Long-Term Tolvaptan Treatment in Refractory Heart Failure

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Background: The vasopressin type-2 receptor antagonist tolvaptan is an essential tool in the management of decompensated heart failure (HF) in the inpatient setting for short-term use with careful monitoring. There is conflicting evidence, however, for its long-term use.

Methods and Results: In this prospective, multi-center, open-labeled, randomized control trial, Assessment of QUAlity of life during long-term treatment of ToLVaptan in refractory HF (AQUA-TLV study), patients with congestive HF refractory to furosemide ≥60 mg/day were randomly assigned to a control group or tolvaptan add-on group and followed for 6 months, after confirmation of baseline urine osmolality ≥350 mOsm/L. Twenty-nine patients (median age, 60 years; 22 male) were enrolled and assigned to a control group (n=16) or a tolvaptan group (n=13). Minnesota Living with Heart Failure Questionnaire score improved significantly in the tolvaptan group (from 58 to 10, P=0.030). In the tolvaptan group, diuretics dose reduced (P=0.001), serum creatinine decreased (P=0.040), and hyponatremia tended to improve (P=0.12). The tolvaptan group had a lower HF readmission rate compared with the control group (0.213 vs. 1.242 events/year, P=0.13).

Conclusions: Six-month tolvaptan therapy improved quality of life and renal function and reduced HF readmissions, when given to the estimated responders (UMIN Clinical Trial Registry Number: UMIN 000009604).

Key Words: Congestion; Diuretic; Vasopressin

Although conventional diuretics including loop diuretics have been essential tools to manage patients with decompensated heart failure (HF), they have various limitations including stimulation of the renin-angiotensin-aldosterone system, intravascular hypovolemia, worsening renal function, and sodium and potassium wasting in the urine. Furthermore, patients with advanced HF often experience refractoriness to conventional diuretics.

Tolvaptan, a vasopressin type-2 antagonist, has been widely used for the past decade as a novel and unique aquaretic agent, because it overcomes various disadvantages of conventional diuretics by ameliorating congestive symptoms and improving hyponatremia while maintaining hemodynamics and renal function. Its use, however, has been proven only in a strictly monitored, short-term inpatient setting. Many patients with advanced HF have reduced quality of life (QOL) owing to frequent readmissions from worsening congestion, despite use of a considerable amount of diuretics. In contrast to the favorable evidence for the use of short-term tolvaptan therapy, the implications of long-term tolvaptan therapy remains controversial. Several retrospective observational studies with small sample sizes showed favorable outcomes for long-term tolvaptan therapy whereas a large-scale randomized control trial (RCT) could not demonstrate an advantage of tolvaptan over conventional diuretics.

Our team previously demonstrated that elevated baseline urine osmolality in the fasting condition (≥350 mOsm/L) was a predictive marker of tolvaptan responders. These patients had an increase in urine output following tolvaptan.
Exclusion Criteria
Patients with general contraindications to tolvaptan therapy were excluded, that is, those with end-stage renal function on hemodialysis, hypernatremia with serum sodium >145 mEq/L, on mechanical circulatory support, or with impaired consciousness.

Urine Osmolality
We enrolled patients with baseline urine osmolality ≥350 mOsm/L, considered to be a predictor of response to tolvaptan therapy, as demonstrated in a previous study (response was defined as any increase in urine output following tolvaptan treatment).

Study Design
Following informed consent, patients received clinical examinations to confirm their eligibility during a 1–3-day observational period (Figure 1), when baseline characteristics including Minnesota Living with Heart Failure Questionnaire (MLHFQ) and transthoracic echocardiography were obtained. After confirmation of eligibility, patients were randomly assigned into the 2 arms: the tolvaptan arm or the control arm, and followed for 6 months. Target sample size was calculated as 100 patients (50 vs. 50) for the condition of $\alpha$ error probability 0.05, power 0.80, and effect size 0.5.

