EDITORIAL

Tolvaptan and Autosomal Dominant Polycystic Kidney Disease

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Approximately half the patients with autosomal dominant polycystic kidney disease (ADPKD), a condition due to deficiency in polycystin 1 or 2, have end-stage kidney disease by 60 years of age.[1,2] Once progression begins, the mean decline in the estimated glomerular filtration rate (GFR) is approximately 4 to 6 ml per minute per 1.73 m^2 of body-surface area per year.

Therapy to prevent deterioration of GFR in patients with ADPKD has been elusive, despite mechanistic studies targeting pathogenesis. In addition, the burden of therapy in patients who have other symptoms from their ADPKD — hypertension, abdominal fullness and pain from cysts, hematuria, urinary tract infections, and nephrolithiasis, for example — is substantial.[3]

The value of various dietary changes (high water intake, low-salt diet, and soy diet) has been investigated, but these changes have limited efficacy. As more is learned about aberrant polycystin trafficking and signaling and other contributors to disease progression, targeted therapy is becoming feasible.[4] Medications that have been evaluated include renoprotective agents, such as angiotensin-converting–enzyme inhibitors and angiotensin-receptor blockers; drugs that specifically interfere with pathways involved in the growth of kidney cysts, such as vasopressin-receptor antagonists, somatostatin, and interrupters of the mechanistic target of rapamycin (mTOR) pathway; and cytokine blockers. To date, studies of medications that inhibit the effects of vasopressin have been particularly encouraging.

Laboratory studies have shown that relatively high levels of cyclic adenosine monophosphate (cAMP) facilitate cystogenesis in patients with ADPKD.[5] Vasopressin V_2-receptor antagonists decrease cAMP within cells and slow the decline in kidney function in animal models.[2] Early clinical studies were encouraging, and a multicenter, placebo-controlled, double-blind trial (the Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes [TEMPO] 3:4 trial)[6] showed that in patients with an estimated GFR of more than 60 ml per minute per 1.73 m^2, tolvaptan slowed the rate of kidney growth (the primary outcome); it also slowed the decline in the estimated GFR. However, more participants in the tolvaptan group than in the placebo group discontinued the medication owing to adverse events (23% vs. 14%; events were most often related to polyuria, polydipsia, nocturia, and urinary frequency). Furthermore, tolvaptan led to more instances of increased liver-enzyme levels, although abnormalities resolved after the discontinuation of the drug. After the publication of the results of the TEMPO 3:4 trial, the European Medicines Agency and the Health Products and Food Branch of Health Canada approved tolvaptan for the prevention of progression of ADPKD, but the Food and Drug Administration (FDA) has not, citing concerns about the surrogate primary outcome in the TEMPO 3:4 trial and the hepatic toxicity of the drug. The FDA requested further studies and has published warnings about hepatotoxicity.[7]

Torres et al.[8] now report in the *Journal* the results of the REPRISE (Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD) trial, which was undertaken in response to the FDA request and which focused on patients with ADPKD who had more severe kidney disease than those

in the TEMPO 3:4 trial. Tolvaptan led to a slower rate of decline in kidney function than placebo over a period of up to 12 months in patients with chronic kidney disease of stage 2 to stage 4 (mean estimated GFR of the participants, 41.0 ml per minute per 1.73 m^2). To minimize withdrawal resulting from adverse drug effects, only patients who had an acceptable burden of side effects from tolvaptan during a prerandomization period that included sequential placebo and tolvaptan phases underwent randomization.

The trial met its primary outcome, assessed as the change in the estimated GFR from baseline to follow-up, with adjustment for the exact duration of each patient's participation. Thus, the results were similar to those in the TEMPO 3:4 trial, with one important difference. In the new trial, many patients had a substantially lower estimated GFR at enrollment than those in the TEMPO 3:4 trial, yet the amount by which the decline in kidney function slowed with tolvaptan, although small, was clinically important — a difference of 1.27 ml per minute per 1.73 m^2 per year (95% confidence interval, 0.86 to 1.68). If such a difference were maintained over a period of several years, which would require that patients continue taking the drug and which was not studied here, the authors estimate that the time elapsed before patients would have progression to stage 5 chronic kidney disease would increase from 6.2 years to 9.0 years.

Despite the promise of tolvaptan, would the side effects be bearable in patients taking this drug for years? Tolvaptan slows renal growth and cyst growth, which appears to decrease some disease-related symptoms. Adverse events during the double-blind period of the trial resulted in the discontinuation of the trial regimen in 9.5% of the patients in the tolvaptan group, as compared with 2.2% of those in the placebo group. Presumably, this rate would have been substantially higher if randomization had not been limited to patients who initially had not had treatment-limiting side effects from tolvaptan. Would this difference be more pronounced over time? Furthermore, as in the TEMPO 3:4 trial, elevations in hepatic enzyme levels were more common in the tolvaptan group than in the placebo group, a worrisome signal.

These results are, like the trial acronym, a reprise, but with the important difference that many participants in the present trial already had a markedly decreased GFR, and those taking tolvaptan enjoyed a small but clinically important slowing of their decline in kidney function. Further studies will be needed to show whether these results can translate into meaningful delays in the need for renal-replacement therapy and whether the adverse events observed presage more substantial issues over time.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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