Tolvaptan Reduces Long-Term Total Medical Expenses and Length of Stay in Aquaporin-Defined Responders

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SUMMARY

The vasopressin type-2 antagonist tolvaptan (TLV) has clinical advantages including amelioration of congestion and normalization of hyponatremia in patients with decompensated heart failure (HF). However, there have been no studies on the cost-effectiveness of TLV therapy. We enrolled 60 consecutive hospitalized patients with stage D HF who received TLV [TLV (+) group], and 60 propensity score-matched HF patients without TLV treatment [TLV (-) group]. We excluded 54 patients who died or received cardiac replacement therapy within 1 year, and finally enrolled 32 patients who received TLV and 34 who did not, who were followed for > 1 year. Among 45 aquaporin-defined responders, whose urine aquaporin-2 relative to plasma arginine vasopressin level was $> 1.4 \times 10^3$ L/g Cre, the TLV (+) group required significantly lower total medical expenses and shorter lengths of stay (LOS) compared with the TLV (-) group [11.2 (1.2-33.3) versus 31.2 (2.2-71.4) $\times 10^5$ JPY/year, $P < 0.001$; 30 (0-304) versus 70 (20-221) days, $P = 0.030$]. In contrast, among the remaining 21 aquaporin-defined non-responders, medical expenses and LOS were comparable irrespective of TLV administration ($P = 0.087$ and $P = 0.407$). In conclusion, TLV therapy may reduce total medical expenses in aquaporin-defined responders with stage D HF. (Int Heart J 2016; 57: 593-599)

Key words: Cost, Vasopressin, Aquaporin

Tolvaptan (TLV), a vasopressin type-2 receptor antagonist, has been shown to ameliorate symptomatic congestion and normalize hyponatremia, thus restoring renal function, not only among patients with mild to moderate heart failure (HF) but also in those with advanced HF.¹⁻¹⁴ Although the long-term efficacy of TLV remains controversial,⁶ we recently demonstrated the benefits of long-term administration of TLV on survival and re-admission, especially in responders to TLV.¹⁵

Despite its clinical advantage, TLV is expensive compared with other conventional diuretics, which is an important limitation considering current increases in total medical expenses.¹⁶ However, so far, there have been few studies investigating the cost-effectiveness of TLV.¹⁷⁻²⁰ In this study, we analyzed the relationship between the cost-effectiveness of TLV and response to TLV in patients with stage D HF.

METHODS

Study design and patients: We enrolled 60 consecutive patients with stage D HF, who had received 3.75-15 mg/day of TLV on a de novo basis at our institute between February 2011 and October 2013. All participants had symptomatic conges-

tive HF, refractory to a considerable amount of conventional diuretics in addition to guideline-directed medical therapy [TLV (+) group]. Patients meeting the following criteria were excluded from the study and did not receive TLV: hypovolemia; dependence on hemodialysis; active systemic infection; acute coronary syndrome within the past 1 month; severe valve disease; hyponatremia with serum sodium concentration > 145 mEq/L; consciousness disorder; and inability to ingest medicine orally.

We also had 120 consecutive, hospitalized patients with stage D HF, who did not receive TLV. Of them, 60 background-matched patients were selected using a propensity score matching technique [TLV (-) group].¹⁵

Among the total of 120 patients consisting of the TLV (+) group and TLV (-) group, we excluded 54 patients who died or received cardiac replacement therapy (ventricular assist device implantation or heart transplantation) within 1 year. Finally, we enrolled 32 TLV (+) group patients and 34 TLV (-) group patients, who were followed for > 1 year (Figure 1).

Written informed consent for inclusion in the study was obtained from all patients before enrollment. This study complies with the Declaration of Helsinki and the institutional review board approved the research protocol.

