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Long-term effects of tolvaptan in patients requiring recurrent hospitalization for heart failure

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ABSTRACT

Although reports suggest that tolvaptan does not reduce survival or subsequent hospitalization rates in heart failure patients, its continuous use has shown good outcomes in some patients who cannot be effectively managed with high doses of loop diuretics. Therefore, we investigated the association of patient characteristics and continued tolvaptan use in heart failure patients with changes in the frequency and annual duration of patient hospitalization due to heart failure. We carefully reviewed the medical records of patients hospitalized due to heart failure who began tolvaptan therapy and continued with outpatient treatment between December 2010 and November 2013 (tolvaptan group); patients hospitalized for heart failure between May 2008 and March 2009 served as controls. We set the reference dates as the start of tolvaptan therapy (tolvaptan group) or as the date of admission (control group). The changes in hospitalization frequency and total hospitalization time due to heart failure, before and after the reference dates, were not significantly different between the tolvaptan and control groups. In the tolvaptan group, a high estimated glomerular filtration rate was a predictor of decreased hospitalization. Continuous tolvaptan use did not decrease hospitalization duration in all heart failure patients, but good renal function was predictive of a good response.

Key Words: tolvaptan, heart failure, hospitalization

INTRODUCTION

Despite recent developments in drug and device therapies for heart failure, the number of patients hospitalized for exacerbated heart failure remains high. With each hospitalization, the patient prognosis worsens because of myocardial and renal damage,[1)] and the quality of life (QOL) declines. Recurrent hospitalizations for heart failure also increase medical treatment costs. Therefore, preventing hospitalization is important for heart failure patients.

Despite receiving appropriate therapy, including beta-blockers and angiotensin-converting enzyme inhibitors, the administration of diuretics is often necessary to manage fluid overload in patients with worsening heart failure. Loop diuretics play pivotal roles in these situations, with some patients requiring increased doses of loop diuretics after each hospitalization.

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Tolvaptan is a vasopressin receptor-2 antagonist with a novel mechanism for managing fluid overload. The drug is reported to improve congestion and dyspnea in heart failure patients over short periods but did not affect survival or subsequent hospitalization.[2] However, long-term tolvaptan use has resulted in good outcomes in some patients not effectively managed with high doses of loop diuretics.[3, 4] A randomized controlled study also suggested that an improved survival rate is associated with long-term tolvaptan use.[5] Thus, the long-term effects of tolvaptan on the hospitalization of heart failure patients is unclear. Additionally, a subset of patients may respond particularly well to continuous tolvaptan use.

In our hospital, long-term tolvaptan use is recommended for outpatients with poorly controlled fluid overload, despite appropriate loop diuretic therapy, to decrease patient hospitalizations. This study assessed whether long-term tolvaptan use decreased hospitalization rates among heart failure patients and investigated the patient characteristics associated with tolvaptan efficacy.

METHODS

The medical records of patients hospitalized at Tosei General Hospital (Seto, Aichi, Japan) for heart failure, who received tolvaptan therapy and continued this therapy as outpatients, between December 2010 and November 2013 (tolvaptan group) were carefully reviewed; patients hospitalized for heart failure between May 2008 and March 2009 served as a control group. We set the reference dates as the start of tolvaptan therapy (tolvaptan group) or as the admission day (control group) (Figure 1). To ensure that only patients who were repeatedly hospitalized were included, patients were enrolled if they had been hospitalized for heart failure more than once within the year prior to the reference date. Patients were excluded from the study if they died or underwent other heart failure therapies, such as cardiac operations, percutaneous coronary interventions, device implantations, or dialysis therapies within a year before and after the reference date.

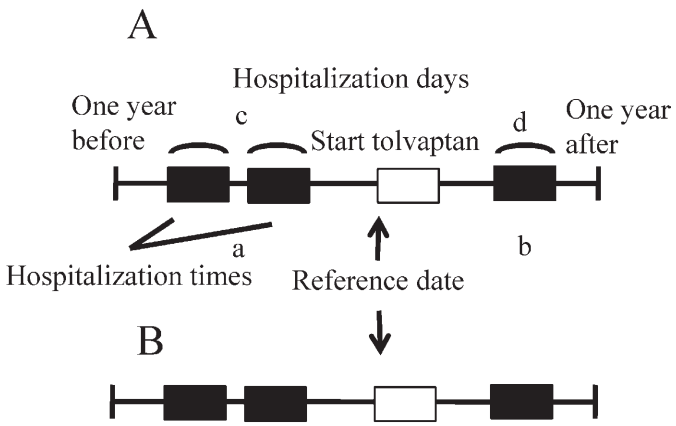

Fig. 1 Definition of the study outcome.
(A) Tolvaptan group and (B) Control group. The boxes in the figure represent each hospitalization. The hospitalization event, during which tolvaptan therapy was initiated, and hospitalization beginning at the reference day in the control group (white boxes) were not included in these comparisons. Changes in the frequency of hospitalization one year before and after the reference date = b - a, Changes in the annual duration of hospitalization one year before and after the reference date = d - c.

