

macrophage activation syndrome. In animals, high levels of interleukin-6 contribute to the triggering of this syndrome<sup>1</sup>; additional cytokines, including interferon- $\gamma$ , interleukin-1, and interleukin-18, might be involved in maintaining and amplifying the inflammatory response.<sup>2</sup> Indeed, interleukin-1 antagonism may be beneficial in a full-blown case of the macrophage activation syndrome.<sup>3</sup> Regarding the possible role of tocilizumab in masking the symptoms of this syndrome, the five patients with the macrophage activation syndrome reported by Shimizu et al.<sup>4</sup> had mild laboratory abnormalities representing either blunted cases of the macrophage activation syndrome, possibly consistent with the above-mentioned role of interleukin-6 in the triggering of the syndrome, or part of the known side effects of tocilizumab (i.e., increased aminotransferase levels and neutropenia). Long-term vigilance on the rate and features of the macrophage activation syndrome during tocilizumab treatment will provide additional useful information for clinical practice.

Fabrizio De Benedetti, M.D., Ph.D.

Ospedale Pediatrico Bambino Gesù  
Rome, Italy  
fabrizio.debenedetti@opbg.net

Since publication of his article, the author reports no further potential conflict of interest.

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## Tolvaptan in Autosomal Dominant Polycystic Kidney Disease

**TO THE EDITOR:** In the Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcome (TEMPO) 3:4 trial, Torres et al. (Dec. 20 issue)<sup>1</sup> found that tolvaptan slowed the increase in renal volume and the decline in renal function, as compared with placebo, in patients with autosomal dominant polycystic kidney disease (ADPKD). Given that the beneficial effect of tolvaptan is thought to operate through the inhibition of V<sub>2</sub>-receptor activation and the suppression of cyclic AMP (cAMP), it seems likely that a similarly beneficial effect on the course of ADPKD could be achieved with a high fluid intake alone, because this suppresses vasopressin release and cAMP formation.<sup>2</sup> Therefore, it is hard to understand why the investigators did not instruct both groups to ingest large amounts of water, as two of the authors had previously recommended.<sup>2</sup> Had they done so, we would have known whether tolvaptan is superior to a high fluid intake alone. In view of the worrisome adverse effects of tolvaptan seen in the trial, including elevated liver-enzyme levels, as well as the extremely high cost

of tolvaptan (cost of daily 90-mg dose >\$25,000 per month<sup>3</sup>), a monitored high water intake may be safer, far cheaper, and equally effective.

Aaron Spital, M.D.

St. Luke's Hospital  
New York, NY  
aspital@att.net

No potential conflict of interest relevant to this letter was reported.

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**TO THE EDITOR:** Torres et al. found that tolvaptan slowed the decline in kidney function in patients with ADPKD. One small, short-term study<sup>1</sup> showed a reversible decline in the glomerular filtration rate (GFR) and an increase of approximately 8% in the serum creatinine after the initiation of tolvaptan in patients with ADPKD.

Therefore, in the study by Torres et al., the kidney-function end points were assessed after the dose-escalation phase was completed.

Did this larger study find a similar effect? Before there is widespread use of tolvaptan in patients with ADPKD, it would be important for practitioners to be aware of the expected average and range of the increase in the creatinine level after the initiation of tolvaptan and whether this would be reversible after 3 years of therapy. Is there a percentage increase in creatinine at which tolvaptan therapy should be stopped?

It is interesting to note that this effect has not been reported when tolvaptan has been used in large studies of hyponatremia or heart failure, although at lower doses than were used in the study by Torres et al. This raises questions about whether this is a dose-related effect or whether it is specific to ADPKD.

Ajay Kher, M.B., B.S.

University of Massachusetts Memorial Medical Center  
Worcester, MA  
ajay.kher@umassmemorial.org

No potential conflict of interest relevant to this letter was reported.

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**TO THE EDITOR:** In a prespecified subgroup analysis, tolvaptan had a beneficial effect on total kidney volume in all subgroups specified according to baseline values for total kidney volume (<1500 ml vs. ≥1500 ml).

Ho et al. examined the central and nephrogenic components of osmoregulation with the use of water-deprivation tests in 10 adults and 10 children with ADPKD and normal renal function.<sup>1</sup> These patients had a peripheral resistance to vasopressin, the extent of which was directly correlated with total kidney volume, as assessed on magnetic resonance imaging.

One might hypothesize that if the nephrogenic resistance to vasopressin is related to total kidney volume, then perhaps the beneficial effects of vasopressin antagonism will be greater in patients with a lower total kidney volume at the start of treatment, as compared with those with a higher total kidney volume, since patients with a lower volume may be inherently more sensitive to the deleterious effects of vasopressin.

