Original Article

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Experience with long-term administration of tolvaptan to patients with acute decompensated heart failure

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Summary **Tolvaptan (TLV) is an oral selective vasopressin type 2 receptor antagonist. Long-term use of TLV is not recommended in patients with heart failure (HF) if fluid retention disappears and/or body weight is within the target range. However, some patients require long-term use of TLV. The current study investigated the efficacy and safety of long-term use of TLV. Subjects were 258 consecutive patients with HF who received TLV during hospitalization from January 2011 to March 2015. The rate of continuing administration of TLV was evaluated. Moreover, the one-year mortality rate and rate of re-hospitalization either with or without TLV were investigated. Results at discharge and one year later were compared for patients who continued to receive TLV one year after discharge. Oral concomitant medications, blood pressures, heart rate, blood tests, chest X-ray and transthoracic echocardiography were investigated. In-hospital and one-year mortality rates were 15.9% and 27.8%, respectively. Moreover, the mortality rate and/or rate of re-hospitalization within one year was 54.4%. The rate of re-hospitalization for HF was significantly higher in patients who continued to receive TLV after discharge compared to patients who ceased receiving TLV after discharge ($p < 0.001$). However, the subjects who continued to receive TLV for up to one year after discharge tended to have a longer duration until re-hospitalization for HF and significantly decreased brain natriuretic peptide levels (577.6 ± 528.5 pg/mL to 397.3 ± 365.8 pg/mL, $p = 0.015$). Long-term use of TLV might delay re-hospitalization for HF in patients with severe HF. Large-scale clinical studies are necessary to verify these results.**

Keywords: Tolvaptan, long-term use, in-hospital death, re-hospitalization, heart failure

1. Introduction

Tolvaptan (TLV), an oral selective vasopressin type 2 receptor antagonist, was approved in Japan on October 27, 2010 and came on the market on December 14th of that same year. Patients with acute decompensated heart failure (ADHF) refractory to diuretics and fluid retention have been treated with TLV in Japan (*1*), but TLV has only been used to treat hyponatremia in other countries. Previous studies revealed that TLV alleviated worsening renal function (*2*) and decreased blood pressure (BP) as a result of taking diuretics (*3*). The duration of use of TLV tended to increase in accordance with its effectiveness.

Initiating TLV during hospitalization while monitoring the patient's serum sodium level has been recommended. Moreover, the package insert also recommends not administering TLV over a prolonged period if fluid retention disappears and/or body weight is within the target range. However, a study has revealed that some patients require TLV over a prolonged period (*4*). In addition, the long-term use of TLV is reported to reduce the dosage of loop diuretics (*5*).

TLV became available at this Hospital in November 2011, and some patients have received TLV for a prolonged period (more than one year). The aim of the current study was to examine the actual consequences of use of TLV and the effects of the long-term use of TLV at this Hospital.

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2. Materials and Methods

2.1. *Statement of ethics*

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Omori Medical Center Ethical Committee of Toho University (24-123). The current study was a single-center, open retrospective study. Formal consent was not required for this type of study.

2.2. *Study subjects*

Subjects were 258 consecutive patients with ADHF who received TLV during hospitalization from January 2011 to March 2015. ADHF was diagnosed according to the Framingham criteria (*6*). The in-hospital mortality rate and the rate of continued administration of TLV were investigated after discharge and one year later. In addition, subjects were divided into three groups (Group A ceased receiving TLV after discharge, Group B continued receiving TLV upon discharge and ceased receiving TLV within one year of discharge, and Group C continued receiving TLV one year after discharge), and the rate of re-hospitalization for HF within one year was examined in these groups. Findings at discharge were compared among these groups. Differences in findings at discharge and one year later were investigated for patients who continued to receive TLV one year after discharge.

