosis: report on the consensus conference of the International Ascites Club. Hepatology 38: 258-266, 2003.
3. Runyon BA. Historical aspects of treatment of patients with cirrhosis and ascites. Semin Liver Dis 17: 163-173, 1997.
4. Assimakopoulos SF, Thomopoulos KC, Kalogeropoulos C, et al. Unilateral leg edema in a cirrhotic patient with tense ascites. World J Gastroenterol 12: 5746-5747, 2006.
5. Gines P, Wong F, Watson H, et al. Effects of satavaptan, a selective vasopressin V(2) receptor antagonist, on ascites and serum sodium in cirrhosis with hyponatremia: a randomized trial. Hepatology 48: 204-213, 2008.
6. Stanley AJ, Forrest EH, Dibos KJ, MacGilchrist AJ, Hayes PC. Comparison between theophylline and spironolactone in the management of cirrhotic ascites: a randomized controlled study. Aliment Pharmacol Ther 12: 389-393, 1998.
7. Gines P, Cárdenas A, Arroyo V, Rodés J. Management of cirmrhosis and ascites. N Engl J Med 350: 1646-1654, 2004.
8. European Association for the Study of the Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. J Hepatol 53: 397-417, 2010.
9. Yamamura Y, Nakamura S, Itoh S, et al. OPC-41061, a highly potent human vasopressin V2-receptor antagonist: pharmacological profile and aquaretic effect by single and multiple oral dosing in

---

**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 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).

**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).
rats. J Pharmacol Exp Ther 287: 860-867, 1998.
10. Okita K, Kawazoe S, Hasebe C, et al. Dose-finding trial of tolvaptan in liver cirrhosis patients with hepatic edema: a randomized, double-blind, placebo-controlled trial. Hepatol Res 44: 83-91, 2014.
11. Sakaida I, Nakajima K, Okita K, et al. Can serum albumin level affect the pharmacological action of tolvaptan in patients with liver cirrhosis? A post hoc analysis of previous clinical trials in Japan. J Gastroenterol 50: 1047-1053, 2015.
12. Sakaida I. Tolvaptan for the treatment of liver cirrhosis oedema. Expert Rev Gastroenterol Hepatol 8: 461-470, 2014.
13. Sakaida I, Okita K. Correlation between changes in bodyweight and changes in ascites volume in liver cirrhosis patients with hepatic edema in short-term diuretic therapy. Hepatol Res 44: 735-739, 2014.
14. Arroyo V, Colmenero J. Ascites and hepatorenal syndrome in cirrhosis: pathophysiological basis of therapy and current management. J Hepatol 38: 869-889, 2003.
15. Okayama D, Suzuki T, Shiga T, Minami Y, Tsuruoka S, Hagiwara N. Blood urea nitrogen/creatinine ratio and response to tolvaptan in patients with decompensated heart failure: a retrospective analysis. Am J Cardiovasc Drugs 14: 289-293, 2015.
16. Shimizu K, Doi K, Imamura T, et al. Ratio of urine and blood urea nitrogen concentration predicts the response of tolvaptan in congestive heart failure. Nephrology (Carlton) 20: 405-412, 2015.
17. Imamura T, Kinugawa K, Shiga T, et al. Novel criteria of urine osmolality effectively predict response to tolvaptan in decompensated heart failure patients. Circ J 77: 397-404, 2013.
18. Imamura I, Kinugawa K, Minatsuki S, et al. Tolvaptan can improve clinical course in responders. Int Heart J 54: 377-381, 2013.
19. Planas R, Montoliu S, Balleste B, et al. Natural history of patients hospitalized for management of cirrhotic ascites. Clin Gastroenterol Hepatol 4: 1385-1394, 2006.
20. Tsutamoto T, Wada A, Sakai H, et al. Relationship between renal function and plasma brain natriuretic peptide in patients with heart failure. J Am Coll Cardiol 47: 582-586, 2006.
21. Anavekar NS, McMurray JJV, Velazquez EJ, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. N Engl J Med 351: 1285-1295, 2004.
22. Suzuki S, Yoshihisa A, Yamaki T, et al. Long-term effects and prognosis in acute heart failure treated with tolvaptan: the AVCMA trial. Biomed Res Int 2014: 704289, 2014.

The Internal Medicine is an Open Access article distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (https://creativecommons.org/licenses/by-nc-nd/4.0/).