Tolvaptan was administered when heart failure could not be effectively managed with appropriate therapy, including loop diuretics, after discharge; these patients continued taking the drug at the same dose, unless dose reduction or discontinuation was clinically indicated.

Changes in the frequency and annual duration of hospitalizations for heart failure were compared, before and after the reference dates, between the tolvaptan and control groups. Hospitalization events, during which tolvaptan therapies were initiated, and control group hospitalizations beginning at the reference date were not included in the comparisons.

To determine the characteristics of the patients showing good responses to long-term tolvaptan use, we divided the patients in the tolvaptan group into two groups based on their outcomes one year after the initiation of tolvaptan therapy. Patients who showed a reduced hospitalization frequency and shorter total annual hospitalization durations, due to heart failure, were defined as showing good responses; all others were defined as not demonstrating good responses.

Hospitalizations for heart failure were defined as those resulting from heart failure symptoms requiring intravenous injection of a vasodilator, diuretic agent, or inotrope within three days of admission. Blood analysis data were collected from the patients when they were stable outpatients, less than three months before tolvaptan therapy was initiated. Estimated glomerular filtration rates (eGFRs) were calculated based on serum creatinine levels, sex, and age.[6] Ejection fractions (EFs) were calculated using transthoracic echocardiography. Pulmonary disease was defined as symptomatic chronic obstructive pulmonary disease, interstitial pneumonitis, or bronchial asthma. Loop diuretic dosages were expressed as furosemide doses, as previously described;[7,8] doses of torsemide (4 mg) were reported as furosemide (10 mg) doses, and doses of azosemide (30 mg) were similarly reported as furosemide (20 mg) doses. This study was approved by our local ethical committee.

All statistical analyses were performed using PASW Statistics, version 18.0 (SPSS, Chicago, IL, USA). Continuous variables, except for serum B-type natriuretic peptide (BNP) levels, were expressed as means ± standard deviations and compared using unpaired *t*-tests. Serum BNP levels and ordered variables, expressed as medians (ranges), were compared using Mann-Whitney tests. Nominal variables were compared using Fisher's exact test.

RESULTS

The patient flowchart is shown in Figure 2. The characteristics of the tolvaptan and control groups are shown in Table 1; the baseline characteristics were similar between the tolvaptan and control groups. The changes in hospitalization frequencies and total annual hospitalization durations for heart failure, before and after the reference dates, were not significantly different between the tolvaptan group (–0.25 ± 1.41 times/year and –0.9 ± 39.7 days/year, respectively) and the control group (–0.33 ± 1.14 times/year, p = 0.864; and 2.3 ± 38.0 days/year, p = 0.825, respectively) (Figure 3).

According to the analysis of the characteristics of patients with and without good responses to tolvaptan, low serum creatinine levels and high eGFRs were predictive of good, long-term responses to tolvaptan (Table 2).

DISCUSSION

Although most studies have reported negative results for the long-term use of tolvaptan, a few have reported uncharacteristically good results.[3, 4] Therefore, to maximize the clinical

