FDA Approval of Tolvaptan for PKD: Breakthrough Therapy vs. Value-Based Care

By Richard Lafayette

In April 2018, the U.S. Food and Drug Administration (FDA) approved the use of tolvaptan for the treatment of autosomal dominant polycystic kidney disease (PKD), allowing the United States to join most of the rest of the world in having the ability to deploy the first disease-specific therapy for PKD. Approval followed the release of results of the REPRISE trial, which demonstrated tolvaptan’s ability to meaningfully slow progression of stage 3 and 4 CKD over 12 months compared to placebo (1). The REPRISE study validated the results of the TEMPO trial, which initially provided strong evidence that tolvaptan could slow the progression of kidney cyst growth and preserve kidney function (2).

Together, the studies suggest that tolvaptan can slow GFR loss by 1–1.5 mL/min/1.73 m² per year (slowing rates by 20% to 30%), enough to extend independent kidney function by many years. These studies strongly suggest a clinically meaningful ability of tolvaptan to improve quality of life by delaying cyst growth (less back pain and kidney pain—but more fatigue and gastrointestinal symptoms), and through slowing decline in renal function, to delay the need for kidney transplantation and/or dialysis.

The drug does cause thirst, polyuria (averaging over a gallon per day) and urinary frequency. It is not tolerated by all who take it, with about 10% to 16% of patients withdrawing from therapy in the REPRISE and TEMPO studies. Furthermore, persistent signals of elevated liver enzyme tests (fortunately with no cases of serious, irreversible liver injury in these trials, but at least one case of hepatic failure requiring liver transplantation attributed to tolvaptan) have led to the requirement of a risk evaluation and mitigation strategy (REMS) program with frequent and long-term monitoring of the liver.

Patients and their physicians will be very eager to learn more about tolvaptan in PKD and likely will wish to have the kidney function benefits, as they appear to be similar to those of renin-angiotensin-aldosterone system inhibitory therapy in diabetic nephropathy. This journey from basic science through drug development and clinical trials has brought us an effective intervention in a disease for which we had nothing to offer for decades. However, the press release for the agent suggests an average wholesale drug cost of $13,041.10 per 28 days. While market pricing will likely be somewhat lower than this figure, the drug’s cost and the cost for the REMS program will make it a very expensive proposition. In a prior cost effectiveness evaluation, Erickson and colleagues modeled an earlier start of tolvaptan that was estimated to delay ESRD by 6.5 years and result in enhanced average survival by 2.6 years (3). They utilized an estimated cost per month of tolvaptan of only $5760 and found that each extra quality adjusted life year would cost roughly $720,000 to $770,000. This poses quite the challenge.

Value-based healthcare is the most likely system that will succeed fee-for-service care. It calls for treatment decisions to be based on evidence—utilizing treatments that clearly benefit patients and improve the outcomes of overall healthcare. However, it also demands that healthcare dollars be used effectively, a call that most physicians would like to heed. At some point, this may mean bundled prices for both episodes of care and for disease management with the provider or provider group bearing responsibility for variation in costs. As the costs for drug and device development are already extreme and rising, new innovations come with huge price tags and require careful consideration for value. Examples include novel cancer therapies, such as CAR-T (chimeric antigen receptor therapy) or improved antiviral therapies such as ledipasvir/sofosbuvir for hepatitis C; both have been considered great clinical advances but have raised questions about cost effectiveness. Healthcare economists have tradition- ally looked at cost effectiveness thresholds as prices that society should reasonably bear, and had fixed them at $50,000 per quality adjusted life year. However, many diseases (including ESRD care with dialysis) have required higher management costs and have pushed that threshold upward toward $100,000 to $150,000 per quality adjusted life year (4). Others argue that you need to blend interventions, accounting for a mix of low-cost interventions and allowing some very high-cost interventions.

Still, for tolvaptan, some accommodation and planning will be needed. The FDA approval already limits the target population as those at “high” risk for progression. Per the Otsuka press release and general knowledge, risk factors for rapid disease progression include a substantially greater total kidney volume than expected for age, family history of end stage renal disease before 58 years of age, high blood pressure before 35 years of age, certain urologic events before 35 years of age (bleeding, pain, etc.), a historical decline in eGFR of ≥5 mL/min/1.73 m² within 1 year, certain inherited genetic profiles, and male gender.

Exactly what criteria will be considered per label by the FDA, and acceptable to payers in the United States, is yet to be seen. In other parts of the world, the approach has varied. In Europe, debates about utilizing risk scores such as the Mayo Clinic classification or the PRO-PKD score have led to differing approaches (5), potentially requiring single or multiple measures of total kidney volume; single or multiple measures of eGFR to define progression risk; as well as examination of family history, genetic findings, and symptoms or signs of disease. Similar approaches are sure to arise in the United States as we attempt to identify the patients most likely to benefit from tolvaptan. This may refine our choices to patients who are better able to benefit and in whom the cost may be more reasonable, but may independently add other costs (measuring the kidney, gene testing, more clinical decision time, prior authorizations, etc.).

Further studies must delineate the long-term benefits and risks, and study other populations, such as early disease, very late disease (to preserve GFR toward the end or even residual function in dialysis) in order to better define options for the most effective, highest value use of tolvaptan in PKD. Of course, the search for other therapies will continue, but for now, using what we have most effectively will be a key challenge and an important learning opportunity.

FDA approval for tolvaptan is a game changer; we must learn how to utilize it to the benefit of our patients and society. If we are fortunate, we will see other breakthrough therapies for our patients with kidney diseases. The hope is that this experience will allow us to gain wisdom regarding how to use them appropriately.

References

Richard Lafayette, MD, is Editor-in-Chief of Kidney News. He is an investigator in the Otsuka PKD program and has received consulting fees in the past year.