RESEARCH LETTER

Tolvaptan and Number Needed to Harm in Autosomal Dominant Polycystic Kidney Disease

To the Editor:

Autosomal dominant polycystic kidney disease (ADPKD) is a progressive inherited disorder in which renal tissue is gradually replaced with fluid-filled cysts.[1,2] As ADPKD advances, loss of kidney function may ultimately lead to kidney failure, at which point dialysis or kidney transplant are the only treatment options.[2] Therefore, slowing the progression of ADPKD is a major goal for patients who are affected, although, until recently, existing treatments focused only on managing symptoms and complications.[3]

The vasopressin V_2-receptor antagonist tolvaptan was the first treatment demonstrated to slow kidney function decline in adults at risk of rapidly progressing ADPKD.[3] Tolvaptan was approved for this indication by the European Commission in 2015 and the US Food and Drug Administration in 2018 based on 2 randomized phase 3 trials: TEMPO 3:4 (NCT00428948) and REPRISE (NCT02160145).[3-6] In TEMPO 3:4, adults with early-stage ADPKD (n = 1,445) who received tolvaptan had significantly reduced kidney function decline compared with placebo by 26% over 3 years (reciprocal of the serum creatinine level, −2.61 versus −3.81 [mg per milliliter]$^{-1}$ per year, respectively; $P < 0.001$).[5] The efficacy of tolvaptan in this trial was sustained over a further 2 years in the open-label extension trial TEMPO 4:4 (NCT01214421) among the same population.[6] Furthermore, in the 1-year REPRISE trial, tolvaptan reduced kidney function decline by 35% among patients with later-stage ADPKD.[4]

Tolvaptan has been reported to be associated with liver injury in TEMPO 3:4 and TEMPO 4:4,[5,6] and the potential risk of liver injury is closely monitored under the Food and Drug Administration by the JYNARQUE Risk Evaluation and Mitigation Strategy (REMS).[7] To assess the safety profile of tolvaptan, this study calculated the number needed to harm (NNH) with tolvaptan versus placebo on measures of liver function using data from TEMPO 3:4.

The safety events considered in this study were elevation in alanine aminotransferase (ALT) to >3 times (3×) and >5 times (5×) the upper limit of the normal range (ULN), and serious ALT or aspartate aminotransferase (AST) elevation. Detailed methods are described in Item S1.

This study included 961 patients from the tolvaptan arm and 483 from the placebo arm of TEMPO 3:4. The NNHs for ALT >3× ULN compared tolvaptan versus the placebo for ADPKD was 56.19 (95% confidence interval [CI], 33.60-171.33) over 12 months and 39.81 (25.59-89.57) over 24 months (Table 1). This means that for every 100 patients treated with tolvaptan instead of placebo, 1.78 and 2.51 additional patients would have ALT >3× ULN over 12 and 24 months, respectively.

The proportions of patients with ALT >5× ULN and serious ALT or AST elevation were not significantly different between the 2 arms in either period, yielding NNH values above 135 (Table 1). This result means that for every 100 patients treated with tolvaptan instead of placebo, fewer than 1 additional patient would experience ALT >5× ULN or serious ALT or AST elevation over 12 or 24 months.

Tolvaptan remains the only treatment to demonstrate efficacy for slowing kidney function decline, which subsequently slows the progression to end-stage kidney failure.[4-6] In the context of the efficacy benefit observed in TEMPO 3:4 (the number needed to treat to prevent one 25% decline in estimated glomerular filtration rate over 3 years was previously reported to be approximately 11),[5,8] the large NNH values estimated in this study demonstrate an acceptable safety profile regarding liver abnormalities for tolvaptan among patients with ADPKD. For every 100 patients treated with tolvaptan, just 2-3 additional patients would experience ALT elevation to >3× ULN over 12 and 24 months, whereas the risks of ALT elevation to >5× ULN and serious ALT or AST elevation were not found to be statistically significantly different between tolvaptan and placebo.