Measurement: Demographic, laboratory, urinary, and

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echocardiographic data were obtained during hospitalization in the TLV (-) group or within 24 hours before the initiation of TLV treatment in the TLV (+) group. Blood samples, for measuring arginine vasopressin (AVP) levels, were obtained after a 15-minute rest in the spine position in the early morning before

Figure 1. Study protocol. TLV indicates tolvaptan; Pt, patients; and AQP, aquaporin.

taking any daily medication. Urine samples for measuring urine aquaporin-2 (U-AQP2) levels were obtained from the first urine in the early morning before taking any medications. U-AQP2 levels were measured using a sandwich enzyme-linked immunosorbent assay (human aquaporin-2 ELISA kit, LSI Medicine),^{15,21)} and corrected by urine creatinine concentration. In this study, “responders” were defined as those with a baseline U-AQP2 relative to plasma AVP level of $> 1.4 \times 10^3$ L/g Cre, as previously reported.¹⁵⁾ During the 1-year study period, total medical expenses and length of stay (LOS) were recorded for all participants. Total medical expenses were calculated by the summation of hospitalization costs and ambulatory follow-up costs including all medications and examinations during the study period.

Statistical analysis: Statistical analysis was performed using PASW Statistics 18 (SPSS Inc, Chicago, IL, USA). Categorical parameters are presented as frequencies and percentages unless otherwise described. For continuous variables, the mean $\pm$ standard deviation was used in cases of standard distribution, and the median (minimum - maximal value) was used in cases of non-standard distribution. Patient background data were compared using the unpaired *t*-test or Mann-Whitney *U* test for continuous variables, and the chi-square test or Fisher’s exact test for categorical variables, as appropriate.

Table I. Background Comparison of Patients With/Without Tolvaptan Administration

	Total (<i>n</i> = 66)	TLV (+) (<i>n</i> = 32)	TLV (-) (<i>n</i> = 34)	<i>P</i>
Demographic Variables				
Age, years	63 $\pm$ 17	63 $\pm$ 16	63 $\pm$ 19	0.930
Male, <i>n</i> (%)	49 (74)	20 (63)	29 (85)	0.076
BSA, m ²	1.67 $\pm$ 0.19	1.67 $\pm$ 0.21	1.67 $\pm$ 0.17	0.890
sBP, mmHg	103 $\pm$ 11	100 $\pm$ 12	106 $\pm$ 10	0.078
HR, bpm	77 $\pm$ 15	82 $\pm$ 15	73 $\pm$ 13	0.009*
Ischemic etiology, <i>n</i> (%)	9 (14)	3 (9)	6 (17)	0.328
Laboratory values				
Hb, g/dL	11.8 $\pm$ 2.3	11.9 $\pm$ 2.2	11.8 $\pm$ 2.5	0.844
ALB, mg/dL	3.5 $\pm$ 0.7	3.5 $\pm$ 0.7	3.4 $\pm$ 0.6	0.708
Serum sodium, mEq/L	135 $\pm$ 5	135 $\pm$ 5	136 $\pm$ 4	0.195
Serum potassium, mEq/L	4.3 $\pm$ 0.5	4.2 $\pm$ 0.5	4.3 $\pm$ 0.5	0.262
BUN, mg/dL	29 $\pm$ 13	31 $\pm$ 13	28 $\pm$ 14	0.367
eGFR, mL/minute/1.73 m ²	47 $\pm$ 25	49 $\pm$ 22	45 $\pm$ 28	0.600
Serum TB, mg/dL	1.2 $\pm$ 1.0	1.4 $\pm$ 1.2	1.0 $\pm$ 0.7	0.157
Plasma BNP, Log ₁₀ pg/mL	2.7 $\pm$ 0.4	2.6 $\pm$ 0.4	2.8 $\pm$ 0.4	0.159
Plasma AVP, mg/dL	4.7 $\pm$ 4.1	4.6 $\pm$ 2.9	4.8 $\pm$ 5.1	0.801
Urinary Data				
U-OSM, mOsm/L	443 $\pm$ 134	423 $\pm$ 122	473 $\pm$ 145	0.078
U-AQP2, ng/mL	3.7 $\pm$ 3.9	3.5 $\pm$ 2.4	3.9 $\pm$ 4.9	0.729
U-AQP2/P-AVP, $\times 10^3$ L/gCre	1.26 $\pm$ 2.07	0.96 $\pm$ 0.82	1.54 $\pm$ 2.77	0.245
Echocardiographic Data				
LVDd, mm	59 $\pm$ 12	58 $\pm$ 12	59 $\pm$ 13	0.715
LVEF, %	37 $\pm$ 20	35 $\pm$ 20	38 $\pm$ 19	0.447
Medications				
BB, mg/day	5.0 $\pm$ 4.7	5.3 $\pm$ 5.1	4.7 $\pm$ 4.4	0.607
ACEI, mg/day	3.1 $\pm$ 2.3	2.9 $\pm$ 2.1	3.4 $\pm$ 2.5	0.329
AA, mg/day	25 $\pm$ 21	30 $\pm$ 21	21 $\pm$ 20	0.105
Furosemide, mg/day	48 $\pm$ 21	50 $\pm$ 26	47 $\pm$ 16	0.503

