

## EDITORIAL



## Aquaretic Treatment in Polycystic Kidney Disease

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Autosomal dominant polycystic kidney disease (ADPKD), the most common hereditary kidney disease, progresses relentlessly to end-stage kidney disease before the age of 60 years in half the affected patients. One in 10 patients undergoing dialysis has ADPKD. The disease is characterized by prominent cystic enlargement of the kidneys, which is often associated with episodes of pain, hematuria, and cyst infection. An effective therapy to slow the progression of this disease does not exist, although several promising drug candidates are being tested.<sup>1</sup>

Vasopressin-mediated cyclic AMP (cAMP) generation is enhanced in polycystic kidneys, driving the proliferation of cyst epithelial cells and the secretion of cyst fluid. Tolvaptan, a selective vasopressin V<sub>2</sub>-receptor antagonist already in clinical use for the treatment of hyponatremia, decreased renal cAMP generation and target-gene expression in preclinical studies and was associated with delayed progression of ADPKD in a phase 2 clinical study.<sup>2</sup>

In the Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes (TEMPO) 3:4 trial, a large, phase 3 study now reported in the *Journal*, Torres et al. tested the efficacy and safety of tolvaptan in 1445 patients with ADPKD.<sup>3</sup> At baseline, the mean age of the participating patients was 39 years. Kidney function was preserved, but nearly 80% of the patients had hypertension. Kidney size was increased by a factor of five, and half the patients had reported kidney pain. The patients were randomly assigned in a 2:1 ratio to receive two doses of tolvaptan or placebo daily.

The study met its primary and secondary end

points — tolvaptan, when given at an average dose of 95 mg per day over a 3-year period, slowed the usual increase in kidney volume by 50% and reduced the decline in the glomerular filtration rate (GFR). The effect of tolvaptan on kidney volume was most pronounced during the first year of the study, probably owing to the early reduction in the secretion of cyst fluid.<sup>4</sup> In contrast, the effect on GFR became apparent only after the first year of treatment. A considerable number of patients discontinued tolvaptan owing to its aquaretic side effects (thirst, polydipsia, polyuria, and nocturia), and tolvaptan treatment was also associated with elevated liver-enzyme levels, hypernatremia, an increased level of uric acid, and gout. However, as compared with patients who received placebo, significantly fewer patients who received tolvaptan had adverse events related to ADPKD, such as kidney and back pain, hematuria, and urinary tract infection.

The rate of increase in kidney volume was low in both study groups (5.5% per year in the placebo group and 2.8% per year in the tolvaptan group), in contrast to growth rates of 6 to 12% per year in other studies.<sup>5,6</sup> Because of the effect of tolvaptan on water excretion, the study design forced all patients to increase their fluid intake in order to avoid dehydration. Increased water intake to suppress vasopressin-mediated cAMP generation is recommended for patients with ADPKD,<sup>7</sup> and the fact that participating patients followed this prescription could explain the reduced growth in kidney volume observed in this study. Nevertheless, tolvaptan, by driving fluid intake, slowed the expansion of cyst volume significantly more than placebo did.

Tolvaptan was associated with a slower decrease in kidney function and with less pain than placebo was, although the number of relevant events was low and contributed to less than 20% of the secondary outcome events. The study did not assess the effects of tolvaptan on kidney pain in a systematic fashion; thus, pain data need to be confirmed. Furthermore, it is unclear why tolvaptan had no effect on worsening trajectories of hypertension and albuminuria. Assuming that tolvaptan causes structural rather than functional improvements, one would have expected beneficial effects on urinary protein excretion and blood pressure.

Despite these criticisms, the TEMPO 3:4 study represents a major advancement in the quest for a cure for ADPKD. How might the information from this trial change the future care of patients with ADPKD? Would tolvaptan be a useful drug for the majority of such patients, or should it be prescribed only for those patients at greatest risk for progression to end-stage kidney disease? As Torres et al. comment, the use of this  $V_2$ -receptor antagonist will depend on a balance between benefits and risks. The side effects of an aquaretic drug (e.g., thirst and polyuria) will affect the quality of life in a substantial number of patients — an issue that must be weighed against the possible benefits of delayed dialysis and transplantation, decreased kidney pain, and fewer urinary tract infections. Some patients with slowly progressive disease might opt for preemptive kidney transplantation (i.e., transplantation before the initiation of dialysis) rather than

treatment with an aquaretic drug that has predictable, bothersome, long-term side effects. On the other hand, patients at risk for rapid progression might prefer treatment with an aquaretic agent and choose to cope with the side effects. The development of comprehensive criteria for aquaretic treatment and appropriate patient selection are needed, if tolvaptan is to be a successful therapy for patients with ADPKD.

Disclosure forms provided by the authors are available with the full text of this article at [NEJM.org](http://NEJM.org).

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