The need to continue receiving TLV was determined at discharge using an on-off test. An on-off test was performed after improvement of ADHF. In the on-off test, TLV was deemed unnecessary when ADHF did not worsen two days after TLV was discontinued. The need for outpatients to continue receiving TLV was determined by the attending physician given the patient's living conditions and diet.

2.3. *Concomitant oral medications*

Changes in the type and dosage of TLV and other concomitant medications were examined. The rate of administration of loop diuretics, a renin-angiotensin-aldosterone system inhibitor (RAAS-I), and a beta blocker (BB) were investigated. An RAAS-I was defined as an angiotensin-converting enzyme inhibitor, an angiotensin II type 1a receptor blocker, or a mineral corticoid receptor antagonist. The dose of a loop diuretic, converted to the furosemide dose (20 mg of furosemide is equivalent to 30 mg of azosemide), was evaluated.

2.4. *Clinical profile*

The New York Heart Association Classification (NYHA) was used to evaluate the severity of HF. BP was measured twice with an aneroid sphygmomanometer after the subject had been seated comfortably for at least five minutes, and the average was calculated (*7*). Systolic BP and diastolic BP were evaluated. Heart rate (HR) was evaluated using standard 12-lead electrocardiography (ECG). ECG was performed after the patient remained in a resting position.

2.5. *Laboratory analysis*

Changes in electrolytes (sodium, potassium, and chloride), liver function (aspartate aminotransferase, alanine aminotransferase and lactate dehydrogenase), renal function (blood urea nitrogen, and creatinine), and uric acid (UA), hemoglobin, and brain natriuretic peptide (BNP) levels were measured. All serum samples were obtained after fasting and resting in a supine position for at least five minutes.

2.6. *Chest X-ray and transthoracic echocardiography*

The cardiothoracic ratio (CTR) was determined from a chest X-ray obtained in the standing position on admission and was assessed by two physicians blinded to the examination. CTR was calculated utilizing the maximal cardiac diameter and the intrathoracic diameter. Transthoracic echocardiography (TTE) was performed to evaluate cardiac size (left atrial dimension and left ventricular end-diastolic/end-systolic dimensions), systolic function (ejection fraction (EF)), wall thickness (interventricular septal wall thickness and posterior wall thickness at end-diastole) were evaluated. EF was calculated with the Teichholz method (*8*) using a parasternal long-axis view or with a modified form of Simpson's method (*9*) using an apical two or four-chamber view.

2.7. *Statistical analysis*

Continuous variables were expressed as the mean ± standard deviation. Differences in findings after discharge were examined among the three groups using an unpaired Student's *t*-test. Values at discharge and one year later were compared using a paired *t*-test. Analyses were performed with Microsoft Excel and the statistical package Stat View (Stat View 4.0, SAS Institute Inc.). A probability (*p*) value of less than 0.05 was considered to indicate statistical significance.

3. Results

3.1. *Prognosis for subjects*

Of the current subjects, 41 (15.9%) died in hospital during follow-up. Thirty-four of those patients (13.2%) died due to cardiovascular disease. One hundred and seven patients (49.3%) continued to receive TLV after discharge, excluding patients who died in hospital.

Table 1. Characteristics of Groups A, B, and C at discharge (no significant differences were apparent)