Endpoints
The primary endpoint was improvement in QOL assessed on a reduction in MLHFQ score. The secondary endpoints were improvements in other clinical outcomes including serum sodium and creatinine, body weight, left ventricular ejection fraction (LVEF), plasma B-type natriuretic peptide (BNP), and HF readmissions.

Statistical Analysis
Statistical analysis was performed with SPSS Statistics 22 (SPSS, Chicago, IL, USA). Two-sided $P<0.05$ was
All patients had serum sodium ≤145 mEq/L, urine osmolality ≥350 mOsm/L, and were on furosemide ≥60 mg/day. Eleven patients (38%) had serum sodium <135 mEq/L. Median LVEF was 21% (IQR, 15–30%).

Patients were randomly assigned to the tolvaptan group (n=13) or to the control group (n=16). There were no significant differences in baseline patient characteristics (P>0.05 for all). The tolvaptan group received a median tolvaptan dose 3.75 mg/day (IQR, 3.75–7.5 mg/day). During the 6-month treatment period, no patients had adverse events associated with tolvaptan.

Primary Outcome

QOL was assessed on MLHFQ score, which decreased (i.e., improved) significantly in the tolvaptan group (P=0.030), whereas it remained unchanged in the control group.
incidence rate ratio, 5.71; 95% CI: 0.61–53.2; P=0.13; Figure 4B).

Discussion
In this prospective, multi-center, open-labeled, RCT, AQUA-TLV study, we investigated the impact of 6-month tolvaptan therapy on QOL and other clinical outcomes in NYHA functional class III or IV patients with symptomatic decompensated HF with a history of HF admission, and who were estimated to be responders to tolvaptan, defined as baseline urine osmolality \(\geq 350 \text{ mOsm/L}.\)

The main findings are as follows: (1) all 13 patients in the tolvaptan group had no adverse events associated with tolvaptan during the 6-month treatment period; (2) in the tolvaptan group, QOL assessed on MLHFQ score improved during the 6-month treatment period and was more improved at 6 months compared with the control group; (3) in the tolvaptan group, the dose of furosemide reduced, serum creatinine recovered, and hyponatremia tended to improve, whereas these remained unchanged in the control group; and (4) the tolvaptan group had fewer HF readmissions compared with the control group.

Secondary Outcomes (Clinical Variables)
Loop diuretic dose was reduced significantly following tolvaptan treatment \((P=0.001)\), but remained unchanged in the control group \((P=0.68; \text{Figure 3A})\). The loop diuretics dose was expressed as an equivalent dose of furosemide, when other diuretics were used. Serum sodium level tended to increase in the tolvaptan group \((P=0.12)\), whereas it remained unchanged in the control group \((P=0.78; \text{Figure 3B})\). As a result, the tolvaptan had lower furosemide dose \((40 \text{ vs. } 80 \text{ mg/day})\) and higher serum sodium \((140 \text{ vs. } 137 \text{ mEq/L})\) compared with the control group at 6 months \((P=0.003 \text{ and } P=0.024)\), respectively.

Body weight remained unchanged in both groups during the 6-month treatment period \((P>0.05 \text{ for both; \text{Figure 3C})}\). Serum creatinine decreased significantly in the tolvaptan group \((P=0.040)\), whereas it remained unchanged in the control group \((P=0.053; \text{Figure 3D})\). As a result, serum creatinine tended to be lower in the tolvaptan group compared with the control group \((1.0 \text{ vs. } 1.3 \text{ mg/dL}, P=0.083)\).

Plasma BNP reduced significantly in the tolvaptan group \((P=0.026)\) whereas it remained unchanged in the control group \((P=0.51; \text{Figure 3E})\). Statistically, however, the levels were similar between the 2 groups at 6 months \((2.46 \text{ vs. } 2.34 \log \text{ pg/mL}, P=0.66)\). LVEF remained unchanged in both group \((P>0.05 \text{ for both; \text{Figure 3F})}\).

Secondary Outcomes (HF Readmission)
Five patients were not discharged due to 3 transfers, 1 death, and 1 LV assist device (LVAD) implantation. The remaining 24 patients were discharged from the index hospitalization. Of those, 1 patient was transferred and another received LVAD implantation. The other 22 patients completed 6 months of follow-up.

