Perspective

CJASN ePress. Published on April 13, 2018 as doi: 10.2215/CJN.00190118

Burden of Proof for Tolvaptan in ADPKD

Did REPRISE Provide the Answer?

Reem A. Mustafa and Alan S.L. Yu

Clin J Am Soc Nephrol 13: ●●●–●●●, 2018. doi: https://doi.org/10.2215/CJN.00190118

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common life-threatening inherited disease in adulthood. It causes lifelong growth in kidney cysts and kidney volume, leading to progressive decline in kidney function, ultimately accounting for 5%–10% of patients with ESKD (1). There is currently no approved therapy for patients with ADPKD in the United States.

The vasopressin V2 receptor antagonist, tolvaptan, is at present the most promising candidate for the treatment of ADPKD. In the Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes (TEMPO) 3:4 Study, tolvaptan treatment in patients with early-stage ADPKD (mean age of 39 years old; mean eGFR of 82 ml/min per 1.73 m^2) reduced the rate of growth in total kidney volume (TKV) by one half and the rate of decline in kidney function by about one third after 3 years of follow-up (2). On the basis of this trial, tolvaptan is now approved in multiple countries for ADPKD, including Japan, Canada, Europe, and Australia. In the United States, the Food and Drug Administration (FDA) did not approve tolvaptan, citing concerns over the potential for liver injury and missing data due to the large dropout rate in the tolvaptan group, which created uncertainty as to the magnitude of benefit on kidney function.

The Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy (REPRISE) Trial was a 1-year phase 3, multicenter, placebo-controlled trial designed to confirm the efficacy and safety of tolvaptan in patients with ADPKD at a later stage of disease (CKD stages 2–4; mean eGFR =41 ml/min per 1.73 m^2) and address the concerns of the FDA. The REPRISE trial, which was recently published (3), found that tolvaptan (at an initial dose of 90 or 60 mg in the morning and 30 mg in the evening) resulted in a slower decline in eGFR compared with placebo. The change from baseline in the eGFR was −2.3 ml/min per 1.73 m^2 (95% confidence interval [95% CI], −2.8 to −1.9) in the tolvaptan group compared with −3.6 ml/min per 1.73 m^2 (95% CI, −4.1 to −3.1) in the placebo group (difference of 1.3 ml/min per 1.73 m^2; 95% CI, 0.9 to 1.7; P value <0.001). This effect was largely consistent across subgroups. The study also showed that, with appropriate monthly surveillance, tolvaptan is safer than initially believed in relation to the frequency of drug-induced liver injury; 5.6% of patients receiving tolvaptan compared with 1.2% who received placebo had an elevation in the alanine aminotransferase level. None met Hy law criteria (elevation of alanine aminotransferase or aspartate aminotransferase by threefold or greater and elevation of serum bilirubin by twofold or greater above the upper limits of normal), which are indicative of patients being at high risk of a fatal drug-induced liver injury, and in all patients, the elevated liver enzyme levels returned to normal after discontinuation of treatment.

The results of the REPRISE trial are consistent with those of the TEMPO 3:4 Study (2). The REPRISE Trial does not provide data to assess long-term treatment benefits and potential harm beyond 1 year, which will be important to investigate in follow-up studies. However, we have some information from the TEMPO 4:4 Study (4), an open label extension study, in which all patients from the TEMPO 3:4 Study were offered treatment with tolvaptan. This showed that the eGFR benefit that accrued in the tolvaptan group compared with the placebo group during the 3 years of the TEMPO 3:4 Study was maintained for another 2 years.

The REPRISE Trial was an elegantly designed and well performed trial. Patients were assessed before drug exposure and during a follow-up period after drug washout to control for the known acute hemodynamic effects of tolvaptan. Using sequential screening, placebo run-in, and single-blind tolvaptan run-in phases allowed the investigators to exclude, before randomization, patients who would not tolerate tolvaptan, which minimized the number of early dropouts and permitted a robust assessment of tolvaptan effects among those who could take it.

Implications for Clinical Practice

On the basis of the treatment effect size in the REPRISE Trial, Torres *et al.* (1–4) estimated that tolvaptan treatment started in a patient with ADPKD and an eGFR of 41 would extend the time to reach CKD stage 5 from 6.2 to 9.0 years. Most would consider this a highly meaningful clinical benefit. Its magnitude compares favorably with that of other well accepted therapies for

Division of Nephrology and Hypertension, Department of Internal Medicine and The Jared Grantham Kidney Institute, University of Kansas Medical Center, Kansas City, Kansas

Correspondence: Dr. Alan S.L. Yu, Department of Internal Medicine, The Jared Grantham Kidney Institute, University of Kansas Medical Center, 3901 Rainbow Boulevard, Mail Stop 3018, Kansas City, KS 66160. Email: ayu@kumc.edu

kidney disease, such as angiotensin receptor antagonists for type 2 diabetes and nephropathy, which delay ESKD by an average of 2 years (5).

