LETTER TO THE EDITOR

Tolvaptan, Kidney Function Decline, and Potential Confounding by Muscle Wasting

To the Editor:

The vasopressin receptor 2 (V_2R) antagonist tolvaptan is the only registered treatment to mitigate kidney function decline in patients at high risk of progression, with autosomal dominant polycystic kidney disease. Recent work by Chebib et al[1] showed that tolvaptan was associated with a reduced annual decline in creatinine-based estimated glomerular filtration rate (eGFRcr) compared with standard-of-care in patients aged >55 years. However, the National Kidney Foundation and Food and Drug Administration only endorse the use of eGFRcr-based end points if it has been reported that an intervention does not affect muscle-derived creatinine generation.[2] Chebib et al[1] do not mention studies showing this, nor are we aware of such studies. Thus, the prerequisite exclusion of an effect on muscle-derived creatinine generation is not met in studies investigating the effects of V_2R antagonists on eGFRcr.

Antagonizing V_2R mimics nephrogenic diabetes insipidus, inducing polyuria up to >10 L/day (Fig 1),[3] subsequent polydipsia, and high compensatory fluid consumption. Extraordinary fluid intake suppresses appetite—evidenced by a higher incidence of anorexia under tolvaptan treatment compared with placebo[4]—which may lead to malnutrition and, ultimately, sarcopenia, reducing creatinine generation.[5] This line of reasoning suggests that the purported renoprotective effects of tolvaptan may, at least partially, be attributed to therapy-related muscle wasting, an argument that remains unchallenged as the long-term effects of tolvaptan on kidney function decline have never been confirmed with clearance methods or muscle mass-insensitive markers of kidney function (eg, cystatin C). In light of this evidential void, renoprotection by tolvaptan can only be fully substantiated with analyses based on these National Kidney Foundation and Food and Drug Administration endorsed alternatives.[2]

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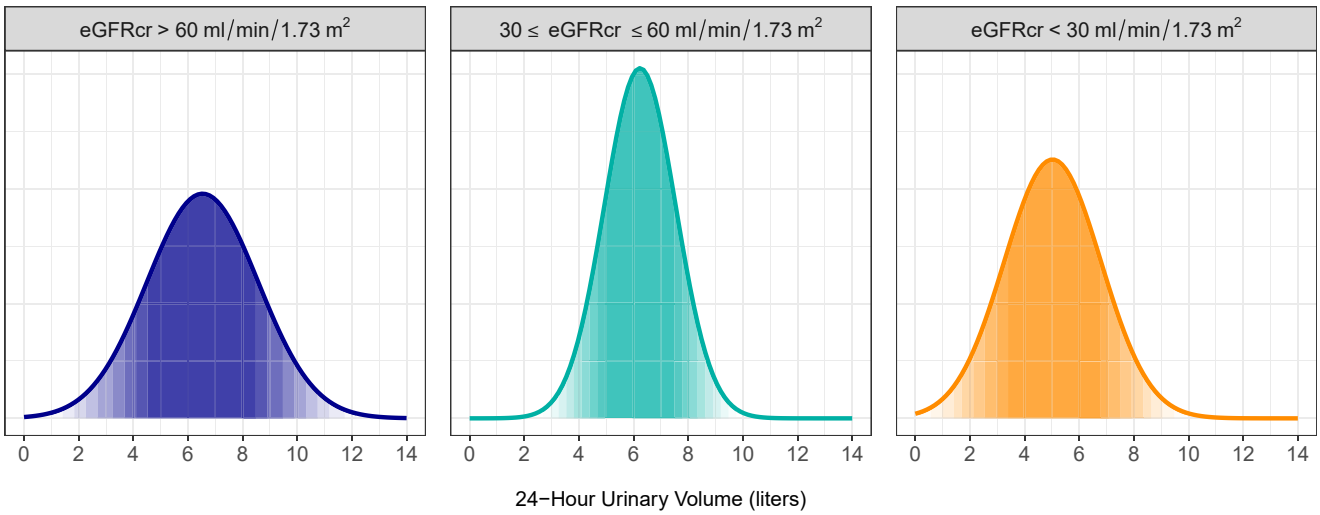

Figure 1. Theoretical distributions of 24-hour urinary volume after 3 weeks of tolvaptan stratified by eGFRcr. The graph depicts density values for 24-hour urinary volume ranging from 0-14 liters per 24 hours, which were calculated based on a set of normal distributions. The means and standard deviations for these distributions were derived from a previous study that reported the 24-hour urinary volume outcomes after 3 weeks of treatment with tolvaptan, stratified by eGFRcr categories (>60, 30-60, and <30 mL/min/1.73 m²).[3] The various levels of transparency in the area under each curve represent the likelihood of observing a particular urinary volume; the more transparent the area, the lower the likelihood it will be observed. Cr, creatinine; eGFR, estimated glomerular filtration rate.

REFERENCES

1. Chebib FT, Zhou X, Garbinsky D, et al. Tolvaptan and kidney function decline in older individuals with autosomal dominant polycystic kidney disease: a pooled analysis of randomized clinical trials and observational studies. *Kidney Med*. 2023;5(6):100639.
2. Levey AS, Inker LA, Matsushita K, et al. GFR decline as an end point for clinical trials in CKD: A scientific workshop sponsored by the national kidney foundation and the US Food and Drug Administration. *Am J Kidney Dis*. 2014; 64(6):821-835.
3. Kramers BJ, van Gastel MDA, Boertien WE, Meijer E, Gansevoort RT. Determinants of urine volume in ADPKD patients using the vasopressin V2 receptor antagonist tolvaptan. *Am J Kidney Dis*. 2019;73(3):354-362.
4. Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl J Med*. 2012;367(25):2407-2418.
5. Vandewoude MFJ, Alish CJ, Sauer AC, Hegazi RA. Malnutrition-sarcopenia syndrome: is this the future of nutrition screening and assessment for older adults? *J Aging Res*. 2012;2012: 651570.

Chebib et al declined to respond.