New Insights Into Tolvaptan Treatment and the Renin-Angiotensin-Aldosterone System

Keisuke Kida, MD

Body fluids are regulated by the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system, and arginine vasopressin (AVP) in patients with congestive heart failure (HF). Angiotensin-converting enzyme inhibitors (ACE-I) have been shown to reduce mortality and morbidity in patients with HF and should be up-titrated to the maximum tolerated dose in order to achieve adequate inhibition of the RAAS. Angiotensin II receptor blockers (ARB) are recommended only as an alternative in patients intolerant of ACE-I. Meanwhile, tolvaptan, a vasopressin V2-receptor antagonist which inhibits vasopressin-mediated water reabsorption in the renal collecting duct and leads to increased free water clearance (aquaresis), is available as a diuretic drug in the treatment of fluid accumulation in HF. Our recent pharmacokinetic and pharmacodynamic studies have reported the effectiveness and safety of add-on tolvaptan to furosemide in HF patients with advanced kidney dysfunction. As compared with furosemide, tolvaptan in patients with acute HF is associated with comparable decongestion, better preservation of renal function, and less activation of the RAAS; however, the efficacy of tolvaptan with or without ARB/ACE-I therapy in hospitalized patients with acute decompensated HF has not been fully investigated. The most recently published study of Adachi, et al suggested that a single use of tolvaptan might induce an increase in urine volume in acute decompensated HF patients who were not previously treated with ARB/ACE-I. This result is quite surprising because ARB/ACE-I are the first-choice drugs for the treatment of HF recommended by the guidelines. Their study retrospectively included 44 patients with acute decompensated HF who were treated with 7.0 mg (initial doses) of tolvaptan. The authors demonstrated that a response to the use of tolvaptan was independently associated with the non-use of ARB/ACE-I. They also reported single-use tolvaptan had an adequate diuretic effect on their study patients who did not receive ARB/ACE-I before the initiation of tolvaptan administration.

Several studies have reported on tolvaptan treatment and RAAS. Kadota, et al provided new insights into the predictors of a response to tolvaptan using the AVP/plasma aldosterone concentration (PAC) ratio. Their study prospectively included 26 patients with decompensated HF who were treated with 15 mg of tolvaptan. They investigated the effects of tolvaptan on the RAAS and predictors for the response to tolvaptan treatment based on multiple laboratory factors, such as plasma renin activity, aldosterone concentration, and AVP. Imamura, et al described the usefulness of the urine aquaporin (AQP) -2/AVP ratio for predicting the tolvaptan response. These results demonstrate that the potential ability to concentrate urine in the renal collecting duct is essential for the tolvaptan response. High urine osmolality basically indicates high secretion of AVP, although AVP alone cannot predict a response to tolvaptan. In patients with congestive HF, AVP is inappropriately secreted through the activation of a non-osmotic pathway because of a reduction in effective circulating volume despite peripheral water retention. Therefore, the increased urine AQP-2 levels in patients with HF are due to inappropriately elevated serum AVP levels. The plasma levels of AVP are increased by an association with HF progression accompanied by activated RAAS and sympathetic nerve system that facilitate water retention. The ratio of AVP/PAC may reflect the activation of AQP-2 in the collecting duct. Kadota, et al suggested that tolvaptan may be more effective in patients with AVP-dominant HF compared to those with RAAS-dominant HF.

The present study has the following two major findings: 1) the increase in urine volume after tolvaptan administration in the non-ARB/ACE-I group was significantly higher than that in the ARB/ACE-I group; and 2) a response to the use of tolvaptan was independently associated with the non-use of ARB/ACE-I. The authors present two reasons for these findings. One is the combination of loop diuretic and ARB/ACE-I which is known to have a synergistic effect. ARB/ACE-I enhances the diuretic effect of a loop diuretic; thus, ARB/ACE-I can overcome the deleterious effects of a loop diuretic. The other reason is the speculated excessive activation of RAAS which exacerbates urine concentration via AQP-2 in decompensated HF patients without ARB/ACE-I. Since the authors did not measure multiple laboratory factors, such as plasma renin activity, aldosterone concentration, AVP and AQP-2, the response to the use of tolvaptan was independently associated with the non-use of ARB/ACE-I. Larger population studies, including the associations of tolvaptan treatment and RAAS, should be conducted for considering the results of the present study.
The prescribing information from the Food and Drug Administration currently notes that sacubitril/valsartan should be used in patients in place of an ACE-I or other ARB; that is, patients receiving these treatments should be switched to angiotensin receptor neprilysin inhibitors (ARNI).

The prospective comparison of ARNI with ACE-I in the Determine Impact on Global Mortality and morbidity in HF (PARADIGM-HF) trial, which is a major clinical outcome trial, demonstrated ARNI LCZ696 as an alternative to the ‘gold-standard’ ACE-I enalapril in patients with HF. As the largest clinical trial in HF, the results of the PARADIGM-HF trial may change our approach to neurohumoral modulation in HF. A large controlled randomized study should be performed to confirm the efficacy of tolvaptan with or without ARNI therapy in hospitalized patients with acute decompensated HF.

In previous studies, the patients whose urine volumes on day 1 increased compared to those on day 0 were defined as responders, whereas those whose urine volumes did not increase were defined as non-responders. A response to tolvaptan was defined by a decrease in body weight by more than 2 kg in a week and an increase in urine volume by 500 mL/day compared to that before tolvaptan administration. In the current guidelines of HF, no statements have been published concerning tolvaptan administration in responders and non-responders. The present study stratified the patients into responders or non-responders based on the average change in urine volumes at baseline and the entire follow-up period after the tolvaptan administration. The result of this study provided no prognostic information associated with tolvaptan. The other concern is the long-term prognosis with tolvaptan in the responders and the further treatment of non-responders. The efficacy of vasopressin antagonism in the HF outcome study with Tolvaptan (EVEREST) did not indicate a survival advantage of long-term tolvaptan treatment.