Items	Group A, *n* = 104	Group B, *n* = 57	Group C, *n* = 48
Age	71.6 ± 14.2	73/2 ± 15.1	73.8 ± 12.4
Gender male/female	55/49	31/26	23/25
NHYA (I/II/III/IV)	0/4/86/14	0/7/35/15	0/4/32/12
Rate of administration of loop diuretics (*n*, %)	72, 69.2%	45, 78.9%	43, 89.6%
Loop diuretics (mg)	25.8 ± 20.9	36.1 ± 25.4	29.3 ± 20.9
Rate of administration of ACE-I / ARB/ MRA (*n*, %)	82, 78.8%	44, 77.2%	39, 81.3%
Rate of administration of beta blocker (*n*, %)	82, 78.8%.	45, 78.9%	40, 85.4%
Systolic BP (mmHg)	108.9 ± 15.2	108.1 ± 24.1	105.5 ± 15.6
Diastolic BP (mmHg)	58.4 ± 8.4	60.1 ± 11.4	58.1 ± 8.9
Heart rate (bpm)	71.6 ± 11.4	74.7 ± 12.5	72.6 ± 12.7
Sodium (mEq/L)	137.1 ± 4.5	138.3 ± 4.3	139.5 ± 4.1
Potassium (mEq/L)	4.2 ± 0.5	4.2 ± 0.5	4.3 ± 0.5
Chloride (mEq/L)	103.0 ± 4.7	103.9 ± 4.8	105.2 ± 4.4
AST (IU/L)	24.9 ± 13.3	23.2 ± 11.3	24.6 ± 11.2
ALT (IU/L)	20.3 ± 16.4	16.7 ± 14.0	19.0 ± 12.6
LDH (IU/L)	224.2 ± 66.6	234.0 ± 69.3	235.4 ± 81.2
BUN (mg/dL)	29.4 ± 14.2	35.5 ± 21.9	29.0 ± 12.3
Creatinine (mg/dL)	1.32 ± 0.74	1.60 ± 0.87	1.50 ± 0.87
Uric acid (mg/dL)	6.7 ± 1.7	6.9 ± 2.2	7.5 ± 2.0
Hemoglobin (mg/dL)	11.7 ± 1.8	11.2 ± 1.9	11.6 ± 1.9
BNP (pg/mL)	460.4 ± 592.0	738.5 ± 731.6	572.0 ± 520.2
Cardiothoracic ratio (%)	58.0 ± 7.8	59.8 ± 7.3	58.3 ± 7.9
Left atrial dimension (mm)	42.6 ± 10.4	44.5 ± 8.8	46.8 ± 10.0
LVDd (mm)	54.9 ± 9.8	56.0 ± 12.6	55.6 ± 12.0
LVDs (mm)	40.7 ± 11.8	42.3 ± 14.3	43.0 ± 14.0
IVSTd (mm)	0.89 ± 0.20	0.91 ± 0.28	0.89 ± 0.21
PWTd (mm)	0.93 ± 0.20	0.97 ± 0.25	0.94 ± 0.24
Ejection fraction (%)	49.5 ± 17.3	48.0 ± 19.4	45.8 ± 18.1

NHYA: New York Heart Association classification, ACE-I: angiotensin-converting enzyme inhibitor, ARB: angiotensin II type 1a receptor blocker, MRA: mineralocorticoid receptor antagonist, BP: blood pressure, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, BUN: blood urea uitrogen. BNP: brain natriuretic peptide, LVDd: left ventricular end-diastolic dimension, LVDs: left ventricular end-systolic dimension, IVSTd: interventricular septal wall thickness at end-diastole, PWTd: posterior wall thickness at end-diastole. Continuous data are expressed as the mean ± standard deviation. We analyzed with the Student's *t*-test.

Eight patients were missing during follow-up. Thus, 209 patients (104 patients in Group A who ceased receiving TLV after discharge and 105 patients who continued to receive TLV after discharge (Groups B and C)) were evaluated after discharge. Group B consisted of 57 patients (54.3%) and Group C consisted of 48 patients (45.7%). Of the 209 patients, 58 (27.8%) died within one year of discharge.

3.2. *Comparison of findings at discharge among the three groups*

Differences in findings among the three groups are shown in Table 1. There were no significant differences in any findings among the three groups. This indicated that the severity of HF at discharge did not differ significantly among the three groups. In addition, the rate of administration of cardio-protective medications such as RAAS-I and BB did not differ significantly among the three groups. There were no significant differences in the dosage of loop diuretics among the three groups.

