Vasopressin Receptor Antagonists, Heart Failure, and Polycystic Kidney Disease

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Keywords

vaptans, aquaretics, vasopressin V2 receptor, vasopressin V1a receptor, baroreceptors, osmoreceptors

Abstract

The synthesis of nonpeptide orally bioavailable vasopressin antagonists devoid of agonistic activity (vaptans) has made possible the selective blockade of vasopressin receptor subtypes for therapeutic purposes. Vaptans acting on the vasopressin V2 receptors (aquaretics) have attracted attention as a possible therapy for heart failure and polycystic kidney disease. Despite a solid rationale and encouraging preclinical testing, aquaretics have not improved clinical outcomes in randomized clinical trials for heart failure. Additional clinical trials with select population targets, more flexible dosing schedules, and possibly a different drug type or combination (balanced V1a/V2 receptor antagonism) may be warranted. Aquaretics are promising for the treatment of autosomal dominant polycystic kidney disease and have been approved in Japan for this indication. More studies are needed to better define their long-term safety and efficacy and optimize their utilization.

INTRODUCTION

PKD: polycystic kidney disease

GsPCR: Gs protein–coupled receptor

PKA: protein kinase A

The synthesis of nonpeptide orally bioavailable vasopressin antagonists devoid of agonistic activity (vaptans), first achieved in 1991 for the V1a receptor (V1aR) and in 1992 for the V2 receptor (V2R), made possible the selective blockade of vasopressin receptor subtypes for therapeutic purposes (1–4). Vaptans have attracted attention as a possible therapy for heart failure and polycystic kidney disease (PKD). This article reviews the current status of these potential therapies.

SIMILARITIES BETWEEN HEART FAILURE AND POLYCYSTIC KIDNEY DISEASE

There are similarities between heart failure and PKD that are easily overlooked. In both, there is a maladaptive neurohumoral response with activation of the sympathetic nervous system, renin-angiotensin system, and vasopressin (5–9) that enhances apoptosis, fibrosis, and organ dilation. In both, elevated serum copeptin levels are associated with worse prognosis (10, 11). The physiologic roles of catecholamines in the heart and of vasopressin in the kidney are mediated by the activation of Gs protein–coupled receptors (GsPCRs), protein kinase A (PKA) signaling, and calcium transients (**Figure 1**). When these responses are sustained for prolonged periods or disrupted by mutations to essential proteins, such as the ryanodine receptor 2 (RyR2) in the heart or the polycystins in the kidney, they become maladaptive (12–17). The result is a depletion of sarcoplasmic/endoplasmic reticulum calcium stores, reduced calcium transients, tissue remodeling, and development of a failing heart or a cystic kidney.

VASOPRESSIN IN HEART FAILURE AND POLYCYSTIC KIDNEY DISEASE

Vasopressin and vasopressin-related peptides are essential for survival and their evolution goes back more than 700 million years, prior to the appearance of heart, kidneys, and pituitary gland (18). In *Caenorhabditis elegans* (19, 20), the vasopressin-related peptide nematocin is produced in neurons, acts on GsPCRs that signal through cyclic adenosine-3′,5′-cyclic monophosphate (cAMP) and calcium, and controls salt chemotaxis. Interestingly, like the polycystins, nematocin also controls male reproductive behavior.

	Regulators	Physiologic	Maladaptive	Disease
Cardiac function	• Catecholamines • β1-AR • cAMP-PKA • P-RyR2 (PC2)/SERCA	• Inotropic and chronotropic effects	• Leaky SR/↓SERCA • SR Ca^{2+} depletion • Apoptosis • Cardiac remodeling	• Heart failure • Volume overload
Renal function	• Vasopressin • V2R • cAMP-PKA • P-RyR1 (PC2)/SERCA	• Urinary concentration	• Leaky ER/↓SERCA • ER Ca^{2+} depletion • Apoptosis • Cystogenesis	• CKD progression • Azotemia

Figure 1

Effects of neurohumoral responses on cardiac and renal function under physiologic and maladaptive pathological conditions. Abbreviations: β1-AR, β1-adrenergic receptor; cAMP-PKA, cyclic adenosine-3′,5′-cyclic monophosphate–protein kinase A; CKD, chronic kidney disease; ER, endoplasmic reticulum; PC2, polycystin-2; P-RyR2, phospho-ryanodine receptor 2; SERCA, sarco/endoplasmic reticulum calcium ATPase; V2R, vasopressin V2 receptor; SR, sarcoplasmic reticulum.

