see meeting report and clinical investigation on pages 17 and 146

Will introduction of tolvaptan change clinical practice in autosomal dominant polycystic kidney disease?

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The vasopressin inhibitor tolvaptan is clinically effective in slowing growth of renal cysts and reduction in estimated glomerular filtration rate (eGFR) in autosomal dominant polycystic kidney disease (ADPKD), but these effects are mitigated by the associated polyuria. Changes of total kidney volume, eGFR, and symptoms will guide physicians and patients in tolvaptan treatment. Guidance about when to initiate treatment in the course of ADPKD may be forthcoming. Ongoing long-term observations will inform future recommendations about tolvaptan use in ADPKD.

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The Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference on ADPKD (see the Meeting Report in this issue[1]) marked a significant step toward establishing a clinical guideline for treatment of autosomal dominant polycystic kidney disease (ADPKD). Various studies have shown a detrimental role of the antidiuretic hormone arginine vasopressin in ADPKD. The recent TEMPO 3:4 trial demonstrated a significant beneficial effect of the vasopressin V2 receptor antagonist tolvaptan on the rate of growth of total kidney volume (TKV) and the rate of estimated glomerular filtration rate (eGFR) decline in ADPKD patients with an estimated creatinine clearance of $\geqslant$60 ml/min and a TKV of $\geqslant$750 ml.[2] On the basis of these outcomes, tolvaptan was approved in Japan and Canada and was recommended for approval in the European Union. In the United States the Food and Drug Administration requested additional data to further evaluate the efficacy and safety of this drug.[4] In addition, there is no general consensus with regard to when to initiate treatment and how to objectively measure the efficacy, let alone when to stop the treatment. The conference was a major step forward in that it allowed us to identify the knowledge gaps between the ever-evolving ADPKD research and clinical practice regarding the management of ADPKD, and especially treatment with tolvaptan.

In ADPKD, changes in TKV occur before the progression of chronic kidney disease (CKD). In this conference, there was a broad consensus for the use of TKV as a prognostic biomarker.[1] However, the measurement of TKV is not an easy task in a daily practice. In TEMPO 3:4, magnetic resonance imaging of the kidney was taken in accordance with the uniform protocol, and the measurement of TKV was centralized to assure accuracy and reproducibility. However, in the actual clinical setting, the measurement of TKV can be inaccurate and inconsistent, because the contour of ADPKD kidneys is often hard to demarcate from the border of the liver, and the kidneys can have deformity. Thus, measuring TKV by considering the kidney as an ellipsoid body can be inaccurate. The feasibility of using software to standardize the measurement of TKV from the computed tomographic or magnetic resonance image needs to be evaluated in terms of reproducibility. Alternatively, clinical research should be done to determine whether a more simplistic, accurately measurable index could be a substitute for TKV to predict the progression of CKD. The report by Bhutani et al.[3] (this issue) shows that kidney length alone may be sufficient to stratify the risk of progression to renal insufficiency early in ADPKD using either ultrasound or magnetic resonance imaging.

At present it is at the physician's discretion whether and when to start therapy, including with tolvaptan (Figure 1). As cyst growth is dependent on vasopressin and increased vasopressin secretion is already observed in pediatric patients,[4] it would appear reasonable to start the inhibition of V2 receptor early while the kidney parenchyma is relatively preserved. TEMPO 3:4 included patients in early stages of disease who were at potential risk for rapid progression.[2] Most of the enrolled patients were in CKD stage 1 or 2. At such an early stage of the disease, the degree of overall improvement in renal function (1 ml/min/1.73 m^2 per year) was relatively small when evaluated at the 3-year point in TEMPO 3:4, as also noted by the Food and Drug Administration that treatment effects to prevent end-stage kidney disease were not directly observed.[5] Therefore it remains unclear whether it is appropriate to recommend that patients with normal GFR and without any abdominal symptoms start taking the medication they may have to take for the rest of their lives. Decisions regarding initiating therapy must also take into account the patient's willingness to undertake treatment. It is important to have a frank discussion with each patient

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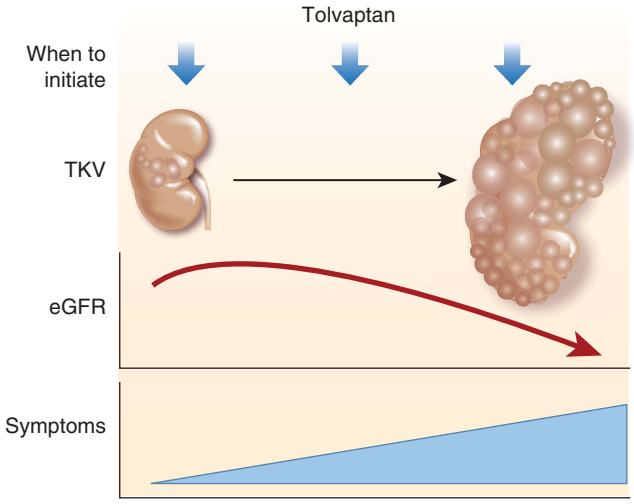

Figure 1 | When to initiate treatment with tolvaptan. Changes of TKV, eGFR, and symptoms will cue the physician and patient with regard to treatment with tolvaptan.