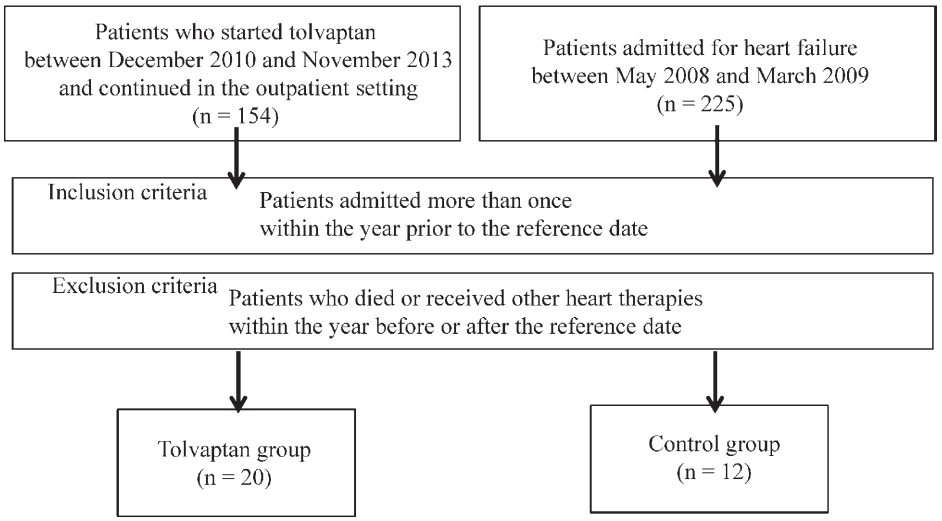

Fig. 2 Patient flowchart

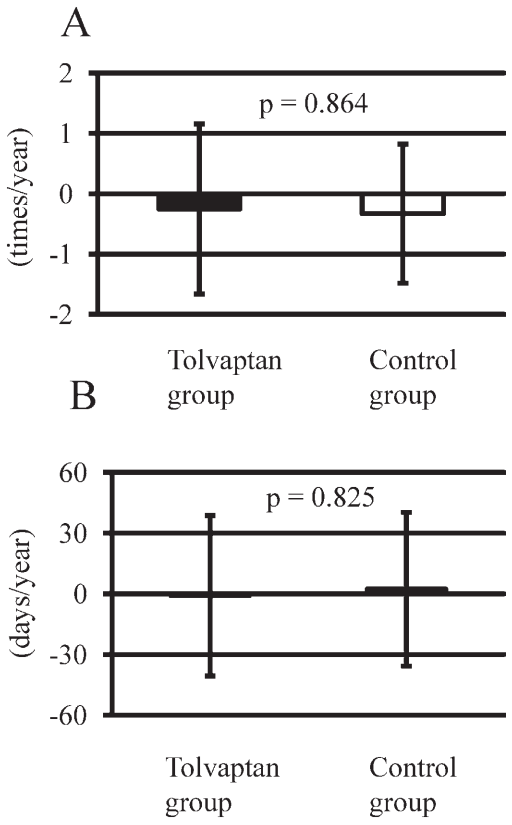

Fig. 3 Comparison of the differences between the tolvaptan and control groups
(A) Changes in the frequency of hospitalization one year before and after the reference date (= b - a in Figure 1), (B) Changes in the annual duration of hospitalization one year before and after the reference date (= d - c in figure 1).

Table 1 Patient characteristics

	Tolvaptan group (n = 20)	Control group (n = 12)	p Value
Duration of tolvaptan therapy, days	351 ± 65	-	NA
Initial tolvaptan dose, mg	8.4 ± 4.7	-	NA
Males, n (%)	10 (50)	6 (50)	0.642
Age, years	75.5 ± 11.4	82.1 ± 8.3	0.092
Ischemic heart failure etiology, n (%)	2 (10)	1 (8)	0.690
NYHA class, III/IV, n (%)	10 (50)	3 (25)	0.153
Pre-reference date hospitalizations for heart failure, times/year	1 (1–4)	1(1–4)	0.552
Pre-reference date hospitalizations for heart failure, days/year	15 (6–132)	13.5 (5–55)	0.604
Post-reference date hospitalizations for heart failure, times/year	1 (0–4)	0.5 (0–4)	0.255
Post-reference date hospitalizations for heart failure, days/year	16.5 (0–93)	3.5 (0–127)	0.224
Medical history			
Hypertension, n (%)	9 (45)	6 (50)	0.536
Diabetes mellitus, n (%)	6 (30)	3 (25)	0.546
Atrial fibrillation, n (%)	12 (60)	4 (33)	0.137
Pulmonary disease, n (%)	2 (10)	0 (0)	0.383
Cirrhosis, n (%)	4 (20)	0 (0)	0.135
Baseline therapy			
ACE inhibitors/ARBs, n (%)	10 (50)	10 (83)	0.063
β-blockers, n (%)	12 (60)	5 (42)	0.261
Loop diuretics, mg [a)]	124 ± 146	65 ± 54	0.116
Aldosterone blockers, n (%)	14 (70)	5 (42)	0.114
Inotropes, n (%) [b)]	2 (10)	1 (8)	0.690
Laboratory parameters			
Serum sodium, mEq/L	139.1 ± 2.6	139.4 ± 3.1	0.718
Serum potassium, mEq/L	3.9 ± 0.6	4.2 ± 0.5	0.129
Serum BUN, mg/dL	35.3 ± 20.8	26.3 ± 16.3	0.212
Serum creatinine, mg/dL	1.43 ± 0.66	1.21 ± 0.56	0.334
eGFR, mL/min/1.73 m^2	38.9 ± 12.1	45.5 ± 19.8	0.303
Serum albumin, g/dL	3.89 ± 0.33	3.81 ± 0.50	0.580
Serum hemoglobin, g/L	10.8 ± 1.3	10.9 ± 1.0	0.720
Plasma BNP, pg/mL	275 (38–630) [c)]	232 (41–2760) [d)]	0.979
Echocardiographic parameters			
LV diastolic diameter, mm	49.1 ± 9.0	47.0 ± 11.2	0.565
LV systolic diameter, mm	34.5 ± 12.2	32.7 ± 13.0	0.697
LA diameter, mm	45.0 ± 8.6	40.4 ± 16.2	0.306
Ejection fraction, %	57.3 ± 18.5	59.0 ± 17.8	0.795
Inferior vena cava diameter, mm	19.9 ± 8.6	14.0 ± 7.4	0.058