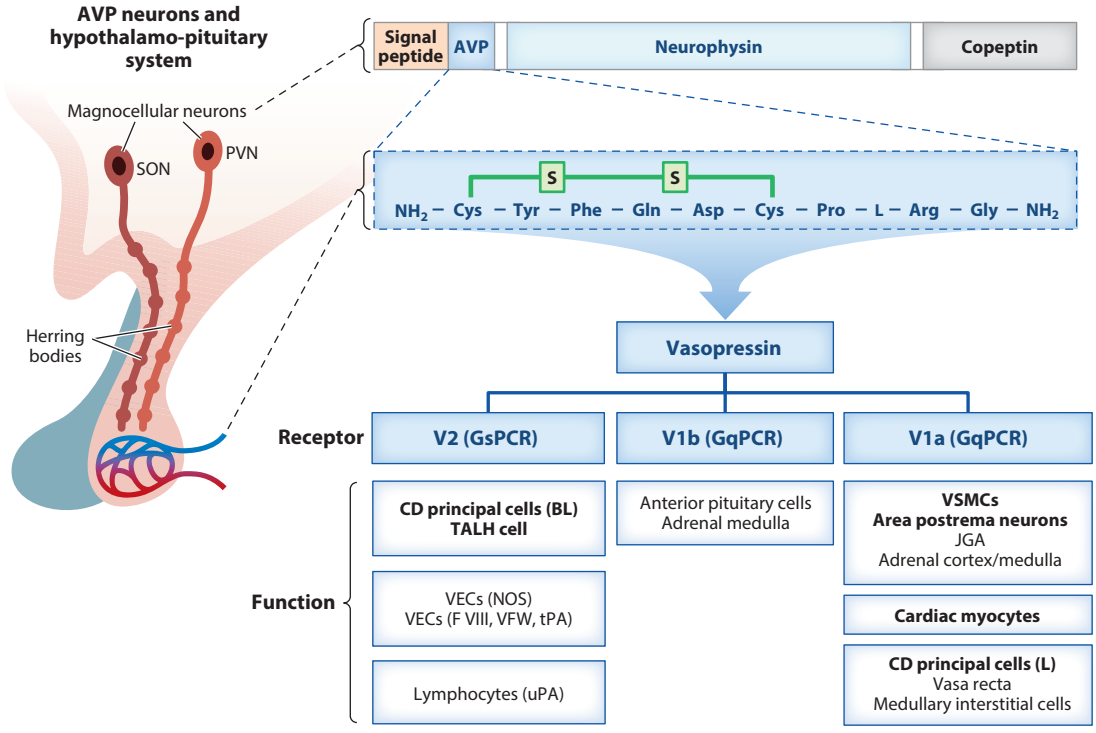

Figure 2

Schematic diagram illustrating the sites of vasopressin synthesis and release; the processing of preprovasopressin into vasopressin, neurophysin, and copeptin; and the types of vasopressin receptors and their functions relevant to heart failure and polycystic kidney disease. Abbreviations: AVP, arginine vasopressin; BL, basolateral; CD, collecting duct; F VIII, factor VIII; JGA, juxtaglomerular apparatus; L, luminal; NOS, nitric oxide synthase; PVN, paraventricular nucleus; PCR, protein-coupled receptor; SON, supraoptic nucleus; TALH, thick ascending loop of Henle; tPA, tissue plasminogen activator; uPA, urokinase plasminogen activator; VEC, vascular endothelial cell; VFW, von Willebrand factor; VSMCs, vascular smooth muscle cells.