Six-month freedom from HF readmission was numerically higher in the tolvaptan group \((90\% \text{ vs. } 54\%, P=0.092; \text{Figure 4A})\). HF readmission rate was numerically lower in the tolvaptan group \((0.213 \text{ vs. } 1.242 \text{ events/patient-year; } P=0.23; \text{Figure 2})\). As a result, the score was lower in the tolvaptan group compared with the control group at 6 months \((P=0.040)\).

Inclusion/Exclusion Criteria
In the EVEREST study, long-term tolvaptan therapy had a negative impact, but often, in real-world daily practice, a favorable clinical outcome is seen. We hypothesized that the different outcomes might come from patient selection, and that optimal patient selection might be the key to successful tolvaptan therapy. To demonstrate the advantage of tolvaptan vs. conventional diuretics, which is also an essential tool to treat mild-moderate congestion, we believe that patients should be “adequately sick” in their HF in order to receive benefit from tolvaptan. Less sick patients would recover solely on conventional diuretics.

Given the previous findings that patients receiving >80 mg/day furosemide had a significantly worse prognosis, we enrolled those with congestive HF refractory to ≥60 mg/day furosemide. Approximately 40% had serum
AQUA-TLV Study previously showed that elevated urine osmolality and urine aquaporin-2, which indicate the preserved function of the collecting duct to concentrate urine in a fasting condition, was associated with better prognosis during tolvaptan therapy.

Recent post-marketing surveillance (SMILE study) also showed that the clinical responders whose urine output increased following tolvaptan had lower all-cause mortality compared with the clinical non-responders whose urine output remained unchanged despite tolvaptan.

In contrast, we believe that preserved kidney function is essential for an optimal response to tolvaptan, given the biological mechanism in which tolvaptan affects vasopressin type-2 receptor located on the surface of the collecting duct and inhibits the active re-absorption of free water. We previously showed that elevated urine osmolality and urine aquaporin-2, which indicate the preserved function of the collecting duct to concentrate urine in a fasting condition, was associated with better prognosis during tolvaptan therapy.

Sodium $<135\text{ mEq/L}$ in this study (although we enrolled patients irrespective of the existence of hyponatremia), whereas the EVEREST trial had only 11% with serum sodium $<135\text{ mEq/L}$.

Figure 3. Trends in (A) dose of loop diuretics, (B) serum sodium, (C) body weight, (D) serum creatinine, (E) plasma level of B-type natriuretic peptide, and (F) left ventricular ejection fraction in refractory heart failure patients. $^*P<0.05$. Intergroup comparisons between the tolvaptan group and the control group were performed using Mann-Whitney U-test. Intragroup trends from the baseline to 24 weeks were assessed using the Friedman test.
Therefore, in order to select appropriate responders, we set the inclusion criterion of baseline urine osmolality ≥350 mOsm/L in this study. In summary, we did our best to enroll suitable patients who would derive optimal clinical benefit from tolvaptan.

Improvement of Hyponatremia

As already shown in many studies, hyponatremia improved during 6-month tolvaptan therapy in this study, probably due to significant reduction in the dose of loop diuretics, excretion of free water by vasopressin type-2 receptor blocking, and amelioration of congestion. Hyponatremia is a marker of HF severity as well as a driver of poor outcomes. Improvement of hyponatremia is associated with better clinical outcomes in HF patients in general. In the EVEREST trial subanalysis, an improvement of hyponatremia by tolvaptan in the subgroup with serum sodium <130 mEq/L was associated with reduced cardiovascular morbidity and mortality. The recently conducted SMILE study also showed that the correction of hyponatremia was associated with a higher survival rate. Therefore, improvement of hyponatremia in the tolvaptan arm would be one of the major contributors to reduced HF readmissions and improved QOL.