TLV indicates tolvaptan; BSA, body surface area; sBP, systolic blood pressure; HR, heart rate; Hb, hemoglobin; ALB, albumin; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration ratio; TB, total bilirubin; BNP, B-type natriuretic peptide; AVP, arginine vasopressin; U-OSM, urine osmolality; U-AQP2, urine aquaporin-2; P-AVP, plasma level of arginine vasopressin; LVDd, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; BB, β -blocker; ACEI, angiotensin converting enzyme inhibitor; and AA, aldosterone antagonist. **P* < 0.05 by unpaired *t*-test or Mann-Whitney *U* test as appropriate.

Propensity score matching analysis was performed to adjust the severity of HF in the TLV (-) group to that in the TLV (+) group on the basis of age, serum sodium, creatinine, total bilirubin, and plasma B-type natriuretic peptide levels.¹⁵⁾ Medical expenses and LOS during the 1-year study period did not show a standard distribution, and were compared using the Mann-Whitney *U* test. All statistical tests were 2-tailed, with *P* < 0.05 regarded as statistically significant.

RESULTS

Background data and medical expenses in the TLV (+) and TLV (-) groups: Of all, 32 patients in the TLV (+) group and 34 background-matched patients in the TLV (-) group were followed for the 1-year study period (Figure 1). The mean age was 63 ± 17 years old, and 74% of the patients were men. Mean serum sodium concentration was 135 ± 5 mEq/L, and the mean estimated glomerular filtration rate was 47 ± 25 mL/minute/1.73 m². Urine osmolality was 443 ± 134 mOsm/L, and U-AQP2/AVP was $1.26 \pm 2.07 \times 10^3$ L/g Cre. Mean furosemide dose was 48 ± 21 mg/day. There were no significant differences between the groups in background data except for heart rate [Table I; TLV (+) group, 82 ± 15 ; TLV (-) group, 73 ± 13 bpm, *P* = 0.009].

The total medical expenses during the 1-year study period tended to be lower in the TLV (+) group compared with the TLV (-) group [Figure 2; 18.2 (1.2-121.2) versus 32.1 (2.2-99.9) $\times 10^5$ JPY/year, *P* = 0.068].

Background data and medical expenses stratified by response to TLV: In the TLV (+) group, 25 patients were AQP-defined responders and 7 patients were non-responders. In the TLV (-) group, 20 patients were AQP-defined responders, and 14 patients were non-responders (Figure 1).

Among responders, there were no significant differences in background data based on TLV administration, except for

Figure 2. Comparison of total medical expenses between patients with TLV administration and those without.

