tubulointerstitial fibrosis. Future studies are needed to comprehensively define the role of the pathway in glomerular and tubulointerstitial health and disease as well as to determine the impact of timing and duration of YAP activation. In the meantime, ongoing clinical trials of small molecule YAP inhibitors in patients with advanced cancer may yield additional insights into the safety of manipulating this pathway in humans.

DISCLOSURE

All the authors declared no competing interests.

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polycystic kidney disease

REPRISE: tolvaptan in advanced polycystic kidney disease

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Autosomal polycystic kidney disease (ADPKD) is the most common Mendelian kidney disease, with a high but variable risk of progression to end-stage kidney disease. Preclinical studies demonstrate an important role for vasopressin in promoting cyst growth and disease progression.[1] The phase 3 Tolvaptan Efficacy and Safety in the Management of ADPKD and its Outcomes (TEMPO) trial included ADPKD patients with a high risk of progression defined by a large kidney volume (total kidney volume >750 ml), but with preserved renal function (creatinine clearance >60 ml/min). TEMPO demonstrated a significant reduction in kidney volume progression and estimated glomerular filtration (eGFR) decline in participants with early ADPKD randomized to receive the vasopressin V2 antagonist tolvaptan.[2] Principal adverse events leading to study drug discontinuation were related to aquaresis. Additionally, elevated transaminase levels were observed more frequently in the tolvaptan arm. As a result, current expert recommendations focus on identifying individuals at high risk of progression in whom the risk-benefit ratio is likely to be more favorable.[3,4] Individuals with more advanced disease, as evidenced by a decreased eGFR, are at higher risk of progression, but TEMPO did not assess the efficacy of tolvaptan in this population.

In a recent issue of the *New England Journal of Medicine*, Torres *et al.*[5] report the results of the Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy in ADPKD (REPRISE) trial in individuals with more advanced ADPKD. REPRISE was a phase 3 randomized trial of tolvaptan in adult participants with an eGFR of 25 to 65 ml/min per 1.73 m^2; older participants 56 to 65 years of age were

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required to have an eGFR of 25 to 44 ml/min per 1.73 m^2 and previous evidence of eGFR decline. Because of the significant incidence of adverse effects leading to study drug discontinuation in TEMPO, REPRISE included a single-blind placebo phase followed by a single-blind run-in phase to exclude participants who were unable to tolerate tolvaptan and to individualize the maximum tolerated dose. Only participants who were able to tolerate tolvaptan at a dose of at least 60 mg each morning and 30 mg each afternoon were randomized to receive tolvaptan (60–90 mg each morning and 30 mg each afternoon) or matching placebo. To ensure equal distribution of key prognostic characteristics, randomization was stratified by age, baseline eGFR, and kidney volume. The primary endpoint was change in CKD-EPI eGFR from baseline to year 1, adjusted for time on treatment to account for anticipated differences in the rate and timing of withdrawal or study drug discontinuation. eGFR values used in the analysis were obtained before receiving tolvaptan (baseline eGFR) and within a 7- to 40-day window after completion of active treatment (year 1 eGFR) so that they would not reflect the acute hemodynamic effect of tolvaptan.

Among 1519 participants who entered the run-in phase, 23 did not complete the placebo run-in, and an additional 126 did not complete the tolvaptan run-in phase. Of the latter group, 75 withdrew because of side effects, most often related to aquaresis, and 19 were withdrawn because of safety concerns or adverse events. The remaining 1370 participants were randomized 1:1 to tolvaptan or matching placebo at the maximum dose tolerated during the run-in phase. At baseline, the mean eGFR was 41 ml/min per 1.73 m^2, and 75% of randomized participants had stage 3 chronic kidney disease (CKD). Although 92% had a history of hypertension, the mean baseline blood pressure was <135/85 mm Hg and 86% of participants were taking a renin-angiotensin aldosterone system inhibitor. All participants, including the placebo group, were instructed to increase their fluid intake to suppress endogenous vasopressin release.

The primary analysis included 1313 participants who completed the month 12 study visit and 18 who withdrew early but had eGFR data available within the prespecified window after study drug discontinuation (97% of randomized participants). Among participants who completed the trial, 11% in the tolvaptan group and 3% in the placebo group discontinued the study drug before month 12. Adjusting for time on treatment, the mean decrease in eGFR was significantly less than that in the tolvaptan group (−2.34 vs. −3.61 ml/min per 1.73 m^2 in the placebo group), with an absolute difference of 1.27 ml/min per 1.73 m^2 (95% confidence interval 0.86–1.68, $P < 0.001$). Results were consistent in prespecified subgroup analyses, except in participants older than 55 years of age, those of nonwhite race, and those with stage 2 CKD, who did not experience a significant benefit with tolvaptan (Figure 1).

Adverse events were reported in >80% of participants in both arms during the double-blind phase of the trial. In contrast to the high rate of adverse events related to aquaresis during the tolvaptan run-in phase, aquaretic events were relatively uncommon after randomization. Serious adverse events were more common in the tolvaptan group compared with placebo (12.5% vs. 8.5%, respectively), as were adverse events leading to study drug discontinuation (9.5% vs. 2.2%, respectively). The rate of hepatic adverse events was also higher in the tolvaptan group (5.6% vs. 1.2%), and elevated levels of transaminases prompted permanent study drug discontinuation in 11 participants in the tolvaptan group and 1 in the placebo group. There were no participants meeting Hy's law criteria, which predict severe liver toxicity resulting in death or liver transplantation.[5]

REPRISE confirms the efficacy of tolvaptan in slowing eGFR decline in ADPKD, a key secondary endpoint of TEMPO, and extends the results of TEMPO to patients with stage 3 and 4 CKD. The magnitude of the effect was similar in TEMPO (0.98 ml/min per 1.73 m^2 per year) and REPRISE (1.27 ml/min per 1.73 m^2 over 1 year). Although confidence intervals are not provided for the subgroup analyses (Figure 1), participants with stage 3a CKD appeared to derive the greatest benefit (eGFR difference: 2.36 vs. ∼0.8 ml/min per 1.73 m^2 in participants with stage 3b and stage 4 CKD). Although this effect could be considered modest, particularly given the known limitations of GFR estimates, a true difference in GFR decline of this magnitude would translate into a delay of ∼1 year in the initiation of dialysis for every 4 years of treatment.[3] Assuming adverse effects are tolerated and the benefit of tolvaptan is sustained over time, as suggested by the