The important question of which subpopulations ought to be offered tolvaptan remains incompletely answered. That question will be even more pressing in the United States if the FDA approves tolvaptan as a treatment for ADPKD. In other countries, there are typically national bodies that make recommendations about who should be offered a new treatment in the health care system. In the United States, access is limited by insurance companies and their policies. This highlights the need for an evidence-based decision-making process to guide who should get the medication.

The consistency of effect size in the TEMPO 3:4 Study and the REPRISE Trial suggests that tolvaptan may be beneficial across a broad range of ages and GFRs (>25 ml/min per 1.73 m^2). However, in patients with preserved kidney function (GFR>60 ml/min per 1.73 m^2) who are presumably in an early stage of disease, additional biomarkers are needed to identify those who are at higher risk of disease progression and hence, more likely to benefit from treatment. Arguably, the best individual biomarker available in ADPKD is still TKV (6), which has been approved as a prognostic enrichment biomarker in polycystic kidney disease trials. The imaging classification devised by Irazabal *et al.* (7) improves on this by adjusting TKV for age and height in patients with typical cyst distribution. The TEMPO 3:4 Study included only patients with a TKV≥750 ml, and those with TKV≥1500 ml had a tendency to benefit more from tolvaptan. Moreover, 90% of them were in intermediate- or high-risk groups by the classification of Irazabal *et al.* (8).

However, the Predicting Renal Outcomes in ADPKD (PROPKD) Score takes a different approach, modeling outcome on the basis of patients' genotype and clinical data (9). In a *post hoc* analysis of the TEMPO 3:4 Study, tolvaptan slowed the decline in GFR in patients at intermediate and high risk by PROPKD Score but not in those in the low-risk group (10). Although such classifications are not validated to guide clinical decisions, it is plausible to think that they might be useful to guide treatment judgments. A major limitation to their use is the limited access to genetic testing and the expense of both genetic testing and the imaging studies.

The REPRISE Trial did raise questions about whether tolvaptan should be used in older patients (>55 years old). In this prespecified subgroup, tolvaptan did not significantly slow the decline in eGFR. This is likely because patients who are much older with still relatively preserved GFR tend to be slow progressors. However, the small number of patients in this subgroup does not allow a firm conclusion to be reached.

Although the trial conduct and robustness of the results in the REPRISE Trial benefited from the randomized withdrawal design, this also limited the broad applicability of the results. Of the patients who entered the tolvaptan run-in period, 6.8% were excluded from randomization due to adverse events that led to the discontinuation of tolvaptan. Most of these were due to aquaretic events, namely polyuria, nocturia, thirst, dry mouth, and polydipsia. The substantial rate of drug intolerance is an important point to be considered for implementation. Additionally, nephrologists should remember that implementation of tolvaptan in the clinic brings some additional challenges that this trial did not directly address. Although tolvaptan did not lead to the report of any patients with hypernatremia in this trial, it is known that this is a potential side effect if patients do not adhere strictly to instructions to remain very well hydrated by consuming several liters of fluids every day. Nephrologists will have to be very diligent in discussing with their patients the potential side effects, the need for monthly laboratory surveillance of liver function, and the potential for harm if patients do not follow instructions. Another important factor that could influence treatment decisions with tolvaptan is its cost, especially for uninsured patients or those who have high copayments for medications.

Future Research

Longer follow-up studies that assess the effects of tolvaptan use on different patient-important outcomes, including progression to ESKD, are now needed. Also, postapproval studies that ensure continued safety and efficacy will be necessary. Studying combination therapy that may synergistically tackle different pathophysiologic mechanisms and additional innovative medications that do not share a similar side effect profile will continue to be of interest.

This is an exciting time for the ADPKD community at large and especially for our patients. The REPRISE Trial is a landmark study that provides strong evidence supporting the efficacy and safety of tolvaptan in patients with ADPKD. We hope that this answers the concerns of the FDA and will be sufficient to support approval of tolvaptan so that, for the first time in the United States, nephrologists will be able to offer a treatment that slows the decline of kidney function in ADPKD.

Acknowledgments

This work was supported by the National Institute of Diabetes and Digestive and Kidney Diseases through grant P30 DK106912 (to the Kansas PKD Research and Translation Core Center).

The content of this article does not reflect the views or opinions of the American Society of Nephrology (ASN) or the *Clinical Journal of the American Society of Nephrology* (CJASN). Responsibility for the information and views expressed therein lies entirely with the author(s).

Disclosures

A.S.L.Y. served on an advisory board for Sanofi and as a consultant for Regulus Therapeutics.

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Published online ahead of print. Publication date available at www.cjasn.org.