Assessment of Quality of Life During Long-Term Treatment of Tolvaptan in Refractory Heart Failure

Design and Rationale of the AQUA-TLV Study

Teruhiko IMAMURA,¹ MD, Koichiro KINUGAWA,² MD, Tomohito OHTANI,³ MD, Yasushi SAKATA,³ MD, Taiki HIGO,⁴ MD, Shintaro KINUGAWA,⁵ MD, Hiroyuki TSUTSUI,⁵ MD, Kenji SUNAGAWA,⁴ MD, and Issei KOMURO,¹ MD

SUMMARY

The vasopressin type 2 receptor antagonist tolvaptan (TLV) has recently become available to treat congestion in in-hospital patients with heart failure (HF). However, there is no evidence confirming the long-term efficacy of TLV. The Assessment of QUALity of life during long-term treatment of TLV in refractory heart failure (AQUA-TLV) study is a multicenter, open-labeled, randomized, controlled clinical trial that will enroll 100 patients from 18 hospitals in Japan. Patients with HF assigned to New York Heart Association class III or IV, who had a previous history of hospitalization due to congestive HF during the past 1 year and ongoing symptomatic congestion with baseline urine osmolality > 350 mOsm/L regardless of being prescribed daily furosemide $\geq$ 60 mg are randomized to the conventional diuretics group (50 patients) and TLV add-on group (50 patients), and their quality of life will be assessed using the Minnesota Living with Heart Failure Questionnaire after 6 months of treatment. This study is the first multicenter prospective randomized study in Japan to evaluate the long-term clinical effectiveness of TLV compared with conventional treatment in patients with congestive HF (UMIN Clinical Trial Registry Number: UMIN 00009604). (Int Heart J 2014; 55: 264-267)

Key words: Vasopressin, Urine osmolality, Responder

Heart failure (HF) has become one of the major causes of death not only in Europe and the United States but also in Japan.¹⁾ Repeated rehospitalizations due to fluid overload, which results from water retention by way of increased activity of the arginine vasopressin (AVP) system, sympathetic nervous system, and renin-angiotensin-aldosterone system along with decreased renal function and reduced cardiac output, worsen patient quality of life (QOL) enormously.²⁻⁴⁾

Conventionally, thiazides and loop diuretics have been essential tools to control congestion in HF patients.⁵⁾ However, such diuretics have several drawbacks, including worsening of hyponatremia, renal dysfunction, and hypotension due to loss of intravascular volume with sodium depletion as well as water retention resulting from inappropriate AVP secretion against low or normal serum osmolality.⁶⁻¹⁰⁾ These drawbacks cause worsening of HF and increases in the dosage of diuretics, both of which result in the development of a vicious cycle.

Recently, the vasopressin type 2 receptor antagonist tolvaptan (TLV) has become available for HF patients with symptomatic congestion with or without hyponatremia. As a new aquaretic agent, TLV has been demonstrated by several

authors, including us, to ameliorate congestion, stabilize hemodynamics, and improve hyponatremia without sacrificing renal function.¹¹⁻²²⁾ However, such evidence has mostly been limited to among in-hospital patients over several weeks.^{20,23)} The EVEREST trial is thus far the only prospective trial that analyzed the long-term prognosis of TLV over placebo, but its no-better-than placebo result was disappointing.¹³⁾ Thus, we conducted this randomized trial to clarify the long-term efficacy of TLV in patients refractory to conventional diuretics in terms of patient QOL.

METHODS

Objectives: The primary objective of the Assessment of QOL during Long-term Treatment of Tolvaptan in Refractory Heart Failure (AQUA-TLV) study is to investigate the clinical effectiveness of TLV add-on treatment for 6 months from the viewpoint of QOL in congestive HF patients refractory to conventional treatment.

Inclusion and exclusion criteria: In-hospital patients with decompensated HF assigned to New York Heart Association

From the Departments of ¹ Cardiovascular Medicine, ² Therapeutic Strategy for Heart Failure, Graduate School of Medicine, University of Tokyo, Tokyo, ³ Department of Cardiovascular Medicine, Graduate School of Medicine, University of Osaka, Osaka, ⁴ Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, and ⁵ Department of Cardiovascular Medicine, Graduate School of Medicine, Hokkaido University, Hokkaido, Japan.

