Pro: Tolvaptan delays the progression of autosomal dominant polycystic kidney disease

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ABSTRACT

No treatment until now has directly targeted the mechanisms responsible for the development and growth of cysts in autosomal dominant polycystic kidney disease (ADPKD). Strong rationale and preclinical studies using *in vitro* and *in vivo* models justified the launching of two large phase 3 clinical trials of tolvaptan in early and later stages of ADPKD. Their design was based on preliminary studies informing on the pharmacokinetics, pharmacodynamics, short-term safety and self-reported tolerability in patients with ADPKD. Tolvaptan slowed kidney growth in the early stage and estimated glomerular filtration rate decline in early and later stages of the disease. All participants had the opportunity to enroll in open-label extension trials to ascertain long-term safety and efficacy. In a single-center analysis of long-term outcomes, the effect of tolvaptan was sustained and cumulative over time supporting a disease-modifying effect of tolvaptan in ADPKD. In the countries where tolvaptan has been approved by regulatory agencies, patients with rapidly progressive ADPKD should be informed about the option of treatment including possible benefits and risks. If a decision to initiate treatment is made, prescribing physicians should educate the patients on the prevention of aquaresis-related adverse events and should be vigilant in the surveillance and management of the potential tolvaptan hepatotoxicity. Other vasopressin V2 receptor antagonists, possibly without potential hepatotoxicity, alternative strategies targeting vasopressin and combination with other drugs able to enhance the efficacy or reduce the aquaresis associated with tolvaptan, deserve further study.

Keywords: autosomal dominant polycystic kidney disease, chronic kidney disease, polycystic kidney disease, total kidney volume, vasopressin, vasopressin V2 receptor, vasopressin V2 receptor antagonist

Autosomal dominant polycystic kidney disease (ADPKD) for centuries has been a disease without a cure. Treatment of hypertension improved its cardiovascular outcomes, but renal survival has not improved in the last two decades. Until now, no treatment has directly targeted the development and growth of

the cysts. This article reviews the rationale and evidence showing that vasopressin V2 receptor (V2R) antagonists are the first such treatment.

At the outset it is remarkable that blocking the hormone responsible for concentrating the urine ameliorates ADPKD. The evolutionary emergence of vasopressin, V2R (the only vasopressin receptor linked to cyclic adenosine 3',5'-cyclic monophosphate, cAMP, signaling), and urine-concentrating mechanisms paralleled the development of loops of Henle and renal medulla and of nephron heterogeneity (short- and long-looped nephrons) in mammals [1]. Lack of nephron heterogeneity in homozygous Brattleboro rats lacking vasopressin and induction of anatomic changes, i.e. hypertrophy and elongation of the thick ascending limb of Henle's loop (TAL) and the inner stripe of the outer medulla and accentuation of nephron heterogeneity, by the administration of the V2R agonist 1-deamino-8-D-arginine vasopressin (DDAVP), suggest the mechanistic coupling of these evolutionary changes [2].

The cellular origin of the cysts may determine the efficacy of pharmacologic interventions. In a study where cysts were defined as tubular dilatations ≥ 1 mm in diameter, 70% stained with collecting duct markers, the remaining being negative for all markers [3]. Similar observations were made in slowly progressive models of ADPKD (*Pkd2*^{-/-WS25}, *Pkd1*^{RC/RC} and *Pkd1*^{nl/nl} mice). Proximal cysts are present or may predominate in human embryos with ADPKD, before post-natal completion of nephrogenesis or in rapidly progressive forms of PKD in rodents, and in uremia-associated acquired renal cystic disease (ARCD). Tubular obstruction and ARCD likely account for proximal tubular dilatations and small cysts in end-stage ADPKD kidneys. Higher cAMP production by cyst-derived cells in response to vasopressin as compared with parathyroid hormone supports the collecting duct and distal nephron origin of most ADPKD cysts [4]. The location of V2Rs mainly restricted to these segments limits the off-target effects of V2R antagonists.

