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counterpoint

Vasopressin V2 receptor antagonists in autosomal dominant polycystic kidney disease: efficacy, safety, and tolerability

Esther Meijer¹ and Ron T. Gansevoort¹

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Wednesday morning, 9:00 AM: Mr. E, a 26-year-old autosomal dominant polycystic kidney disease (ADPKD) patient with an estimated glomerular filtration

rate (eGFR) of 80 ml/min per 1.73 m² and total kidney volume (TKV) of 2652 ml (Mayo class 1E), visits the outpatient clinic at our University Hospital to discuss the benefits and disadvantages of treatment with a vasopressin V2 receptor antagonist (V2RA). Although he is interested to hear additional information on this drug, he is reluctant to start, because of the polyuria he has heard about.

When he is gone, Ms. W, a 29-year-old ADPKD patient with an eGFR of 113 ml/min per 1.73 m², historic TKV of 1216 ml (Mayo class 1E), and truncating PKD1 mutation, tells me she is happy she stopped treatment with a V2RA. Due to nocturia, she did not sleep well and felt tired. This resolved after cessation of treatment.

In this article, we discuss briefly the efficacy, safety, and tolerability of V2RAs and argue in favor of informing patients with rapidly progressive ADPKD of the possibility of starting treatment with a V2RA.

Efficacy of vasopressin receptor antagonists in ADPKD

After animal experiments had shown a detrimental role for vasopressin and a beneficial effect of vasopressin receptor antagonists by limiting the generation of cyclic adenosine monophosphate in collecting ducts,¹ in 2012, the landmark clinical trial with a vasopressin receptor antagonist (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes [TEMPO] 3:4 trial) was published.² In this multicenter trial, 1445 ADPKD patients were included, with relatively early-stage disease but a high likelihood of rapid disease progression, defined as age 18–50 years with an estimated creatinine clearance of >60 ml/min, and a TKV > 750 ml. In these patients, the V2RA tolvaptan (90/30 mg split dose) decreased both TKV growth (the primary outcome) by 49% and the rate of eGFR decline on treatment by 26% (Table 1). After this trial, 871 patients continued in a 2-year open-label follow-up study. This TEMPO² 4:4 study showed that the beneficial effect of tolvaptan on TKV decreased over time, whereas the effect on eGFR was sustained.³ This difference could indicate that the beneficial effect of tolvaptan on eGFR is at least partly independent from its effect on TKV.

To investigate treatment efficacy in later-stage disease (eGFR 25–65 ml/min per 1.73 m²), the Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy in ADPKD (REPRISE) trial

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Table 1 | Change in kidney function on treatment, and withdrawal rate with various interventions, including vasopressin V2 receptor antagonists (V2RAs) in selected landmark trials in nephrology

Study	Condition	N	Intervention	eGFR decline ml/min per 1.73 m ² per yr		eGFR gain placebo corrected	Relative %	Withdrawal rate due to AE percentage		Withdrawal rate, placebo corrected	Reference
				Placebo	Treatment	Absolute ml/min per 1.73 m ² per yr		Placebo	Treatment	%	
TEMPO 3:4	ADPKD	1445	V2RA	-3.70	-2.72	0.98	26	5.0	15.4	10.4	2
REPRISE	1370 ADPKD	1370	V2RA	-3.61	-2.34	1.27	35	2.2	9.5	7.3	4
REIN stratum 2	CKD, no DM Uprot >3 g/d	166	ACEi	-10.6	-6.4	4.2	40	12	11	-1	S1
REIN stratum 1	CKD, no DM Uprot 1-3 g/d	186	ACEi	-3.48	-2.52	0.96	28	6.9	11	4.1	S2
RENAAL	DM2 + CKD	1513	A2RA	-5.2	-4.4	0.8	15	21.7	17.2	4.5	S3
IDNT	DM2 + CKD	1715	A2RA	-6.5	-5.5	1.0	15	N/A	N/A	N/A	S4
CREDENCE	DM2 + CKD	4401	SGLT2i	-4.71	-3.19	1.52	32	13	12	-1	S5

ACEi, angiotensin converting enzyme inhibitor; ADPKD, autosomal dominant polycystic kidney disease; AE, adverse event; A2RA, angiotensin 2 receptor blocker; CKD, chronic kidney disease; CREDENCE, Canagliflozin and Renal Events in Diabetes and Nephropathy Clinical Evaluation; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; IDNT, Irbesartan Diabetic Nephropathy Trial; N/A, not available; REIN, Ramipril Efficacy in Nephropathy; RENAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; REPRISE, Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy in ADPKD trial; SGLT2i, sodium-glucose cotransporter 2 inhibitor; TEMPO, Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes; Uprot, proteinuria.

was performed, which included 1370 ADPKD patients with a high likelihood of rapid disease progression, defined as low kidney function for age.⁴ The primary endpoint of this trial, change from baseline in eGFR, was again in favor of tolvaptan, now with a 35% reduction in rate of eGFR decline. The beneficial effects of tolvaptan are found in chronic kidney disease stages 1–4, although in chronic kidney disease stage 1, when there is only minimal eGFR decline in untreated patients, the beneficial effect can be seen only on TKV growth,^{4,5} and not in subjects aged >55 years. When such older ADPKD patients still have an eGFR >25 ml/min per 1.73 m², they apparently have slowly progressive disease, which may be the reason that tolvaptan is less efficacious.