Improvement of Renal Function

Renal dysfunction is another well-known risk factor of worse prognosis in general and in HF patients in particular. We recently performed a meta-analysis in which the reduction in diuretic dose given concomitantly with tolvaptan had a linear correlation with the reduction of serum creatinine. Particularly, the dose of furosemide remained high (>70 mg/day) during the tolvaptan therapy in the EVEREST trial, and serum creatinine was higher in the tolvaptan arm compared with the control arm. In the EVEREST trial, subanalysis patients with higher serum osmolality (≥300 mOsm/L) at discharge, probably due to too much dehydration by tolvaptan and furosemide, had a higher serum creatinine after discharge and worse outcomes compared with the normal serum osmolality group.

Improvement in renal function by the dose reduction of loop diuretics following tolvaptan treatment may be another major contributor to favorable clinical outcomes in the tolvaptan arm. Tolvaptan may also have the potential to preserve renal function by inhibiting the proliferation of epithelial cells, as seen in patients with polycystic kidney disease, although it is uncertain whether it is applicable to the low-dose tolvaptan given in this study (3.75–7.5 mg).

In the clinical responders, it is well known that urine output increases following tolvaptan treatment, and congestion is ameliorated. As a result, we can prevent the recurrence of decompensated congestive HF. Both improvement of hyponatremia and preservation of renal function would also have a favorable effect on the prevention of worsening HF during long-term follow-up. Both relief of daily HF symptom and prevention of worsening HF would improve QOL.

Limitations and Future Perspective

There are several limitations in this study. We could not complete the target enrollment of 100 patients because clinicians tended to hesitate to enroll patients into the RCT given their favorable experience with long-term tolvaptan. Despite a moderate sample size, we still observed significant advantages of tolvaptan therapy in the primary endpoint, although several secondary outcomes did not reach statistical significance. This study was open-labeled, similar to other tolvaptan studies, because blinded trials are not realistic considering the strong aquaretic effect of tolvaptan. Body weight remained unchanged in both groups. We believe that body weight may not be a good indicator of fluid retention for long-term follow-up. Loss of body weight may instead represent cardiac cachexia. The present trial involved 6 months of follow-up, considering the natural course of this sick population, therefore the longer term effects of tolvaptan remain uncertain. Considering the severity of the enrolled cohort, we did not fix the doses of other medications. We cannot completely exclude the effect of other medications, although all enrolled patients were already well-treated at baseline.

Although the short-term efficacy of tolvaptan is well known, we could not observe significant differences at 4

Figure 4. (A) Kaplan-Meier freedom from heart failure (HF) readmission (log-rank test) and (B) HF readmission rate (comparison on negative binomial regression analysis) in refractory HF patients. IRR, incidence rate ratio.
weeks between the 2 arms. Given the relatively small sample size, the very sick population, and the low dose of tolvaptan, it might have taken time (over months) to observe a significant effect of tolvaptan.

Because we do not have data on the patients who were excluded due to lower baseline urine osmolality, we do not know the prevalence of responders to tolvaptan in this study. In our previous study that enrolled a similar advanced HF cohort, a total of 61% were clinical responders. More responders might be found in less sick populations.

In contrast, we enrolled only 4 patients aged >80 years, whereas tolvaptan is used in a much older population with relatively less severe HF in real-world practice. Given that renal function depends on age, some non-responders may be included in such an aged population. Given the lower cost-effectiveness and higher readmission rate in the non-responders receiving tolvaptan, tolvaptan therapy is not recommended in such populations.

Conclusions
On comparison with a randomly assigned control group receiving conventional diuretic therapy, 6-month tolvaptan therapy improved QOL, recovered renal function, and reduced heart failure readmissions in decompensated HF patients, who were estimated to be responders to tolvaptan on urine osmolality.

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Conflict of Interest
T.I. receives financial support from Teraura-Sayoko Memorial Scholarship Foundation. K.K. receives a lecture fee from Otsuka Pharmaceutical. H.T. receives honoraria from Otsuka Pharmaceutical. N.H., I.K., and K.K. are members of Circulation Reports’ Editorial Team. The other authors declare no conflicts of interest.

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