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Light and Shadow in Oral Tolvaptan Treatment

By Yong Chul Kim and Hajeong Lee

Tolvaptan, an oral selective vasopressin V2 receptor antagonist, was approved by the US Food and Drug Administration (FDA) for the treatment of clinically significant hypervolemic or euvolemic hyponatremia and rapidly progressing autosomal dominant polycystic kidney disease (ADPKD). It antagonizes the effect of an arginine vasopressin (antidiuretic hormone), which has a key role in water and circulatory homeostasis in the collecting duct of the kidney. Tolvaptan leads to an increase in urine water excretion (aquaresis) that results in enhanced free-water clearance in states of relative vasopressin excess, increasing serum sodium concentrations. Additionally, tolvaptan induces a reduction in cyclic adenosine monophosphate (cAMP), a key second messenger in the pathogenesis of ADPKD, resulting in decreased kidney cyst proliferation and fluid secretion, diminishing ADPKD cyst growth.

Two randomized, double-blind, placebo-controlled trials (Study of Ascending Levels of Tolvaptan in Hyponatremia [SALT]-1, SALT-2) demonstrated both short-term and long-term efficacy of tolvaptan in patients with hyponatremia from various causes, such as syndrome of inappropriate antidiuretic (SIAD) hormone and heart failure (1, 2). In view of ADPKD, tolvaptan slowed kidney cyst growth and functional decline with reduced frequencies of ADPKD-related complications at both early and later stages of chronic kidney disease (CKD) in two large trials: Tolvaptan Efficacy and Safety in Management of ADPKD and Its Outcomes (TEMPO 3:4) (3) and Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy in ADPKD (REPRISE) trials (4, 5).

Although the treatment of hyponatremia and ADPKD with tolvaptan is an important advance, there are several drawbacks. First, common adverse effects of tolvaptan should be considered, which include thirst, urination frequency, fatigue, polydipsia, and polyuria. All of these are the main causes of discontinuation during the treatment of ADPKD. Second, patients taking tolvaptan should monitor their liver function regularly due to possible drug-induced hepatotoxicity. Third, one should remain vigilant for osmotic demyelination syndrome, a rare but devastating complication arising from an overly rapid hyponatremia correction, especially if tolvaptan is used with diuretics or hypertonic saline solution concomitantly (6). Frequent monitoring of serum electrolyte and volume status is warranted, and physicians should consider using low doses at initiation because of the potential for overcorrection (7). Forth, tolvaptan is an expensive medication, and there is a huge difference in insurance coverage by the healthcare system among countries that approved tolvaptan. Currently, there are only a few studies looking at the cost-effectiveness of the treatment of ADPKD or SIAD with tolvaptan (8, 9). Last, although there is a recommendation for the timing of the initiation of tolvaptan in patients with ADPKD, it is unclear when to stop the medication. For example, do patients have to take it until dialysis? Do they quit around CKD stage 4?

Although these advances are certainly exciting and pave the way for continued investment of novel therapeutics in these areas, there are several concerns and questions about using tolvaptan in patients having either hyponatremia or ADPKD (10–12). Both require patient engagement to describe the risks and benefits before prescribing. The development of antagonists to vasopressin has ushered in a new era in clinical trials for hyponatremia and ADPKD and will hopefully only be the start of ushering in new therapies (13). ■

Yong Chul Kim is an associate professor and Hajeong Lee is a professor in the Division of Nephrology, Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea.

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