In 97 ADPKD patients who were treated in the Mayo Clinic (USA), longer-term treatment efficacy was shown. Tolvaptan treatment to up to 11.2 years (average follow-up, 4.6 years) reduced the annual rate of eGFR decline by 37% compared to historical controls.⁶ Efficacy has thus been shown and confirmed in ADPKD patients who have rapidly progressive disease. This evidence has led regulatory authorities across the world to grant tolvaptan marketing authorization. Of note, reimbursement and funding of tolvaptan vary among health care systems, and therefore, patient access to treatment differs throughout the world. When tolvaptan can be prescribed in clinical care, the first question that emerges is obviously who to treat. Based on the trials performed, V2RAs should only be prescribed to subjects who have

rapid disease progression and are <55 years of age. Although not 100% perfect, tools are available that can help to identify rapidly progressive disease, such as Mayo classification (a method to stratify total kidney volume for age and length),⁷ PROPKD score,⁸ and/or eGFR indexed for age.^{9,10} When patients reach chronic kidney disease stage 5, it is advised that they stop taking tolvaptan. This drug causes a small, reversible, probably hemodynamically induced decrease in eGFR. Stopping is therefore expected to result in some increase in eGFR, which might postpone the start of renal replacement therapy.

Another important issue is determination of the optimal dose. Should all patients be titrated to the highest tolerated dose, aiming for 90/30 mg/d, similar to what was done in the TEMPO² and REPRISE⁴ trials? *Post hoc* analyses of these trials showed that changes in urinary osmolality¹¹ and copeptin¹² after administration of tolvaptan were associated with treatment efficacy. Unfortunately, it is not known whether changes in these biomarkers can be used as reliable short-term indicators for individual treatment response and to target dosing. Until studies become available that prospectively address these issues, we advise treating patients as in the clinical studies and thus not to use urinary osmolality as a marker for treatment response or to routinely use lower dosages.

Safety

Adverse events that are attributed to tolvaptan treatment are in general related to aquaresis or

Figure 1 | (a) Open circles represent autosomal dominant polycystic kidney disease (ADPKD) patients without tolvaptan (n = 27).

When disease progresses, more cysts are formed that interfere with normal renal medullary architecture and function. Consequently, ADPKD patients at lower glomerular filtration rate (GFR) have less urine concentrating capacity and a higher 24-hour urinary volume (standardized β , -0.55 ; $P = 0.003$). Solid circles represent the same 27 ADPKD patients, now using 120 mg of the vasopressin V2 receptor antagonist (V2RA) tolvaptan (90/30 mg split dose), which causes near-maximal urine dilution. At a lower GFR, there are fewer nephrons, and consequently, the V2RA can cause less increase in 24-hour urinary volume when compared to ADPKD patients at a higher GFR (standardized β , 0.39 ; $P = 0.05$). This explains the strongest increase in urinary volume after the administration of a V2RA in patients with good renal function. (b) Solid circles represent the same 27 ADPKD patients using a V2RA. A strong association between 24-hour osmolar excretion and 24-hour urine volume is found (standardized β , 0.73 ; $P < 0.001$), illustrating that during maximal urine dilution, urinary volume will be determined by osmolar excretion. Adapted with permission from Kramers BJ, van Gastel MDA, Boertien WE, et al. Determinants of urine volume in ADPKD patients using the vasopressin V2 receptor antagonist tolvaptan. *Am J Kidney Dis.* 2019;73:354–362.¹⁶ © 2018 by the National Kidney Foundation, Inc.

hepatotoxicity. Tolvaptan should not be used in patients who are volume depleted or have hypernatremia or in patients who cannot perceive or respond to thirst. Tolvaptan has a “black box” warning in the US¹³ and in the European Union¹⁴ indicating that it may cause serious liver injury. The mechanism that causes this injury is as yet unknown. Regular monitoring of liver function tests is therefore warranted during the first 18 months of treatment monthly and thereafter every 3 months. Clear decision rules have been defined as to when to stop treatment in case of abnormalities revealed by liver function tests.^{13,14} There is another V2RA, lixivaptan, that is hypothesized to have less liver toxicity. A large-scale, randomized, placebo-controlled trial testing this drug will start this fall (NCT04064346).

Tolerability

Inherent to blockade of the vasopressin V2 receptor is blockade of urinary concentrating capacity, thus inducing aquaretic adverse events. In the TEMPO 3:4 trial, 8.3% of tolvaptan-treated patients discontinued treatment because of aquaresis-related symptoms, such as polyuria, thirst, and dry mouth.² These

subjects were younger, had better renal function, and higher fasting baseline urine osmolality.¹⁵ Figure 1, left panel, makes clear that such subjects with relatively early-stage disease can concentrate urine better, and they will have the largest increase in 24-hour urinary volume with a V2RA.¹⁶ Unfortunately, these are also the patients that are likely to benefit most from treatment, as the longer treatment can be given, the more time can be won before the onset of end-stage renal disease. It is therefore a clinical challenge to increase tolerability in these subjects.