A wealth of evidence supports that generation of cyclic AMP (cAMP), propelled by the activation of G α s-protein-coupled receptors such as V2Rs, promotes cystogenesis through stimulation of fluid secretion and cell proliferation [4–6]. Fluid

secretion into cysts is driven by chloride exit through apical cystic fibrosis transmembrane conductance regulator channels activated by protein kinase A (PKA)-dependent phosphorylation, an effect also observed in wild-type collecting duct principal cells. The effect on cell proliferation is more complex. cAMP stimulates the proliferation of cyst-derived cells, while it inhibits proliferation in normal human kidney cortex cells [4]. Calcium deprivation or treatment of wild-type collecting duct cells with calcium channel blockers replicates the proliferative response of cyst-derived cells to cAMP [5]. Conversely, intracellular calcium is reduced in cyst-derived cells and treatment with L-type calcium channel activators or calcium ionophores reverses their proliferative response to cAMP [6]. These observations in cultured cells, 48–72 h after addition of 8-Br-cAMP or cAMP agonists, linked the proliferative response of the cystic epithelium to a reduction in intracellular calcium. Administration of DDAVP for at least 3 days in wild-type Sprague-Dawley rats, however, also stimulated the proliferation of collecting duct and of TAL cells, suggesting that sustained V2R stimulation *in vivo* altered the wild-type response to cAMP [7]. More prolonged DDAVP administration induced tubular dilation and interstitial inflammation [8] and constitutive activation of PKA in collecting ducts and distal nephron caused microcystic disease, interstitial inflammation and fibrosis [9].

Chronic upregulation of cAMP signaling may enhance the susceptibility of polycystic kidneys to the cystogenic effects of cAMP agonists. Accumulation of cAMP in cystic kidneys is a feature common to rodent models orthologous to human ADPKD (*Pkd2*^{-fWS25}, *Pkd1*^{RC/RC}, *Pkd1*^{nl/nl} mice) and autosomal recessive polycystic kidney disease (ARPKD) (PCK rat), possibly because polycystin disruption lowers intracellular calcium, activates calcium-inhibitable adenylyl cyclase-5 and -6, and inhibits calcium-dependent phosphodiesterase-1 [10]. The inhibition of cystogenesis in murine models of ADPKD, when adenylyl cyclase-5 or -6 are knocked out [11, 12], and in zebrafish *pkd2* morphants, when phosphodiesterase-1a is overexpressed [13], supported this hypothesis.

Among cAMP agonists, vasopressin has the greatest impact on ADPKD. Vasopressin acting on V2Rs is the main agonist of adenylyl cyclase in freshly dissociated collecting ducts. Mammals are constantly subjected to the tonic action of vasopressin, more so in patients with ADPKD whose circulating levels of vasopressin and copeptin are increased due to an impairment of urinary-concentrating capacity [14]. Furthermore, plasma copeptin levels correlate with the severity of ADPKD in cross-sectional and with the rate of disease progression in prospective studies.

Preclinical studies confirmed that V2R activation aggravated PKD in rodent models (*Pkd2*^{WS25/-}, *Pkd1*^{RC/RC} mice; PCK rat). Conversely, suppression of vasopressin production, release or action by means of hydration [15], V2R blockade [10, 16] or genetic mutation [17] reduced cyst burden, protected kidney function and prolonged survival. Sustained suppression was critical for the protective effect [16, 17]; nearly complete suppression of cystogenesis in double homozygous Brattleboro/PCK mutant rats lacking vasopressin illustrated the potential efficacy of this approach, if completely blocking V2Rs was feasible in humans.

The success of V2R antagonists in rodent models led to the initiation of clinical studies of tolvaptan for ADPKD in 2004. This coincided with the end of a decade of breakthroughs with the identification of *PKD1* and *PKD2* in 1994 and 1996 and the implementation in 1999 of the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP). Beyond providing a rationale for using total kidney volume (TKV) as a surrogate of disease progression, CRISP underlined the importance of prognostic biomarkers to preferentially enroll informative patients in clinical trials and to select patients likely to benefit from effective therapies when available (Figure 1) [18].

Initial studies with tolvaptan, conducted in small numbers of patients with ADPKD treated for 1–3 weeks, showed that split twice daily doses were necessary for effective V2R inhibition (urine osmolality < 300 mOsm/kg continuously for 24 h) [19]. Aquaresis induced by daily split doses in patients with chronic kidney disease (CKD) Stages 1–4 was accompanied by small reductions in glomerular filtration rate (GFR) without significant changes in renal plasma or blood flow, likely due to activation of tubuloglomerular feedback [20, 21]. These changes, rapidly reversible after discontinuation of tolvaptan, underlined the importance of using estimated glomerular filtration rate (eGFR) values either off treatment (baseline and after washout) or on treatment when comparing the effects of tolvaptan and placebo on the rate of eGFR decline.