Table II. Background Comparison in AQP-Defined Responders

	TLV (+) (n = 25)	TLV (-) (n = 19)	<i>P</i>
Demographic Variables			
Age, years	61 $\pm$ 16	57 $\pm$ 22	0.934
Male, n (%)	17 (68)	15 (79)	0.873
BSA, m ²	1.7 $\pm$ 0.2	1.7 $\pm$ 0.2	0.992
sBP, mmHg			
HR, bpm	82 $\pm$ 16	75 $\pm$ 11	0.375
Ischemic etiology, n (%)	3 (12)	3 (16)	0.854
Laboratory values			
Hb, g/dL	12.1 $\pm$ 2.2	11.5 $\pm$ 2.4	0.999
Serum Alb, mg/dL	3.5 $\pm$ 0.7	3.4 $\pm$ 0.8	0.958
Serum sodium, mEq/L	135 $\pm$ 5	135 $\pm$ 5	0.999
Serum potassium, mEq/L	4.2 $\pm$ 0.5	4.1 $\pm$ 0.3	0.700
BUN, mg/dL	31 $\pm$ 13	20 $\pm$ 6	0.019*
eGFR, mL/minute/1.73 m ²	48 $\pm$ 20	58 $\pm$ 28	0.476
Serum TB, mg/dL	1.2 $\pm$ 0.9	1.2 $\pm$ 0.8	0.980
Plasma BNP, Log ₁₀ pg/mL	2.6 $\pm$ 0.4	2.7 $\pm$ 0.4	0.979
Plasma AVP, mg/dL	3.9 $\pm$ 1.7	3.4 $\pm$ 2.4	0.979
Urinary Data			
U-OSM, mOsm/L	443 $\pm$ 116	554 $\pm$ 144	0.154
U-APQ2	4.1 $\pm$ 2.1	5.8 $\pm$ 5.7	0.366
U-AQP2/P-AVP, $\times 10^3$ L/gCre	1.17 $\pm$ 0.80	2.34 $\pm$ 2.91	0.096
Echocardiographic Data			
LVDd, mm	59 $\pm$ 12	59 $\pm$ 16	0.970
LVEF, %	33 $\pm$ 19	38 $\pm$ 18	0.840
Medications			
BB, mg/day	5.8 $\pm$ 5.4	4.8 $\pm$ 4.0	0.903
ACEI, mg/day	2.7 $\pm$ 2.2	3.9 $\pm$ 3.1	0.354
AA, mg/day	31 $\pm$ 22	23 $\pm$ 22	0.536
Furosemide, mg/day	50 $\pm$ 27	44 $\pm$ 13	0.775

Abbreviations as in Table I. **P* < 0.05 by unpaired *t*-test or Mann-Whitney *U* test as appropriate.

Figure 3. Comparison of total medical expenses between patients with and without TLV administration in responders (A) and non-responders (B). * $P < 0.05$ by Mann-Whitney U test.

Table III. Background Comparison in AQP-Defined Non-Responders

	TLV (+) (n = 7)	TLV (-) (n = 15)	P
Demographic Variables			
Age, years	71 ± 16	69 ± 10	0.988
Male, n (%)	3 (43)	14 (93)	0.085
BSA, m ²	1.60 ± 0.18	1.68 ± 0.12	0.805
sBP, mmHg	97 ± 10	108 ± 10	0.139
HR, bpm	82 ± 16	70 ± 15	0.233
Ischemic etiology, n (%)	0 (0)	3 (20)	0.654
Laboratory values			
Hb, g/dL	11.1 ± 2.3	11.5 ± 2.4	0.983
Serum Alb, mg/dL	3.3 ± 0.6	3.4 ± 0.4	0.991
Serum sodium, mEq/L	132 ± 6	137 ± 4	0.120
Serum potassium, mEq/L	4.1 ± 0.2	4.7 ± 0.6	0.038*
BUN, mg/dL	30 ± 15	38 ± 14	0.493
eGFR, mL/minute/1.73 m ²	40 ± 31	29 ± 18	0.192
Serum TB, mg/dL	1.9 ± 2.0	0.8 ± 0.4	0.071
Plasma BNP, Log ₁₀ pg/mL	2.5 ± 0.3	2.8 ± 0.5	0.290
Plasma AVP, mg/dL	7.2 ± 4.6	6.7 ± 6.9	0.993
Urinary Data			
U-OSM, mOsm/L	350 ± 123	336 ± 143	0.645
U-AQP2	1.72 ± 2.90	1.41 ± 1.31	0.998
U-AQP2/P-AVP, × 10 ³ L/gCre	0.21 ± 0.22	0.28 ± 0.18	0.945
Echocardiographic Data			
LVDd, mm	55 ± 11	60 ± 9	0.859
LVEF, %	41 ± 24	39 ± 22	0.996
Medications			
BB, mg/day	3.6 ± 3.5	4.6 ± 5.0	0.967
ACEI, mg/day	3.4 ± 1.6	2.8 ± 1.5	0.953
AA, mg/day	25 ± 14	20 ± 19	0.952
Furosemide, mg/day	49 ± 25	49 ± 18	0.998