Data are presented as the means ± SD or the medians (range), unless otherwise indicated.
NA, not applicable; ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; LV, left ventricle; LA, left atrium; NYHA, New York Heart Association functional classification.
[a)] Loop diuretic dosages were expressed as furosemide doses, as previously described (7,8); doses of torsemide (4 mg) were reported as furosemide (10 mg) doses, and doses of azosemide (30 mg) were similarly reported as furosemide (20 mg) doses. [b)] pimobendan (an oral phosphodiesterase III inhibitor), docarpamine (a prodrug of dopamine), and denopamine (a prodrug of dobutamine). [c)] n = 16; [d)] n = 10

Table 2 Univariate analysis results of good response [a] among patients receiving continuous tolvaptan therapy

	Patients with good response [a] (n = 9)	Patient without good response (n = 11)	P Value
Duration of tolvaptan therapy, days	338 ± 87	365 ± 0	0.366
Initial tolvaptan dose, mg	8.5 ± 5.3	8.3 ± 4.1	0.931
Males, n (%)	4 (44)	6 (55)	0.500
Age, years	78.2 ± 7.6	73.2 ± 13.7	0.347
Ischemic heart failure etiology, n (%)	0 (0)	2 (18)	0.289
NYHA class, III/IV, n (%)	5 (56)	5 (45)	0.500
Pre-reference date hospitalizations for heart failure, times/year	2 (1–4)	1(1–4)	0.112
Pre-reference date hospitalizations for heart failure, days/year	21 (6–132)	13 (8–60)	0.152
Post-reference date hospitalizations for heart failure, times/year	1 (0–2)	1 (1–4)	0.038
Post-reference date hospitalizations for heart failure, days/year	5 (0–34)	19 (5–93)	0.038
Medical history			
Hypertension, n (%)	3 (33)	6 (55)	0.311
Diabetes mellitus, n (%)	3 (33)	3 (27)	0.574
Atrial fibrillation, n (%)	7 (78)	5 (45)	0.157
Pulmonary disease, n (%)	1 (11)	1 (9)	0.711
Cirrhosis, n (%)	2 (22)	2 (18)	0.625
Baseline therapy			
ACE inhibitors/ARBs, n (%)	3 (33)	7 (64)	0.185
β-blockers, n (%)	5 (55)	7 (64)	0.535
Loop diuretics, mg [b]	97.7 ± 105.3	157.8 ± 186.2	0.375
Aldosterone blockers, n (%)	8 (89)	6 (55)	0.119
Inotropes, n (%) [c]	2 (22)	0 (0)	0.189
Laboratory parameters			
Serum sodium, mEq/L	139.9 ± 2.9	138.4 ± 2.2	0.193
Serum potassium, mEq/L	3.6 ± 0.5	4.1 ± 0.7	0.068
Serum BUN, mg/dL	28.4 ± 16.76	40.9 ± 22.7	0.192
Serum creatinine, mg/dL	1.02 ± 0.20	1.77 ± 0.72	0.007
eGFR, mL/min/1.73 m^2	48.1 ± 12.1	31.4 ± 14.3	0.012
Serum albumin, g/dL	3.92 ± 0.48	3.86 ± 0.16	0.731
Serum hemoglobin, g/L	10.8 ± 1.3	10.7 ± 1.3	0.909
Plasma BNP, pg/mL	229.2 (45.1–362.7) [d]	439.1 (38.2–629.7) [e]	0.328
Echocardiographic parameters			
LV diastolic diameter, mm	48.4 ± 9.9	49.6 ± 8.8	0.778
LV systolic diameter, mm	34.0 ± 12.6	34.9 ± 12.7	0.874
LA diameter, mm	48.1 ± 10.8	42.5 ± 5.7	0.149
Ejection fraction, %	58.3 ± 15.3	56.4 ±21.5	0.820
Inferior vena cava diameter, mm	18.8 ± 5.4	20.8 ± 10.8	0.615

