Refining Tolvaptan Dosing in ADPKD: The Role of Urinary Biomarkers in Enhancing Outcomes

To the Editor We read with great interest the article by *Dahl and Torres.*,[1] which underscores the importance of individualized tolvaptan dosing in autosomal dominant polycystic kidney disease.[2] Their findings align with our real-world clinical experience and reinforce the need for personalized dose adjustments to optimize therapeutic efficacy while minimizing adverse effects.

Over the past 15 years, our autosomal dominant polycystic kidney disease clinic has managed over 80 patients on tolvaptan, with 60 currently under active follow-up. As an investigational center in major trials,[1] we have observed that though high-dose tolvaptan slows disease progression, it is not universally well-tolerated. Notably, in approximately 10% of our patients—particularly those with chronic kidney disease stage IIIb–IV on the maximum recommended dose (90/30 mg) for over a year—we observed an accelerated decline in renal function. This deterioration was frequently associated with increased urinary osmolality ($>$ 250 mOsm/kg) and specific gravity ($>$ 1.005). Initially attributed to disease progression, renal function improved upon dose reduction to an intermediate (60/30 mg) or lower regimen, with corresponding decreases in urinary osmolality and specific gravity. This adjustment correlated with stabilization or partial recovery of renal function, mirroring the concerns raised by Torres *et al.* regarding the need for individualized treatment approaches. Thus, urinary biomarkers may serve as reliable indicators in a more precise alternative to fixed high-dose titration.

Recent studies further support this concept, emphasizing that urinary osmolality is a good predictor of treatment response and that maintaining levels $<$ 250 mOsm/kg correlates with optimal therapeutic effects.[3,4]

Consistent with the authors' observations, high-dose tolvaptan frequently leads to excessive aquaresis, unrelenting thirst, and, in some cases, severe hyponatremia, particularly in patients adhering to low-sodium diets with high fluid intake, exacerbating an already challenging and psychological disease burden.[5]

Beyond immediate patient management, our findings reinforce that a biomarker-driven dosing strategy could refine clinical practice guidelines, shifting from a one-size-fits-all approach to a more dynamic, individualized treatment model. We commend Dahl and Torres for their valuable contribution to this evolving area of research. Our real-world experience corroborates their conclusions and further supports the role of urinary biomarkers in guiding tolvaptan dose optimization to maximize benefits and minimize risks.

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Received 23 March 2025; accepted 28 March 2025; published online 27 May 2025

Kidney Int Rep (2025) **10,** 2879; https://doi.org/10.1016/j.ekir.2025.03.059