Was the slowing of the increase in total kidney volume associated with a baseline value that was defined as a continuous variable, rather than dichotomized into groups (<1500 ml vs. ≥1500 ml)? One might expect that patients with a lower total kidney volume at baseline had a greater reduction in the rate of growth in total kidney volume, as compared with those with a higher total kidney volume at baseline.

Donal J. Sexton, M.D.

National University of Ireland Galway  
Galway, Ireland  
donalsexton0@hotmail.com

No potential conflict of interest relevant to this letter was reported.

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**TO THE EDITOR:** A history of urinary tract infection is regarded as an independent prognostic factor for a decline in GFR in patients with ADPKD.<sup>1</sup> Furthermore, evidence indicates substantial overlap between biologic processes involved in cystogenesis and in kidney injury, with macrophages having a key role.<sup>2,3</sup> In the TEMPO 3:4 trial, patients who received tolvaptan had a significantly lower rate of urinary tract infection and renal cyst infection, as compared with patients who received placebo.<sup>4</sup> This finding probably reflects the importance of polyuria and pollakiuria in preventing urinary tract infection.<sup>5</sup> On the basis of the emerging concept of renal inflammation as an essential pathogenic component of naturally progressing cystic kidney disease, we speculate that the lower incidence of urinary tract infection and renal cyst infection observed in the tolvaptan group contributes to the potential benefit of this drug on the decline in GFR in patients with ADPKD. Further prospective trials comparing the use and nonuse of tolvaptan in patients with ADPKD with equivalent urinary volume and frequency would provide data regarding the protective effect of tolvaptan per se.

François Jouret, M.D., Ph.D.

Jean-Marie Krzesinski, M.D., Ph.D.

University of Liege Hospital  
Liege, Belgium  
francois.jouret@chu.ulg.ac.be

No potential conflict of interest relevant to this letter was reported.

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**THE AUTHORS REPLY:** Spital points out that increasing water intake may slow down the progression of ADPKD.<sup>1</sup> However, adherence to a regimen of high water intake that would be sufficient to suppress vasopressin during prolonged periods of time may be difficult<sup>2</sup> and, as some authors have suggested, possibly deleterious.<sup>3</sup> In the TEMPO 3:4 study, all patients were encouraged to drink enough water to avoid dehydration. As a result, water intake in placebo-treated patients increased, as reflected by the reduction of median nonfasting first-morning-urine osmolality from a baseline value of 511 mOsm per kilogram of water (95% confidence interval [CI], 164 to 863) to 438 mOsm per kilogram (95% CI, 159 to 792) during the trial. A specifically designed clinical trial would be necessary to determine whether high water intake and tolvaptan are equally effective treatments. Tolvaptan has not been approved for the treatment of ADPKD; therefore, pricing information is not available.

Kher raises important questions regarding creatinine levels. The median serum creatinine level in the tolvaptan group increased from 1.00 mg per deciliter (95% CI, 0.61 to 1.76) to 1.06 mg per deciliter (95% CI, 0.64 to 1.88; median change, 0.05 mg per deciliter [95% CI, -0.14 to 0.30]) during the dose-escalation phase and decreased from 1.14 mg per deciliter (95% CI, 0.67 to 2.47) to 1.08 mg per deciliter (95% CI, 0.63 to 2.33; median change, -0.04 mg per deciliter [95% CI, -0.32 to 0.16]) during the washout phase. The initial, reversible reduction in GFR probably reflects the reversal of the dampening effect of vasopressin on tubuloglomerular feedback.<sup>4</sup> As such, it is expected to be dose-related and not specific to ADPKD. It is premature to speculate

on the increase in serum creatinine that would require the discontinuation of tolvaptan, since the drug is not currently approved for the treatment of ADPKD.

Sexton suggests that patients with a total kidney volume of 1500 ml or more may benefit the least from tolvaptan, since in such patients vasopressin is less likely to result in a maximum urine concentration. This hypothesis would be reasonable if the concentrating defect was due to reduced production or increased degradation of cAMP or decreased protein kinase A activity, since tolvaptan is thought to inhibit cyst growth by restraining cAMP and protein kinase A signaling. However, the concentrating defect in patients with ADPKD is probably due to downstream cellular processes or to the reduced efficiency of countercurrent exchange caused by disruption of the medullary architecture.<sup>5</sup> This is consistent with the similar reductions (approximately 50%) in the rate of growth in total kidney volume that was observed in the two groups of patients (total kidney volume, <1500 ml or ≥1500 ml), as shown in Figure 2B of the article.

We concur with the comments of Jouret and Krzesinski regarding urinary tract infection and renal cyst infection in patients with ADPKD.

Vicente E. Torres, M.D., Ph.D.

Mayo Clinic  
Rochester, MN  
torres.vicente@mayo.edu

Ron T. Gansevoort, M.D., Ph.D.

University of Groningen  
Groningen, the Netherlands

Frank S. Czerwiec, M.D., Ph.D.

Otsuka Pharmaceutical Development and Commercialization  
Rockville, MD

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