Shaping Tomorrow's Nephrology: Insight-Driven Kidney Care
KSN 2026 SEOUL, KOREA
The 46th Annual Meeting of the Korean Society of Nephrology
Jun 11 (Thu) – 14 (Sun), 2026
COEX, Seoul, Korea

Lecture Code : SS02-S3
Session Name : Satellite Symposium 1 (Sponsored by Otsuka)
Session Topic : Satellite Symposium 1 (Sponsored by Otsuka)
Date & Time, Place : June 12 (Fri) / 10:20-12:00 / Room 4 (203), 2F

Beyond Tolvaptan: Combination Strategies to Further Suppress Kidney Volume Growth in ADPKD

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Autosomal dominant polycystic kidney disease (ADPKD) is characterized by progressive cyst growth leading to kidney enlargement and eventual renal failure. Currently, tolvaptan, a vasopressin V2 receptor antagonist, is the only therapeutic agent with robust clinical evidence demonstrating its efficacy in slowing disease progression. Large-scale clinical trials have shown that tolvaptan reduces the rate of total kidney volume (TKV) increase and attenuates the decline in estimated glomerular filtration rate (eGFR) . Therefore, it remains the cornerstone of disease-modifying therapy in ADPKD. At the molecular level, increased intracellular cyclic AMP (cAMP) plays a central role in cystogenesis by promoting epithelial cell proliferation and fluid secretion. Tolvaptan exerts its effect by inhibiting vasopressin-mediated cAMP production. However, strategies to further suppress cAMP signaling may enhance therapeutic efficacy. Thiazide diuretics, when used alone, may paradoxically increase vasopressin activity and potentially exacerbate cyst growth. However, experimental studies suggest that when combined with tolvaptan, thiazides may reduce cyst volume more effectively than tolvaptan monotherapy. This effect may be mediated through modulation of vasopressin dynamics and compensatory tubular mechanisms . In addition, calcimimetics, which activate the calcium-sensing receptor (CaSR), has been shown to suppress intracellular cAMP levels in renal tubular cells. Preclinical and clinical observations indicate that calcimimetics, such as cinacalcet, may attenuate cyst growth. Notably, combination therapy with tolvaptan and calcimimetics has demonstrated greater suppression of cyst progression compared with either agent alone, suggesting a potential synergistic effect. While the development of novel therapeutic agents remains essential, revisiting existing drugs from a

mechanistic perspective offers an alternative strategy to improve clinical outcomes. Combination approaches targeting multiple pathways involved in cyst growth, particularly cAMP signaling, may represent a promising direction for future ADPKD

Keywords: ADPKD, Thiazide diuretics, Calcimimetics