Abbreviations as in Table I. * $P < 0.05$ by unpaired t -test or Mann-Whitney U test as appropriate.

blood urea nitrogen level [Table II; responders with TLV, 31 ± 13 ; responders without TLV, 20 ± 6 mg/dL, $P = 0.019$]. Responders with TLV had significantly lower medical expenses compared with those without TLV [Figure 3A; $11.2 (1.2-33.3)$

versus $31.2 (2.2-71.4) \times 10^5$ JPY/year, $P < 0.001$].

Among non-responders also, there were no significant differences in background data based on TLV administration, except for serum potassium concentration [Table III; non-re-

Figure 4. Comparison of length of stay between patients with and without TLV administration in responders (A) and non-responders (B). * $P < 0.05$ by Mann-Whitney U test.

sponders with TLV, 4.1 ± 0.2 mEq/L; non-responders without TLV, 4.7 ± 0.6 mEq/L, $P = 0.038$]. Medical expenses were comparable between non-responders with TLV and those without [Figure 3B; non-responders with TLV, 61.2 (36.7-121.1); non-responders without TLV, 42.9 (24.7-99.9); $P = 0.087$].

Among those receiving TLV, medical expenses were significantly lower in responders compared with non-responders ($P < 0.01$).

LOS stratified by responses to TLV: Among responders, LOS was significantly shorter in those with TLV compared with those without TLV [Figure 4A; 30 (0-304) versus 70 (20-221) days, $P = 0.030$]. Among non-responders, there was no significant difference in LOS based on TLV administration [Figure 4B; non-responders with TLV, 150 (0-335) days; non-responders without TLV, 82 (0-200) days; $P = 0.407$]. Among those receiving TLV, LOS was significantly shorter in responders compared with non-responders ($P = 0.042$).

DISCUSSION

We demonstrated here that 1) 1-year total medical expenses were comparable between the TLV (+) group and the background-matched TLV (-) group; 2) Among AQP-defined responders, TLV therapy significantly reduced 1-year medical expenses and shortened LOS; and 3) Among AQP-defined non-responders, TLV therapy slightly increased 1-year medical expenses and LOS.

Propensity score matching analyses: The clinical use of TLV has increased recently, and many authors have showed that TLV is beneficial in ameliorating symptomatic congestion and in normalizing hyponatremia, thus improving renal function in patients with decompensated HF.¹⁻¹⁸ Therefore, prospective recruitment of a control group has thus far been ethically difficult considering the obvious clinical advantage of TLV treatment.

Selection bias exists in TLV therapy in the clinical setting

because TLV is indicated in patients with symptomatic congestion refractory to considerable amounts of conventional diuretics.^{5,11} Therefore, we adopted the propensity score matching technique to recruit a background-matched control group of patients with advanced HF.¹⁵

Total medical expenses: Two investigators previously compared the cost of TLV itself with that of other medicines. Suzuki, *et al* showed in a randomized prospective study that the cost of TLV in the TLV group was lower than that of carperitide in the carperitide group.¹⁸ Takimura, *et al* demonstrated in a retrospective observational study that the cost of carperitide in the carperitide group was higher than that of carperitide and TLV in the TLV+carperitide group.¹⁹ They speculated that TLV therapy improved symptomatic congestion rapidly, shortened the therapeutic duration, and eventually saved medication costs. However, they did not analyze the “total medical expenses” during TLV therapy, and they compared only the cost of medications. Furthermore, their study periods were restricted only to the acute phase.

We analyzed the 1-year total medical expenses during TLV therapy in comparison with the background-matched control group, and found there was no statistically significant advantage of the add-on TLV treatment over conventional therapy with respect to medical expenses (Figure 2).

Considering the high cost of TLV itself compared with that of conventional diuretics such as a loop diuretic (eg, 1707 JPY for 7.5 mg of TLV versus 9.6 JPY for 20 mg of furosemide), optimal patient selection for TLV therapy may repress the total medical cost. For example, only responders to TLV, who can derive sufficient efficacy from TLV, and not responders, may enjoy a reduction of total medical expenses due to add-on TLV treatment.