In the double-blind Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes (TEMPO) 3:4 trial, 1445 patients were randomly assigned to tolvaptan, at the highest tolerated dose (45/15, 60/30 or 90/30 mg), or placebo [22]. Entry criteria were designed to enrich for patients with relatively preserved renal function and rapidly progressive disease (18- to 50-year olds, estimated creatinine clearance ≥ 60 mL/min, TKV ≥ 750 mL). TKV increased 2.8% per year in the tolvaptan group and 5.5% per year in the placebo group (*P* < 0.001). Tolvaptan significantly reduced the decline in eGFR from 10.1 to 6.8 mL/min/1.73 m² over 3 years, as well as the frequency of kidney pain and urine excretion of albumin and monocyte chemoattractant protein-1. The eGFR benefit accumulated by tolvaptan compared with placebo-treated patients at the end of TEMPO 3:4 (3.34 mL/min/1.73 m², *P* < 0.001) was maintained 2 years later (3.15 mL/min/1.73 m², *P* < 0.001) in TEMPO 4:4 when all patients were treated with tolvaptan [23] (Figure 2A). With monitoring every 3–4 months in TEMPO 3:4 and TEMPO 4:4, transaminase elevations > 3 times the upper limit of normal (ULN) occurred in 4.4% of tolvaptan and 1% of placebo patients. Three of 1271 tolvaptan-treated patients met Hy's law criteria denoting a 10% risk of progression to hepatic failure. On the basis of the TEMPO 3:4 results, tolvaptan was approved for rapidly progressive ADPKD in Japan, Canada, the European Union, Switzerland, Nordic countries, South Korea and Australia. In the USA, the Food and Drug Administration did not approve tolvaptan and asked for additional data from patients with more advanced CKD stages.

The double-blind Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in later stage ADPKD (REPRISE) was designed as a randomized

FIGURE 1: Imaging classification of ADPKD as a prognostic biomarker: this classification is applicable to ~95% of patients with ADPKD with typical renal involvement characterized by bilateral and diffuse distribution of cysts (see reference for criteria used to identify atypical cases where the classification cannot be used). (Left) Typical ADPKD cases are divided according to the estimated annual rate of kidney growth [derived from the age of the patient, height-adjusted TKV (HtTKV) and a theoretical starting HtTKV of 150 mL/m] into class 1A ($\leq 1.5\%$), 1B ($> 1.5\text{--}3\%$), 1C ($> 3\text{--}4.5\%$), 1D ($> 4.5\text{--}6\%$) or 1E ($> 6\%$). Class 1A patients have a very low risk for end-stage renal disease during their life-times and should not be included in clinical trials or subjected to treatments with potential side effects to slow down cyst growth. Patients in class 1C–1E, who have rapidly progressive disease, are most informative in clinical trials and most likely to benefit from an effective therapy. Patients in class 1B have an intermediate risk and could be re-evaluated at yearly intervals to more precisely determine their risk for progression. (Right) Coronal abdominal magnetic resonance images of three 41-year-old male patients with ADPKD class 1A (HtTKV 229 mL/m, eGFR 83 mL/min/1.73 m²), 1C (HtTKV 736 mL/m, eGFR 48 mL/min/1.73 m²) and 1E (HtTKV 2,765 mL/m, eGFR 26 mL/min/1.73 m²). Other prognostic models such as genetic information (gene and type of mutation), PROPDK score that combines genetic and clinical information, and image texture analysis can be used in combination or independently from the image classification.

withdrawal trial to limit early discontinuations due to aquaretic side effects [24]. After an 8-week pre-randomization, sequential placebo and tolvaptan run-in phases, 1370 of 1496 patients who entered the tolvaptan run-in phase, 18- to 55-year olds with eGFRs 25–65 mL/min/1.73 m² or 56- to 65-year olds with eGFRs 25–44 mL/min/1.73 m², were able to tolerate 60/30 mg tolvaptan and were randomly assigned to tolvaptan or placebo for 12 months with monthly safety and serum creatinine measurements. Three additional serum creatinines were measured 7–40 days after discontinuation of tolvaptan or placebo. During the double-blind period, adverse events led to the discontinuation of the trial regimen in 65 of 681 patients (9.5%) receiving tolvaptan, as compared with 15 of 685 (2.2%) receiving placebo. The eGFR change from baseline (primary endpoint) was -2.34 mL/min/1.73 m² in the tolvaptan and -3.61 mL/min/1.73 m² in the placebo group, a 1.27 mL/min/1.73 m² difference [95% confidence interval (CI) 0.86–1.68; $P < 0.001$] (Figure 2B). The mean slopes of the change in eGFR with adjustment for the acute effect of tolvaptan (secondary endpoint) were -3.16 in the tolvaptan and 4.17 mL/min/1.73 m²/year in the placebo group, with a 1.01 mL/min/1.73 m² difference (95% CI 0.62–1.40; $P < 0.001$). Transaminase elevations > 3 times ULN occurred in 5.6% of tolvaptan and 1.2% of placebo patients. No cases met Hy’s law criteria, likely due to more frequent monitoring and earlier discontinuation of tolvaptan.