Several pieces of advice can be given to patients to increase tolerability. Because tolvaptan reduces urinary concentrating capacity, osmolar intake determines urinary volume (Figure 1, right panel).¹⁶ As in nephrogenic diabetes insipidus, patients can be advised to reduce sodium and protein intake to reduce urinary volume, especially in the evening, to reduce nocturia. For the latter purpose, the second dose could be taken earlier (an 8-hour window between morning and evening dose is advised). Another strategy to reduce polyuria could be reducing the tolvaptan dose. As described in the previous paragraph, whether a dose reduction will influence treatment efficacy

is unknown. To optimize tolerability in daily life, patients can be told that dosing can be skipped for 1 day when they have a special event, that aquaretic effects will disappear immediately, and that this is unlikely to have negative effects on disease progression. An alternative, yet unproven approach to decrease polyuria is use of medication that also has a role in the treatment of nephrogenic diabetes insipidus, such as hydrochlorothiazide¹⁷ and/or metformin.¹⁸ Whether these treatments work in patients with tolvaptan-induced diabetes insipidus, are safe, and do not influence the renoprotective efficacy of tolvaptan in ADPKD remains to be studied.

Epilogue

Although Ms. W felt relieved that she had stopped the V2RA, she was also happy that later she would not blame herself and regret that she had not tried it. Mr. E started tolvaptan in reality 10 years ago and found that he could easily deal with the adverse events. His kidney function has decreased less rapidly than would be expected based upon his Mayo class (approximately -2.6 vs. -4.6^7 ml/min per 1.73 m^2 per year, respectively), which will likely postpone the start of end-stage renal disease by several years.

Although V2RA tolvaptan is not 100% effective in stopping renal function decline, its efficacy is comparable to that of other interventions that nephrologists prescribe daily (Table 1^{2,4} and Supplementary References). Moreover, in ADPKD, it is the only renoprotective treatment available at the moment. Withdrawal rates due to adverse events with V2RAs are higher than those for other interventions in nephrology (Table 1), but who are we to decide for patients what influences their lives more—polyuria or an earlier start on renal replacement therapy with all its complications? Given these considerations, it is our task to inform patients of the benefits and disadvantages of V2RAs, not to decide for them whether or not to start such medication. In the present era of patient-centered medicine, it is the well-informed patient who should decide.

DISCLOSURE

RTG was member of the Steering Committee of several large-scale trials with the V2RA tolvaptan. EM participated as investigator in these trials. Both received several unrestricted grants for investigator-driven research from Otsuka Pharmaceuticals (the manufacturer of tolvaptan). All money is paid to their employing institution.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

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from the editor

A tolvaptan skeptic repents

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I will come clean to the world. I have been skeptical of the tolvaptan story in polycystic kidney disease (PKD). To be clear, I was not skeptical of the basic or clinical science leading to the development and eventual approval of this drug for PKD. Rather, I was underwhelmed by the clinical benefits tolvaptan affords, and I was very concerned about its side effects. Nonetheless, in response to the needs of our PKD population, and the approval of tolvaptan by the US Food and Drug Administration (and other regulatory bodies), we established a clinic at our medical center to evaluate patients for treatment and to use this medication appropriately.

In this edition of *Kidney International*, PKD experts debated whether to use tolvaptan to buy patients a bit more time before renal replacement therapy is needed, or to let patients progress and undergo transplantation sooner. The underlying issue motivating this discussion was that delaying end-stage disease could result in PKD patients “aging out” of transplant eligibility. Some form of dialysis would then be their only option. Gordon and Perrone handily dismissed such a notion.¹ Modeling several patient scenarios, based on kidney function trajectories in PKD and the slight but realistic effects of tolvaptan on slowing the decline in glomerular filtration rate, it appears very unlikely that any patient would miss an opportunity to get a kidney transplant. Remaining was the issue of side

effects and tolerability, and this was convincingly dealt with by Meijer and Gansevoort.² Most of our therapies in nephrology have the potential for adverse effects. Many of these effects, such as those from the immunosuppressives I use in caring for patients with glomerular disease, could be considered much more significant than frequent urination and (mostly) reversible increases in liver enzymes. But as Meijer and Gansevoort remind us, we as healthcare providers should not decide what our patients want.² We should provide our patients with all reasonable options, provide an honest discussion of benefits and harms, and support the route the patient ultimately wants to take. I suspect many patients would like to put off the need for renal replacement therapy as long as possible, and would be willing to at least try tolvaptan, even with all of its potential side effects.

After reading these 2 excellent editorials, I am a reformed skeptic. Although the attenuation of the decline of glomerular filtration rate with tolvaptan in PKD is small, it is certainly within the effect size being sought for other drugs used in other kidney diseases, with other side effects, that the nephrology community currently embraces.³ I think a frank discussion of the risks and benefits of tolvaptan with appropriate PKD patients, including an individual assessment of the projected delay in renal replacement therapy, will result in patient engagement with their nephrologist and lead to design of an optimal management plan for each case.

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