Response to TLV stratified by U-AQP2 and total medical expense: Response to TLV is mainly dependent on the residual function of the renal collecting duct,^{4,22} and we recently proposed U-AQP2 relative to plasma AVP level as a novel predic-

tor of the response to TLV.^{8,15)} Consistently, we previously showed improved survival and a reduced re-admission rate in AQP-defined responders during TLV treatment compared with background-matched responders without TLV.¹⁵⁾

Add-on TLV therapy reduced the total medical expense in AQP-defined responders, but not in non-responders (Figure 3A,B). Considering the absolute difference in median medical expenses in responders, ie, TLV (+) group, 11.2×10^5 JPY; TLV (-) group, 31.2×10^5 JPY, the cost for the measurement of U-AQP2, which is only approximately 0.1×10^5 JPY thus far, for optimal patient selection for TLV therapy is quite insignificant. Therefore, U-AQP2 is a novel marker to select good candidates for TLV therapy with respect to not only clinical benefit but also cost-effectiveness.

Add-on TLV therapy shortens LOS in patients with HF.²³⁾ Consistently, responders with TLV had significantly shorter LOS compared with those without TLV during the 1-year study period. As Chiong, *et al* and Dasta, *et al* reported in the EVEREST trial sub-analysis and SALT-1/SALT-2 trials sub-analysis, shorter LOS during TLV therapy may dominantly contribute to a reduction in the total medical expenses.^{17,20)} Suppression of the readmission rate by TLV therapy is also an important factor to suppress total medical costs, because treatment for acute HF is one of the most expensive phases during HF follow-up.

In contrast, TLV therapy did not shorten LOS and somewhat increased total medical expenses among the non-responders. TLV cannot improve the clinical course of the disease in non-responders, and may instead be a waste of time and money. More invasive therapies such as hemodialysis may be superior to TLV for treating congestion rapidly as well as reducing medical costs.

We acknowledge that our study has some limitations. First, this was a retrospective, single-center study, and consequently included a limited number of patients. Although propensity matching score analysis was performed to enroll background-matched patients as a control group, there were 2 unmatched sets of data, ie, blood urea nitrogen in responders and serum potassium concentration in non-responders. Prospective randomized trials should be performed among patients stratified by their response to TLV. However, randomized trials using TLV may be difficult considering the obvious advantage of TLV therapy over conventional diuretics.

Second, the dose of TLV was determined by the attending physicians considering the stability of the hemodynamics and degree of congestion of the patients. It is often difficult to fix the dose of TLV among patients with advanced HF considering the instability of their hemodynamics.

Third, the present study had a patient selection bias because TLV administration was determined by the attending physicians. However, the patient backgrounds were statistically matched by using propensity score matching analyses.

Fourth, we excluded patients who died or received cardiac replacement therapy within 1 year because we intended to compare daily medical expenses among those with TLV and those without. Medical costs just before death or those for cardiac replacement therapy are specific, and should be assessed separately. We already demonstrated the advantage of TLV in terms of long-term survival and readmission rate in a previous study.¹⁵⁾

Fifth, we enrolled patients with advanced HF, and the re-

sults may not be applicable to a population with less severe disease. Considering the higher cost of TLV over other conventional diuretics such as loop diuretics, less sick patients may not be good candidates for TLV therapy from the viewpoint of cost-effectiveness.

Lastly, we used urine aquaporin-2 rather than urine osmolality to predict the response to TLV because of the predictive advantage of urine aquaporin-2 over urine osmolality.¹⁵⁾ However, urine osmolality is a good alternative to urine aquaporin-2, especially from the viewpoint of its low cost and early assay speed. We do not at all deny the usefulness of using urine osmolality to predict the response to TLV.

In conclusion, U-AQP2 is a useful marker to optimize responders to TLV, who can be managed by lower medical costs compared with those without TLV.

DISCLOSURE

K.K. has a potential conflict of interest with Otsuka Pharmaceutical Co. that includes lecture fees.

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