3.3. *One-year mortality rate and/or rate of re-hospitalization and TLV*

Twenty-six patients (25.0%) died in Group A. Similarly, 32 (30.5%) of 105 patients who continued to receive TLV after discharge died within one year of discharge. The mortality rate did not differ significantly ($p = 0.811$). Within one year of discharge, 47 patients (45.2%) in Group A and 67 (63.8%) out of 105 patients who continued to receive TLV after discharge died from any cause or were re-hospitalized for HF. Twenty-six patients (25.0%) in Group A were re-hospitalized for HF within one year of discharge. Twenty-nine patients (50.9%) in Group B were re-hospitalized for HF within one year of discharge. Similarly, 23 patients (47.9%) in Group C were re-hospitalized for HF within one year of discharge. The rate of re-hospitalization for HF was significantly higher in Groups C and B compared to that in Group A (Figure 1, $p < 0.001$). Continuous administration of TLV for one year after discharge tended to delay re-hospitalization for HF (Figure 1), but the duration until re-hospitalization did not differ significantly between Groups C and B.

3.4. *Changes in oral concomitant medication*

Forty-five patients who received TLV after discharge and who continued to receive TLV for one year were evaluated, excluding three patients who were

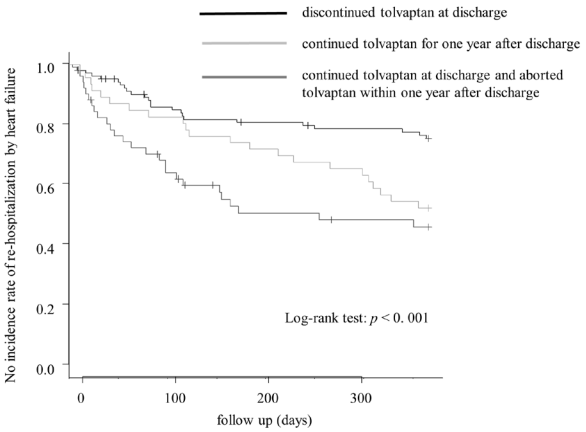

Figure 1. Re-hospitalization for heart failure within one year of discharge. Patients who continued to receive tolvaptan after discharge had a significantly higher rate of re-hospitalization for heart failure within one year of discharge compared to patients who ceased receiving tolvaptan after discharge. Continued administration of tolvaptan after discharge tended to extend the duration until re-hospitalization for heart failure. *p*-values were determined using the log rank test.

unavailable for follow-up. These patients consisted of 23 males (51.1%) with an average age of 73.8 ± 12.4 years (range: 45 to 91 years).

Forty-two patients (93.3%) received a loop diuretic one year after discharge, 37 (82.2%) received an RAAS-I, 39 (86.7%) received a BB, 9 (20.0%) received pimobendan, and 8 (17.8%) received amiodarone. The changes in concomitant medications, including TLV, did not differ significantly (Table 2).

3.5. *Changes in laboratory results and findings from chest X-rays and transthoracic echocardiography*

There were no significant changes in BP and HR (Table 2). Laboratory results indicated that sodium and UA levels decreased significantly (sodium: 139.8 ± 3.9 mg/dL to 138.6 ± 3.5 mg/dL, $p = 0.043$, UA: 7.9 ± 1.9 mg/dL to 6.8 ± 1.9 mg/dL, $p = 0.023$, Table3). In addition, BNP levels also decreased significantly (577.6 ± 528.5 pg/mL to 397.3 ± 365.8 pg/mL, $p = 0.015$, Table 3).