A sub-analysis of the EVEREST study showed that the patients with severe hyponatremia (< 130 mEq/L) on long-term tolvaptan treatment revealed reduced cardiovascular morbidity and mortality. Among the AQP-defined responders, tolvaptan treatment was accompanied by better survival after 2-year follow-up compared with the propensity-matched tolvaptan (–) patients. More detailed guidelines, including the prediction for responders and the effect of tolvaptan on long-term prognosis, are required.

The Japanese phase III study has demonstrated that tolvaptan exerts diuretic effects and causes body weight loss at a low dose of 7.5 mg/day; however, these effects are less than those elicited by 15 mg/day. Our previous study showed that tolvaptan 15 mg once daily was effective; the urine volumes of patients receiving these treatments should be switched to angiotensin receptor neprilysin inhibitors (ARNI). The prospec- tion of response to tolvaptan in patients with severe hyponatremia (< 130 mEq/L) on long-term tolvaptan treatment revealed reduced cardiovascular morbidity and mortality. Among the AQP-defined responders, tolvaptan treatment was accompanied by better survival after 2-year follow-up compared with the propensity-matched tolvaptan (–) patients. More detailed guidelines, including the prediction for responders and the effect of tolvaptan on long-term prognosis, are required.

The Japanese phase III study has demonstrated that tolvaptan exerts diuretic effects and causes body weight loss at a low dose of 7.5 mg/day; however, these effects are less than those elicited by 15 mg/day. Our previous study showed that tolvaptan 15 mg once daily was effective; the urine volumes of patients receiving these treatments should be switched to angiotensin receptor neprilysin inhibitors (ARNI). The prospec- tion of response to tolvaptan in patients with severe hyponatremia (< 130 mEq/L) on long-term tolvaptan treatment revealed reduced cardiovascular morbidity and mortality. Among the AQP-defined responders, tolvaptan treatment was accompanied by better survival after 2-year follow-up compared with the propensity-matched tolvaptan (–) patients. More detailed guidelines, including the prediction for responders and the effect of tolvaptan on long-term prognosis, are required.

The Japanese phase III study has demonstrated that tolvaptan exerts diuretic effects and causes body weight loss at a low dose of 7.5 mg/day; however, these effects are less than those elicited by 15 mg/day. Our previous study showed that tolvaptan 15 mg once daily was effective; the urine volumes of patients receiving these treatments should be switched to angiotensin receptor neprilysin inhibitors (ARNI). The prospec- tion of response to tolvaptan in patients with severe hyponatremia (< 130 mEq/L) on long-term tolvaptan treatment revealed reduced cardiovascular morbidity and mortality. Among the AQP-defined responders, tolvaptan treatment was accompanied by better survival after 2-year follow-up compared with the propensity-matched tolvaptan (–) patients. More detailed guidelines, including the prediction for responders and the effect of tolvaptan on long-term prognosis, are required.

The Japanese phase III study has demonstrated that tolvaptan exerts diuretic effects and causes body weight loss at a low dose of 7.5 mg/day; however, these effects are less than those elicited by 15 mg/day. Our previous study showed that tolvaptan 15 mg once daily was effective; the urine volumes of patients receiving these treatments should be switched to angiotensin receptor neprilysin inhibitors (ARNI). The prospec- tion of response to tolvaptan in patients with severe hyponatremia (< 130 mEq/L) on long-term tolvaptan treatment revealed reduced cardiovascular morbidity and mortality. Among the AQP-defined responders, tolvaptan treatment was accompanied by better survival after 2-year follow-up compared with the propensity-matched tolvaptan (–) patients. More detailed guidelines, including the prediction for responders and the effect of tolvaptan on long-term prognosis, are required.

The Japanese phase III study has demonstrated that tolvaptan exerts diuretic effects and causes body weight loss at a low dose of 7.5 mg/day; however, these effects are less than those elicited by 15 mg/day. Our previous study showed that tolvaptan 15 mg once daily was effective; the urine volumes of patients receiving these treatments should be switched to angiotensin receptor neprilysin inhibitors (ARNI). The prospec- tion of response to tolvaptan in patients with severe hyponatremia (< 130 mEq/L) on long-term tolvaptan treatment revealed reduced cardiovascular morbidity and mortality. Among the AQP-defined responders, tolvaptan treatment was accompanied by better survival after 2-year follow-up compared with the propensity-matched tolvaptan (–) patients. More detailed guidelines, including the prediction for responders and the effect of tolvaptan on long-term prognosis, are required.

The Japanese phase III study has demonstrated that tolvaptan exerts diuretic effects and causes body weight loss at a low dose of 7.5 mg/day; however, these effects are less than those elicited by 15 mg/day. Our previous study showed that tolvaptan 15 mg once daily was effective; the urine volumes of patients receiving these treatments should be switched to angiotensin receptor neprilysin inhibitors (ARNI). The prospec- tion of response to tolvaptan in patients with severe hyponatremia (< 130 mEq/L) on long-term tolvaptan treatment revealed reduced cardiovascular morbidity and mortality. Among the AQP-defined responders, tolvaptan treatment was accompanied by better survival after 2-year follow-up compared with the propensity-matched tolvaptan (–) patients. More detailed guidelines, including the prediction for responders and the effect of tolvaptan on long-term prognosis, are required.