about the predicted course of the disease, the side effects of therapy, and the cost of treatment, and the impact of treatment on the patient's quality of life during the treatment course. Extrapolating from the results of TEMPO 3:4, tolvaptan could potentially postpone the median age of onset of end-stage renal disease by 6.5 years and increase life expectancy by 2.6 years.[6] However, in terms of pharmacoeconomic investigation, tolvaptan's cost per quality-adjusted life year gained is extraordinarily high.[6] On the other hand, patients with significantly deteriorated renal function tend to have enlarged kidneys, and are well aware of the possibility of end-stage renal disease in the near future. Thus, these patients are more than willing to take medication that potentially prolongs the time to the introduction of end-stage renal disease in spite of side effects. In order to demonstrate tolvaptan efficacy in the later stages of CKD, clinical trials for later stages of CKD (eGFR 25–65 ml/min/1.73 m^2) are now under way internationally. In the subanalysis of TEMPO 3:4 consisting of the Japanese patients who participated in the trial, tolvaptan showed efficacy for inhibiting the growth of TKV and the decline of GFR in CKD stage G3a.[7] Offsetting the high cost of therapy may be the fact that medical expenditure soars rapidly when CKD progresses from stage G3 to G4 in ADPKD.[8] Thus in the later stages of CKD with greater eGFR decline per year, maintaining renal function may be conducive to offsetting the cost of tolvaptan therapy per quality-adjusted life year gained.[6] At present the recommendation for initiation of treatment with tolvaptan in Japan is a TKV of more than 750 ml and an annual TKV growth of more than 5% per year.

Tolvaptan exerts its aquaretic effects by vasopressin antagonism resulting in polydipsia and polyuria and causes frequent urination in almost all patients. These side effects of tolvaptan can change the lifestyle of patients. The challenge is how to balance these side effects that potentially affect the patients' quality of life against the potential benefits of tolvaptan, such as slowing cyst growth and CKD progression and improving ADPKD symptoms (such as kidney pain, back pain, and urinary tract infections). Thus, patient selection may be critical to optimize the benefit and minimize the risks associated with tolvaptan. A stratified analysis in TEMPO 3:4 showed that tolvaptan is more likely to be beneficial in patients older than 35 years, those with hypertension, and those with TKV 1500 ml or higher than baseline.[2] Hence, it seems reasonable to recommend starting tolvaptan treatment in those patients. The Japanese subanalysis of TEMPO 3:4 showed that the effects of tolvaptan to curb the deterioration of eGFR greatly vary among patients.[7] To identify individuals who will benefit most by the use of tolvaptan, more detailed stratifications of patients and the development of new biomarkers indicating progression are urgently needed. Additionally, it would be helpful if we could identify specific genetic traits common to individuals responding to the treatment.

Dosage titration of tolvaptan is another issue that needs to be addressed. In the TEMPO 3:4 trial, participants were assigned to the highest tolerable doses: 60, 90, or 120 mg/d. It is noteworthy that half of the participants continued to take the maximum 120 mg/d for 3 years.[2] Thus 120 mg/d should be the target dose. However, to date, there are no data demonstrating a positive correlation between the tolvaptan dosage and its effect. The inhibitory effect of tolvaptan on the vasopressin activity can be measured by the decrease in urine osmolality. Theoretically, tolvaptan dosage should be inversely correlated with urine osmolality. However, at present it is not established whether urine osmolality can be a surrogate biomarker for the long-term efficacy of tolvaptan.

In the KDIGO Controversies Conference on ADPKD, delegates from patient advocacy groups participated in the discussions and organized the section on practical integrated patient support.[1] Needless to say, shared decision making among physicians, patients, and caregivers is prerequisite to initiating treatment with tolvaptan. Moreover, the value of patient care given by a multidisciplinary team was emphasized as well as the value of patient support groups. Especially the importance of peer support programs cannot be overemphasized for offering patients and their caregivers the opportunity to speak with each other and share their experiences.

ADPKD is the most prevalent genetic renal disease, with an incidence of approximately 1 in 2000–3000, but at present lacks a curative therapy.

Tolvaptan will not cure ADPKD, but hopefully it may be able to lessen the burden of disease. With the advent of tolvaptan as a new drug in the treatment of ADPKD, nephrologists should be encouraged to form expert networks both domestically and internationally to share their experience and clinical data, which hopefully will lead to better treatment and clinical studies to fill in knowledge gaps clarified in this meeting.

DISCLOSURE
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REFERENCES

1. Chapman AB, Devuyst O, Eckardt K-U *et al.* Autosomal-dominant polycystic kidney disease (ADPKD): executive summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int* 2015; **88**: 17–27.
2. Torres VE, Chapman AB, Devuyst O *et al.* Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl J Med* 2012; **367**: 2407–2418.
3. Bhutani H, Smith V, Rahbari-Oskoui F *et al.* A comparison of ultrasound and magnetic resonance imaging shows that kidney length predicts chronic kidney disease in autosomal dominant polycystic kidney disease. *Kidney Int* 2015; **88**: 146–151.
4. Ivy DD, Shaffer EM, Johnson AM *et al.* Cardiovascular abnormalities in children with autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 1995; **5**: 2032–2036.
5. US Food and Drug Administration. Cardiovascular and Renal Drugs Advisory Committee Meeting, 5 August 2013. FDA transcript. FDA White Oak Campus Silver Spring, MD.
6. Erickson KF, Chertow GM, Goldhaber-Fiebert JD. Cost-effectiveness of tolvaptan in autosomal dominant polycystic kidney disease. *Ann Intern Med* 2013; **159**: 382–389.
7. Muto S, Kawano H, Higashihara E *et al.* The effect of tolvaptan on autosomal dominant polycystic kidney disease patients: a subgroup analysis of the Japanese patient subset from TEMPO 3:4 trial. *Clin Exp Nephrol* advance online publication 7 February 2015; (e-pub ahead of print).
8. Lentine KL, Xiao H, Machnicki G *et al.* Renal function and healthcare costs in patients with polycystic kidney disease. *Clin J Am Soc Nephrol* 2010; **5**: 1471–1479.