Data are presented as the means ± SD or the medians (range), unless otherwise indicated.
ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; LV, left ventricle; LA, left atrium; NYHA, New York Heart Association functional classification.

[a] Patients who survived for a year after starting tolvaptan therapy, continued tolvaptan in the outpatient setting, and demonstrated a reduced frequency and total duration of hospitalization for heart failure (compared with before starting tolvaptan therapy) were defined as patients with good responses.

[b] Loop diuretic dosages were expressed as furosemide doses, as previously described (7,8); doses of torsemide (4 mg) were reported as furosemide (10 mg) doses, and doses of azosemide (30 mg) were similarly reported as furosemide (20 mg) doses.

[c] pimobendan (an oral phosphodiesterase III inhibitor), docarpamine (a prodrug of dopamine), and denopamine (a prodrug of dobutamine). [d] n = 6; [e] n = 10

usefulness of this treatment, examination of the factors associated with good long-term responses are necessary.

In this study, the heart failure-associated hospitalization frequency and total annual hospitalization time did not decrease significantly in the tolvaptan group, compared with the control group. However, some patients showed good responses to tolvaptan therapy, and low serum creatinine levels and high eGFRs were predictive of good outcomes. This result suggests that the focus should be on the patient characteristics associated with good long-term effects of tolvaptan therapy.

We can interpret the results of this predictive analysis in two ways. First, renal failure may attenuate the diuretic effects of tolvaptan. In patients with advanced renal failure, the kidneys are unable to concentrate or dilute urine, producing only isotonic urine. Tolvaptan is believed to have little effect on patients incapable of adjusting their urine osmolality. Clinically, however, patients undergoing tolvaptan therapy, including those with severe renal failure, have been reported to have increased urine volumes and decreased osmolalities.[9] In contrast, another study indicated that patients with low eGFRs tended to show poor responses to short-term tolvaptan treatment.[10] Thus, although low eGFRs may influence the diuretic effects of tolvaptan, they may not indicate that the drug is ineffective in patients with renal failure. Second, renal failure is an independent predictor of heart failure.[11] Thus, a decline in the diuretic effects of tolvaptan in patients with renal failure and the poor prognosis of heart failure patients with renal failure may influence the long-term effectiveness of tolvaptan.

At the same time, the results from this study do not disallow the long-term use of tolvaptan in heart failure patients with severe renal failure. We regard tolvaptan as a promising treatment for patients with advanced heart failure. Additionally, these observations suggest that tolvaptan therapy should be initiated before a patient develops severe complications, such as renal failure.

In acute heart failure settings, some patients may derive benefit from tolvaptan treatment, but most may be effectively treated with dialysis or cardiac-assist devices. In contrast, in the outpatient setting, dialysis and cardiac-assist devices are uncommonly used, making tolvaptan more amenable for use in outpatients.

Unlike other studies, we assessed the effects of tolvaptan, based on hospitalization outcomes, to adequately reflect the clinical course of heart failure patients. In prior studies, the long-term prognosis of heart failure patients was assessed based on mortality and the time between discharge and subsequent re-admission.[2] Because heart failure patients, especially those requiring prolonged tolvaptan administration, often experience repeated exacerbations, the time between discharge and re-admission is often too short to ascertain a prognosis. Further, more than 33% of hospitalizations due to heart failure have other obvious precipitating factors (e.g., anemia, infectious disease, angina, arrhythmia, or poor compliance), which cannot be prevented by heart failure treatment[12] and which may easily affect the period between discharge and re-admission. Therefore, the use of revised endpoints, hospitalization frequencies, and total annual hospitalization durations enables better assessments of the drug in heart failure patients.

CONCLUSION

This study suggested that the continuous use of tolvaptan does not decrease the frequency or total annual duration of hospitalization due to heart failure among all heart failure patients. However, good renal function is predictive of good responses. Further examinations of the predictors of good, long-term responses are needed to allow the more effective use of tolvaptan.

Conflicts of interest: None to declare.

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