The risk of liver injury among patients with ADPKD receiving tolvaptan can be mitigated through frequent monitoring, as demonstrated in the REPRISE trial.[4] In the United States, tolvaptan is currently available only through the JYNARQUE REMS program, which mandates monitoring of liver function at 2 and 4 weeks after initiation, then monthly for 18 months, and every 3 months thereafter.[7] In the interim analysis of 6,711 patients treated with

Table 1. NNH for Liver Function Abnormalities Associated With Tolvaptan Over 12 and 24 Months

	12 M			24 M		
	% with ≥ 1 event			% with ≥ 1 event		
Liver Function Abnormalities	Tolvaptan	Placebo	NNH (95% CI)	Tolvaptan	Placebo	NNH (95% CI)
ALT elevation						
> 3× ULN	2.4%	0.6%	56.19 (33.60-171.33)	3.3%	0.8%	39.81 (25.59-89.57)
> 5× ULN	0.9%	0.2%	136.53 (ns)	0.9%	0.2%	136.53 (ns)
Serious ALT or AST elevation[a]	0.8%	0.2%	159.89 (ns)	0.9%	0.4%	191.41 (ns)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; NNH, number needed to harm; ns, not significant; ULN, upper limit of the normal range.
[a]As defined in TEMPO 3:4.[5]

tolvaptan through the REMS program, <1% experienced possible severe drug-induced liver injury, confirming that frequent monitoring enables timely identification of liver enzyme abnormalities and appropriate drug discontinuation.[7] Thus, with sufficient monitoring, the benefits of tolvaptan outweigh the potential harm for most patients at risk of rapidly progressing ADPKD.

The results should be interpreted in light of several limitations, including those of TEMPO 3:4. In addition, these results may not be generalizable to patients with ADPKD in the real-world because the analysis were based on data from a randomized clinical trial performed in a controlled environment, which is not the situation in real-world clinical practice. Moreover, the estimates in this study may be conservative because liver enzyme testing was performed every 4 months in the TEMPO 3:4 trial, which may be less frequent than in real-world clinical practice.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Item S1: Detailed methods.

ARTICLE INFORMATION

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Data Sharing: To submit inquiries related to Otsuka clinical research, or to request access to individual participant data (IPD) associated with any Otsuka clinical trial, please visit https://clinicaltrials.otsuka.com/. For all approved IPD access requests, Otsuka will share anonymized IPD on a remotely accessible data sharing platform.

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REFERENCES

1. Willey CJ, Blais JD, Hall AK, Krasa HB, Makin AJ, Czerwiec FS. Prevalence of autosomal dominant polycystic kidney disease in the European Union. *Nephrol Dial Transplant*. 2017;32(8):1356-1363. doi:10.1093/ndt/gfw240
2. Cornec-Le GE, Alam A, Perrone RD. Autosomal dominant polycystic kidney disease. *Lancet*. 2019;393(10174):919-935. doi:10.1016/S0140-6736(18)32782-X
3. Chebib FT, Perrone RD, Chapman AB, et al. A practical guide for treatment of rapidly progressive ADPKD with tolvaptan. *J Am Soc Nephrol*. 2018;29(10):2458-2470. doi:10.1681/ASN.2018060590
4. Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in later-stage autosomal dominant polycystic kidney disease. *N Engl J Med*. 2017;377(20):1930-1942. doi:10.1056/NEJMoa1710030
5. Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl J Med*. 2012;367(25):2407-2418. doi:10.1056/NEJMoa1205511
6. Torres VE, Chapman AB, Devuyst O, et al. Multicenter, open-label, extension trial to evaluate the long-term efficacy and safety of early versus delayed treatment with tolvaptan in autosomal dominant polycystic kidney disease: the TEMPO 4:4 trial. *Nephrol Dial Transplant*. 2018;33(3):477-489. doi:10.1093/ndt/gfx079
7. Estilo A, Tracy L, Matthews C, et al. Evaluating the impact of a risk evaluation and mitigation strategy with tolvaptan to monitor liver safety in patients with autosomal dominant polycystic kidney disease. *Clin Kidney J*. 2022;15(8):1553-1561. doi:10.1093/ckj/sfac076
8. Gansevoort RT, Arici M, Benzing T, et al. Recommendations for the use of tolvaptan in autosomal dominant polycystic kidney disease: a position statement on behalf of the ERA-EDTA Working Groups on Inherited Kidney Disorders and European Renal Best Practice. *Nephrol Dial Transplant*. 2016;31(3):337-348. doi:10.1093/ndt/gfv456