Address for correspondence: Koichiro Kinugawa, MD, Department of Therapeutic Strategy for Heart Failure, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. E-mail address: kinugawa-ty@umin.ac.jp

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(NYHA) III or IV are enrolled in this study. Decompensated HF is diagnosed on the basis of Framingham criteria by attending physicians.²⁴ All patients have one or more previous hospitalizations due to worsening of decompensated HF during the past 1 year. Eligible patients have either hepatomegaly, lower limb edema, pulmonary congestion described as cardiomegaly, vascular redistribution, and interstitial and alveolar edema by chest X-ray, or jugular venous distension due to fluid retention despite a considerable amount of diuretics (equivalent to oral or intravenous administration of furosemide ≥ 60 mg/day) in addition to appropriate restriction of sodium and water intake.²⁵ There is no restriction of left ventricular ejection fraction.

Patients are excluded if they had hypovolemia, severe stenotic valvular disease, severe systemic infection or inflammation, end-stage renal failure on hemodialysis, acute coronary syndrome, or hypernatremia with serum sodium concentration > 145 mEq/L. Patients who are dependent on or planned to receive any mechanical supports such as ventricular assist devices, intra-aortic balloon pumping, extracorporeal membranous oxygenation, mechanical ventilation, or combination of these devices, are also excluded. Patients with impaired consciousness who lack a sense of thirst or have difficulty in oral intake are excluded from the study. Patients with baseline urine osmolality of < 350 mOsm/L, which also can be calculated by the formula $2 \times [\text{urinary sodium concentration (mEq/L)}] + [\text{urinary urea nitrogen concentration (mg/dL)}] / 2.8 + [\text{urinary creatinine concentration (mg/dL)}] \times 2/3 + 16$,¹⁸ are also excluded considering our previous studies.¹⁶

Study design (Figure): After written informed consent is obtained, patients receive several clinical examinations such as blood tests measuring serum sodium, potassium, creatinine concentration, and plasma B-type natriuretic peptide concentration, a chest X-ray test, physical assessment, transthoracic echocardiogram, and Minnesota Living with Heart Failure Questionnaire (MHLHFQ) during 1-3 days of the observation period before the randomization. When eligible for this study, patients are enrolled and randomized into each of 2 different treatment arms, ie TLV add-on group and conventional treatment group.

In the TLV add-on group, TLV is initiated at 3.75 mg or 7.5 mg daily in addition to conventional diuretics, and the target body weight is set as the level at the latest discharge. Doses of TLV and other diuretics can be altered by the attending physician. TLV can be continued after the study period if necessary. If TLV is discontinued, the patients are excluded from the study.

In the conventional treatment group, doses of diuretics are adjusted taking into consideration the body weight at the latest discharge. If a physician decides to administer TLV, the patient is excluded from the study.

The study protocol was approved by the Ethics Committee of Graduate School of Medicine, University of Tokyo (UMIN Clinical Trial Registry Number: UMIN 000009604).

Endpoints: The primary endpoint is patient QOL calculated by MHLHFQ during the study period.^{3,4} Secondary endpoints include body weight, NYHA class, cardio-thoracic ratio, ejection fraction, physical congestion, renal function, serum sodium concentration, and plasma B-type natriuretic peptide concentration during the study period.

Statistical analysis: The total sample size consists of 50 pa-

Figure. Study protocol of the AQUA-TLV study.

tients in the TLV group and 50 patients in the conventional treatment group considering the result of a power analysis (alpha error probability, 0.05; power, 0.80). Categorical variables are summarized as frequencies and percentages, and are compared using the chi-square test or Fisher's exact test as appropriate. Continuous variables are represented as the mean $\pm$ standard deviation unless otherwise specified, and compared using the unpaired *t*-test or Mann-Whitney test as appropriate. All hypothesis tests reported are two-tailed, and use a $P < 0.05$ as significant.