Table 2. Changes in concomitant medication and blood pressure at discharge and one year later in patients who continued to receive tolvaptan for one year

Items	At discharge	One year later	*p* value
Tolvaptan (mg)	9.21 ± 6.37	9.50 ± 5.57	0.619
Rate of administration of loop diuretics (*n*, %)	39, 86.7%	42, 93.3%	0.851
Loop diuretics (mg)	28.10 ± 21.89	27.14 ± 26.90	0.395
Rate of administration of ACE-I / ARB/ MRA (*n*, %)	37, 82.2%	35, 77.8%	0.210
Rate of administration of beta blocker (*n*, %)	39, 86.7%	42, 93.3%	0.958
Systolic BP (mmHg)	106.5 ± 15.5	115.0 ± 13.8	0.998
Diastolic BP (mmHg)	58.7 ± 8.6	63.9 ± 10.8	0.991
Heart rate (bpm)	69.1 ± 8.2	73.6 ± 10.8	0.980

ACE-I: angiotensin-converting enzyme inhibitor, ARB: angiotensin II receptor blocker, MRA: mineralocorticoid receptor antagonist, BP: blood pressure. Continuous data are expressed as the mean ± standard deviation. *p*-values were determined using the paired *t*-test.

Table 3. Changes in laboratory results and findings from chest X-rays and transthoracic echocardiography at discharge and one year later in patients who continued to receive tolvaptan for one year

Items	At discharge	One year later	*p* value
Sodium (mEq/L)	139.8 ± 3.9	138.6 ± 3.5	0.043
Potassium (mEq/L)	4.3 ± 0.5	4.5 ± 0.6	0.959
Chloride (mEq/L)	105.2 ± 4.4	104.4 ± 4.4	0.102
AST (IU/L)	24.3 ± 11.4	23.8 ± 6.4	0.356
ALT (IU/L)	18.4 ± 12.7	16.4 ± 7.4	0.135
LDH (IU/L)	238.5 ± 83.9	236.9 ± 48.2	0.456
BUN (mg/dL)	28.4 ± 12.0	33.4 ± 18.3	0.974
Creatinine (mg/dL)	1.51 ± 0.89	1.59 ± 0.86	0.951
Uric acid (mg/dL)	7.9 ± 1.9	6.8 ± 1.9	0.023
Hemoglobin (mg/dL)	11.6 ± 1.9	11.8 ± 1.9	0.780
BNP (pg/mL)	577.6 ± 528.5	397.3 ± 365.8	0.015
Cardiothoracic ratio (%)	59.4 ± 8.0	59.4 ± 9.2	0.508
Left atrial dimension (mm)	46.9 ± 9.5	45.4 ± 10.6	0.057
LVDd (mm)	55.4 ± 12.3	54.9 ± 12.8	0.345
LVDs (mm)	43.2 ± 14.3	45.8 ± 33.9	0.706
IVSTd (mm)	0.90 ± 0.21	0.91 ± 0.23	0.594
PWTd (mm)	0.95 ± 0.23	0.91 ± 0.20	0.179
Ejection fraction (%)	45.2 ± 18.4	50.0 ± 18.7	0.955

AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, BUN: blood urea uitrogen. BNP: brain natriuretic peptide, LVDd: left ventricular end-diastolic dimension, LVDs: left ventricular end-systolic dimension, IVSTd: interventricular septal wall thickness at end-diastole, PWTd: posterior wall thickness at end-diastole. Continuous data are expressed as the mean ± standard deviation. *p*-values were determined using the paired *t*-test.

CTR and TTE findings did not change significantly (Table 3).

4. Discussion

4.1. *The severity of heart failure in subjects*

In the current study, the in-hospital mortality rate was 15.9% and the one-year mortality rate was 27.8%. Moreover, the mortality rate and/or rate of re-hospitalization within one year was 54.4%. Previous studies in Japan revealed that the in-hospital mortality rate was about 6% and the mortality rate and/or rate of re-hospitalization within one year of ADHF was about 40% (*10-12*). Therefore, the current study may have included patients who had more severe ADHF. Patients with worsening renal function are often encountered during the treatment of ADHF. Previous studies also reported that TLV alleviated renal dysfunction while treating ADHF, so TLV is a useful medication for treatment of patients with ADHF and renal dysfunction (*2,13*). In addition, serum sodium levels must be cautiously monitored because TLV was developed as a medication to treat hyponatremia (*14*). That said, hyponatremia has been reported to worsen the prognosis for ADHF (*15,16*). The use of TLV might have a renal protective effect and elevate serum sodium levels, but long-term use of TLV did not alleviate renal dysfunction or reduce serum sodium levels in the current study. These results were presumably due to the severity of HF in the current sample. Two patients ceased to receive RAAS-I one year after discharge due to renal dysfunction. This result could be due to the fact that BP tended to be high one year after discharge. However, BP was controlled to within the optimal range recommended by the Guidelines of the Japanese Society of Hypertension (*7*).

