Aquaporin-2-Guided Tolvaptan Therapy in Patients With Congestive Heart Failure Accompanied by Chronic Kidney Disease

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Recently, there has been increasing evidence supporting the efficacy and safety of the arginine vasopressin (AVP) type 2 (V₂) antagonist tolvaptan (TLV) in the improvement of hyponatremia or amelioration of congestion sparing renal function in acute/chronic heart failure (HF) patients refractory to considerable amounts of loop diuretics.¹ However, such a clinical benefit of TLV-incorporated diuretic therapy is not necessarily observed in all HF patients. In other words, we sometimes experience non-responders to TLV, whose clinical course worsens regardless of the initiation of TLV.²

Although the precise mechanism of resistance to TLV is unknown, we previously speculated that aging and chronic kidney disease (CKD) were major risk factors of non-responders.³ In fact, concentrating and diluting ability in the collecting ducts is essential for the efficacy of TLV, but is often impaired in elderly or those with advanced CKD. However, according to our clinical experience, there were several responders to TLV even though they were complicated with stage G4 CKD.⁴

The efficacy of TLV treatment in patients with CKD is controversial. Sato, et al demonstrated in a recent study that some responders with diabetes mellitus nephropathy received a clinical benefit from TLV treatment even though their renal dysfunction was approximately equivalent to stage G4 CKD (22.1 ± 18.1 mL/minute/1.73m² of estimated glomerular filtration ratio).⁵ Among the 8 patients from whom renal specimens were obtained, 7 were responders and simultaneously had explicit expression of aquaporin-2 (AQP2) in the collecting ducts. The remaining patient was a non-responder showing no expression of AQP2 with histological evidence of tubulointerstitial damage. Although the sample number was very small, we could confirm that U-AQP2 was proportionally excreted to plasma levels of AVP in responders, whereas virtually no U-AQP2 was measured in non-responders.

There were several limitations in the study of Sato, et al. First, they only analyzed a small number of kidney specimens from patients with diabetes mellitus nephropathy. CKD refractory to TLV treatment may result from various other etiologies such as acute tubular necrosis, renal sclerosis, and pre-renal or post-renal renal dysfunction. AQP2 expression and responses to TLV should be analyzed in patients with CKD due to such other etiologies. However, their results may imply that diabetes nephropathy often preserves the function of the collecting ducts relative to that of the glomeruli.

The second limitation was that the long-term effect of TLV was not clear in the true responders diagnosed by expression of AQP2. Although the EVEREST study could not demonstrate a survival advantage of TLV over placebo, some non-responders with poor prognosis might have been enrolled.⁶ When analyzing the efficacy of TLV accurately, some novel methods to distinguish responders, such as measurement of U-AQP2, would be essential, especially when including patients with CKD.

We recently reported various short-term clinical advan-
tages of TLV only in responders defined by urine osmolality.\textsuperscript{11,12} We also reported in a propensity-matched retrospective study that the survival advantage of long-term TLV treatment was observed only in the responders defined by U-AQP2.\textsuperscript{8} A prospective study to analyze the long-term efficacy of TLV, such as improved survival, reduced readmission rate, or freedom from renal replacement therapy in responders would be of value.\textsuperscript{13}

REFERENCES