SAN DIEGO -- A vasopressin receptor antagonist slowed both the rise in kidney volume and the decline in kidney function in patients with autosomal dominant polycystic kidney disease (ADPKD), researchers said here.

In a phase III trial, gains in total kidney volume were higher for patients treated with placebo compared with those on tolvaptan (5.5% per year versus 2.8% per year), reported Vicente Torres, MD, PhD, of the Mayo Clinic in Rochester, Minn., and colleagues online in the New England Journal of Medicine and at Kidney Week.

However, tolvaptan treatment was associated with a higher discontinuation rate because of certain adverse events compared with placebo, the authors warned.

Currently, there are no effective therapies to slow the progression of the disease, but some work has shown that vasopressin V2 receptor antagonists -- mainly used to treat hyponatremia -- may reduce cyst burden and protect kidney function in these patients.

So Torres and colleagues conducted the randomized, multicenter, double-blind, placebo-controlled Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and its Outcomes (TEMPO) trial in 1,445 patients, mean age 39, with the disease.

Patients had a large kidney volume (750 ml or more) but a relatively preserved glomerular filtration rate (GFR) with an estimated creatinine clearance of 60 ml/min or more.

Patients were randomized 2:1 to either tolvaptan (Samsca) at the highest of three twice-daily dose regimens that they could tolerate, or to placebo.

The primary outcome over 3 years was the annual rate of change in the total kidney volume, and secondary endpoints included a composite of time to clinical progression and rate of decline in kidney function.

Torres and colleagues found that the increase in kidney volume was higher in placebo group (P=0.01).

That change in total kidney volume was more pronounced in the first year of treatment with tolvaptan, the researchers noted, and an acute decrease in secretion of cyst fluid probably contributed to this effect.

Tolvaptan was also associated with a slower decline in kidney function, they reported (reciprocal of serum creatinine level -2.61 mg/mL\(^{-1}\) per year versus -3.81 mg/mL\(^{-1}\) per year, P<0.001).

The secondary composite endpoint showed fewer ADPKD-related events per 100 person-years of follow-up with the drug than with placebo (44 events versus 50 events, HR 0.87, 95% CI 0.78 to 0.97, P=0.01).

That result was driven largely by effects on kidney function decline (two events versus five events per 100 person-years, P=0.001) and kidney pain (five events versus seven events, P=0.007), they wrote.

Overall, there were fewer ADPKD-related adverse events in the tolvaptan group, but there were more events related to aquaresis (including thirst and polyuria) and more hepatic adverse events which contributed to higher discontinuation rates with the drug (23% versus 14%).

*Thirst, polyuria, and related adverse events may affect the ability of some patients to take effective
doses of tolvaptan," Torres and colleagues wrote. "The potential effects on liver-enzyme levels and plasma levels of sodium and uric acid require monitoring."

The study was limited because the researchers could not detect any of the drug's effects on hypertension, and because all patients were asked to maintain good hydration and avoid thirst, which may have underestimated the drug's effects on the disease.

In an accompanying editorial, Rudolf Wuthrich, MD, of University Hospital Zurich, and Changlin Mei, MD, of Changzheng Hospital in Shanghai, noted that there were no effects on the "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," they wrote.

Nonetheless, they said the trial "represents a major advancement in the quest for a cure for ADPKD," adding that clinicians will need to balance the risks and benefits of an aquaretic drug with its impact on delays in dialysis and transplantation, as well as diminished pain.

When asked about off-label use of the agent for this condition, David Jayne, MD, of the University of Cambridge in England, told MedPage Today that given the "high unmet need" for therapies for genetic polycystic kidney disease, "you can imagine that there's high interest amongst our patients and their physicians for agents that are going to retard the decline of kidney function."

But he cautioned that it's important "to temper the results of the trial, which in general were very positive and very exciting, [because] this was not a trial primarily driven to demonstrate clinical benefit."

"This is really looking essentially at a biomarker and not hard clinical endpoints," added Jayne, who moderated the Kidney Week session at which the results were presented.

The study was supported by Otsuka Pharmaceuticals.

The researchers reported relationships with Otsuka, Pfizer, Amgen, Boehringer Ingelheim, Merck, Bayer, Baxter, Abbott, MSD, GSK, Roche, PKD Foundation, Ipsen, and Primrose Therapeutics.

The editorialists reported relationships with Otsuka, Wyeth, and Novartis.

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