4.2. *TLV and the long-term prognosis for heart failure*

In the current study, the long-term use of TLV did not reduce the dosage of loop diuretics or the mortality rate. A study has reported that continuous administration of TLV does not improve the prognosis for HF (*17*). In contrast, another study reported that continuous administration of TLV reduced the rate of re-hospitalization (*18*). In the current study, however, the long-term use of TLV did not reduce the rate of re-hospitalization. These results were presumably due to the severity of HF in the current sample. However, the long-term use of TLV tended to delay re-hospitalization for HF and significantly reduced BNP levels. Long-term use of TLV is possibly a useful treatment for patients with severe ADHF. However, the effects of the long-term use of TLV are still unclear, and the current study was an open-label retrospective study of 45 patients. Therefore, large-scale clinical studies need to be conducted to verify these results.

4.3. *The necessity for the long-term use of TLV*

The need for continuous administration of TLV after discharge was evaluated with an on-off test. Since many studies have reported that the diuretic effect of TLV lasts several days, the on-off test was conducted two days after the discontinuation of TLV (*19,20*). An attending physician evaluated the patient's general condition based on urine volume, a chest X-ray, and symptoms such as dyspnea. The on-off test includes subjective evaluations, but assessment of the necessity for the long-term use of TLV in the on-off test helped to evaluate re-hospitalization for HF.

4.4. *Study limitations*

The current study was a small-scale, single-center, open retrospective study. The sample included only 45 patients who continued to receive TLV for one year after discharge. Thus, the classification of HF-reduced EF (HFrEF) and HF-preserved EF (HFpEF) was difficult. Therapeutic medications for HFrEF and HFpEF differ, but TLV has been reported to be useful and effective in treating both (*21*). Medications with a cardio-protective effect such as RAAS-I and BB are a class I recommendation for patients with HFrEF, but the only class I medication for patients with HFpEF is a diuretic. These cardio-protective medications also have antihypertensive action. BP also affects the prognosis for HF. Therefore, the different uses of these medications might have affected the current results. A second limitation of this study was that the duration of use of TLV has changed from year to year. When TLV originally became available, its use was only recommended for patients with more severe HF in comparison recent recommendations for it use. Thus, changes in the usage of TLV might have affected the current results. Further evaluation was difficult in the current study because the sample was small.

5. Conclusions

The current study has described experience with long-term administration of TLV at this hospital. Patients with ADHF treated with TLV after discharge had a higher rate of re-hospitalization at one year compared to patients with ADHF who ceased receiving TLV after discharge. However, long-term use of TLV decreased BNP levels in patients with ADHF. Patients who required continued administration of TLV had more severe HF, and the long-term use of TLV might delay re-hospitalization in patients with ADHF. Large-scale clinical studies are necessary to verify these results since the current study was a small-scale, single-center, retrospective study.

Conflict of Interest

T.I. has received grant support through his institution from Daiichi Sankyo, Bristol-Myers Squibb, and Boehringer Ingelheim and honoraria for lectures from Bayer Healthcare, Daiichi Sankyo, Bristol-Myers Squibb, Pfizer, Tanabe-Mitsubishi, and Ono Pharmaceutical. The author declares that he has no potential conflicts of interest with regard to current study. The co-authors report that they also have no conflicts of interest with regard to current study.

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