Transaminase elevations were reversible after stopping tolvaptan. Based on the results of the REPRISE trial, the Food and Drug Administration approved tolvaptan for patients with ADPKD at risk for rapid progression.

While accepting that the reduction in eGFR decline by 1.27 mL/min/1.73 m² per year in REPRISE could be clinically important, the editorial accompanying its publication pointed out that further studies were needed to ascertain whether it could meaningfully delay the need for renal replacement. A retrospective analysis of 97 patients enrolled into an open-label extension study who have been treated with tolvaptan for at least 1 year (median 4.0, range 1.1–11.2 years) at the Mayo Clinic has provided preliminary information on long-term outcomes [25]. These patients had lower rates of eGFR decline (-2.20 ± 2.18 from baseline before starting tolvaptan and -1.97 ± 2.44 mL/min/1.73 m² from Month 1 on tolvaptan) compared with gender-, age- and baseline eGFR-matched controls from the CRISP and HALT PKD study B studies (-3.50 ± 2.09 mL/min/1.73 m², $P < 0.001$) and with placebo-treated patients in TEMPO 3:4 and REPRISE (-3.69 and -3.61 mL/min/1.73 m²). Differences between observed and predicted (using a validated predictive equation) eGFR values at the last visit on tolvaptan increased with the duration of follow-up. The estimated benefit of 8.3 mL/min/1.73 m² over an average follow-up of 7.7 years in the subset of patients who had taken tolvaptan for at least

FIGURE 2: Changes in eGFR during the TEMPO 3:4, TEMPO 4:4 and REPRIS clinical trials. (A) Change in eGFR from the TEMPO 3:4 baseline to the Month 24 visit of TEMPO 4:4. TEMPO 3:4 participants from Japan were not enrolled in TEMPO 4:4 and they are not included in the figure. Open circles and triangles represent off-treatment time points. Note the small, acute reduction in eGFR when tolvaptan was started in TEMPO 3:4 and TEMPO 4:4 and its reversal when it was discontinued in the tolvaptan group at the end of TEMPO 3:4. The eGFR benefit accumulated by tolvaptan compared with placebo-treated patients at the end of TEMPO 3:4 (3.34 mL/min/1.73 m², *P* < 0.001) was maintained 2 years later (3.15 mL/min/1.73 m², *P* < 0.001) in TEMPO 4:4 when all patients were treated with tolvaptan. (B) Illustration of the results of REPRIS showing the changes from baseline (i) in eGFR that were due to the renal hemodynamic effect of tolvaptan during the single-blind tolvaptan period (ii) and the rapid reversal of these changes after randomization into the placebo group (iii) and after discontinuation of the drug in the tolvaptan group (iv); the vertical lines indicate these four time periods [(i)–(iv)]. The red bar along the X axis indicates the period during which patients received placebo, and the blue bar the period during which patients received tolvaptan. Plus signs on the X axis indicate trial visits at which the eGFR was assessed. The annualized mean change in eGFR ($\pm$ SE) from pre-treatment baseline to post-treatment follow-up in the intention-to-treat population was -2.34 ± 0.24 with tolvaptan versus -3.61 ± 0.24 mL/min/1.73 m² with placebo (treatment effect 1.27 mL/min/1.73 m², 95% CI 0.86–1.68, *P* < 0.001). Panels (A) and (B) are modified from published papers [23, 24].

5 years represented an annual effect of 1.08 mL/min/1.73 m². These results suggest that the effect of tolvaptan on eGFR is sustained, cumulative and consistent with potentially delaying the need of kidney replacement.

In summary, tolvaptan is the first effective treatment targeting the development and growth of the cysts in ADPKD. In the countries where it has been approved by regulatory agencies, patients with rapidly progressive ADPKD should be informed about the option of treatment, including possible benefits and risks. If a decision to initiate treatment is made, prescribing physicians should educate the patients on the prevention of aquaresis-related adverse events and should be vigilant in the surveillance and management of the potential tolvaptan hepatotoxicity. Other vasopressin V2R antagonists, possibly without potential hepatotoxicity, alternative strategies targeting vasopressin and combination with other drugs able to enhance the efficacy and/or reduce the aquaresis associated with tolvaptan, deserve further study.

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Only 25 references are allowed in the review, additional supportive references are available on demand.

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CONFLICT OF INTEREST STATEMENT

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