DISCUSSION

The AQUA-TLV study is designed to evaluate the long-term clinical advantage of TLV add-on therapy over conventional diuretic therapy by assessing the improvement of QOL in patients with congestive HF during a 6 month period.

The EVEREST trial is thus far the only prospective trial that has analyzed the long-term efficacy of TLV from the viewpoint of prognosis in patients with mild to moderate HF, but failed to show the benefit of TLV over placebo.¹³ However, as discussed below the EVEREST trial has several potential issues in the study design to lessen the efficacy of TLV. Therefore, we here propose the AQUA-TLV study to clarify the effectiveness of TLV on a long-term basis.

Inclusion/exclusion criteria: First of all, long-term administration of TLV is best indicated among patients with advanced HF who have a previous history of multiple hospitalizations regardless of being prescribed a considerable amount of conventional diuretics. In other words, most de novo HF can possibly be treated solely by low doses of conventional diuretics without TLV. The no-better-than placebo result of the EVEREST trial may have resulted from the enrollment criteria, which allowed de novo HF patients into the TLV-treatment arm. Many previous reports agreed that furosemide ≥ 80 mg/day was significantly associated with higher mortality in patients with HF,^{26,27} and 60 mg/day could be a reasonable number for a lower limit of furosemide in our inclusion criteria. Collectively, the inclusion criteria of our study are essential to select patients who are refractory to conventional diuretics, and such patients would be better candidates for long-term administration of TLV.

As for the serum sodium concentration, only 11% of the patients had hyponatremia in the EVEREST trial,¹³ and the rate was less than half that of other studies.^{28,29} In the sub-analysis of the EVEREST trial, patients with severe hyponatremia

(< 130 mEq/L) enjoyed a better prognostic benefit from TLV treatment compared to the placebo group. Increases in serum sodium concentration by TLV treatment itself may possibly improve the long-term prognosis in patients with progressed HF.³⁰⁾ Fortunately, at least 20% of the patients enrolled in the AQUA-TLV trial will be hyponatremia patients based on our recent experience.¹⁶⁾

Moreover, the EVEREST trial might have included non-responders to TLV. The efficacy of TLV is limited only to responders, as we reported.^{20,21)} Nonresponders are associated with reduced ability to concentrate and dilute urine, which is probably due to dysfunction of the collecting ducts and/or loss of the medullar osmotic gradient.¹⁸⁾ We recently proposed new criteria with a baseline urine osmolality of ≥ 350 mOsm/L that can efficiently predict responsiveness to TLV.¹⁶⁾ By using these criteria, we can exclude nonresponders to TLV. The EVEREST study only enrolled patients with reduced ejection fraction, but according to our recent data,¹⁶⁾ responders had better clinical outcomes regardless of the level of left ventricular ejection fraction. We do not exclude patients with preserved ejection fraction from the AQUA-TLV study.

Endpoint: Time to the first rehospitalization due to HF was analyzed as an endpoint in the EVEREST trial, but there was no significant difference between the TLV and placebo groups in the observational period that averaged approximately 10 months.¹³⁾ It may be difficult for TLV treatment to significantly inhibit rehospitalization among patients with refractory HF over such a short period. Instead of clinical endpoints, we analyze patient QOL as a primary endpoint in this study. We have previously demonstrated that better QOL has significant correlation with improved composite endpoints including cardiac death as well as HF hospitalizations in patients with HF.³⁾

Limitations: 1. Because we can change the dose of diuretics such as furosemide during the study period in the TLV group, we would not be able to evaluate the pure benefit of TLV. However, we would like to analyze the real clinical effect of TLV in clinical settings, and we often introduce TLV together with dose adaptation of diuretics in order to minimize the adverse effects.

2. The study period is set at 6 months in this study. Longer observation periods may provide convincing evidence for the longer-term safety and efficacy of TLV. However, the severity of HF in patients with stage D HF would not permit longer observation.

Conclusion: The AQUA-TLV study is the first prospective, open-labeled, randomized TLV add-on trial versus conventional treatment in patients with decompensated HF designed to evaluate the long-term efficacy of TLV from the viewpoint of patient QOL.

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