Prospective Study on Individualized Dose Adjustment of Tolvaptan Based on Urinary Osmolality in Patients With ADPKD

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To the Editor: In their editorial, Dahl *et al.*[1] write that the study by Roca Oporto *et al.*[2] offers reassurance that most patients with autosomal dominant polycystic kidney disease can remain on the starting dose of tolvaptan (45/15 mg once daily) without requiring dose escalation, if urine osmolality stays below 200 mOsm/kg in 24-hour urine. The study by Roca Oporto *et al.* deals with an important subject and is well-reported. However, we think it is too early to advocate that dose escalation may not be necessary.

As the authors state, the conclusion is based on a limited set of uncontrolled data ($n = 40$). In comparison, the efficacy of tolvaptan is based on randomized controlled trials in nearly 900 patients on active treatment.[3] Our main concern is that efficacy needs to be based on controlled data with sufficient power to show a clinically relevant benefit. As the authors mention in their study, the slow decline in estimated glomerular filtration rate after starting treatment may reflect regression to the mean instead of a treatment effect.

Furthermore, urine osmolality may not accurately reflect vasopressin blockade, particularly in patients with more severe disease (chronic kidney disease stage G3 and higher). These patients may exhibit urine osmolality <200 mOsm/kg and elevated copeptin levels even without tolvaptan because of impaired urine concentrating ability.[4] Thus, basing dosing solely on urine osmolality may not indicate true vasopressin receptor blockade, although such patients may particularly benefit from treatment. Roca Oporto's study does not report changes in vasopressin or copeptin levels during treatment.

Finally, in most patients, the most significant reduction in urine osmolality and increase in 24-hour urine volume occurs at the lowest tolvaptan dose, with minimal additional changes from subsequent increase in dose.[5] Thus, up-titration is unlikely to increase the incidence of aquaretic adverse events but may reduce treatment efficacy on disease progression.

We therefore agree with the original study authors in calling for randomized trials to determine whether dosing tolvaptan based on urine osmolality is as effective as titrating to 90/30 mg once daily based on tolerability.

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