In mammals, preprovasopressin (**Figure 2**) is produced in the magnocellular neurons of supraoptic and paraventricular nuclei in the hypothalamus. It undergoes proteolytic processing into vasopressin, neurophysin, and copeptin as it is transported to the neurohypophysis, from which vasopressin is released in response to various stimuli (21). Because copeptin is released in equimolar proportion and is more stable than vasopressin in the circulation, it is an excellent surrogate for vasopressin release (22).

Vasopressin acts on three receptors that have been identified in an increasing number of tissues (23, 24). Particularly relevant to heart failure and PKD are V2R and V1aR. V2Rs are found at the basolateral aspect of the principal cells in the collecting ducts and in the thick ascending limb of Henle, stimulating water and sodium retention. V1aRs are known in vascular smooth muscle cells and cardiac myocytes for their pressor and myocyte hypertrophic effects, in area postrema neurons for enhancing the baroreceptor inhibitory activity on vasopressin release, and at the luminal aspect in the collecting duct principal cells for exerting diuretic and natriuretic effects (**Figure 2**).

Under physiologic conditions, the concentration of circulating vasopressin is very low, and the release of vasopressin is regulated by plasma osmolality (**Figure 3**). The osmoreceptors detect very small changes in plasma osmolality (<1 mOsm/kg H_2O), but the levels of circulating vasopressin in response to even extreme increases in plasma osmolality do not exceed 20 pg/ml. Nevertheless,

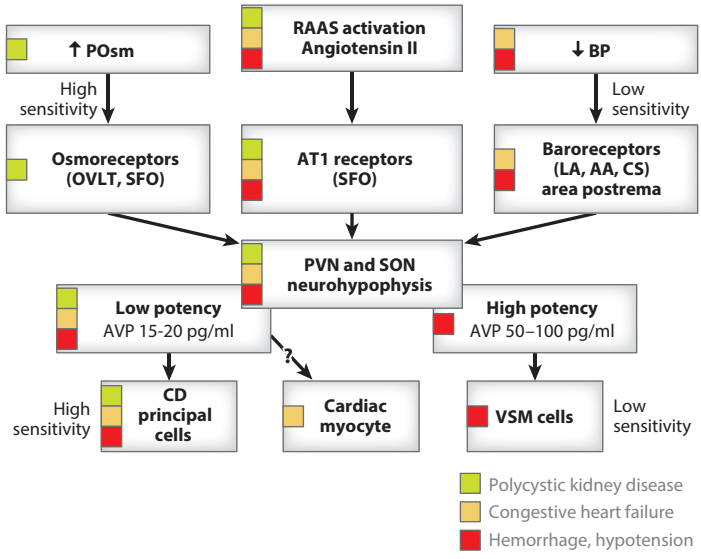

Figure 3

Regulation of vasopressin release by osmosensors, baroreceptors, and angiotensin 2, and alterations associated with polycystic kidney disease and heart failure as compared to acute hemorrhage. Colored boxes denote regulatory mechanisms and effects of vasopressin release associated with polycystic kidney disease, heart failure, and hemorrhage or hypotension. Abbreviations: AA, aortic arc; AVP, arginine vasopressin; BP, blood pressure; CD, collecting duct; CS, carotid sinus; LA, left atrium; OVLT, organum vasculosum of the lamina terminalis; POsm, plasma osmolality; PVN, paraventricular nucleus; RAAS, renin-angiotensin-aldosterone system; SFO, subfornical organ; SON, supraoptic nucleus; VSM cells, vascular smooth muscle cells.

these moderate levels of vasopressin are sufficient to maximally concentrate the urine. In contrast, the plasma volume has to decrease by 10% before a change is sensed by the baroreceptors, but the response is vigorous, with levels of circulating vasopressin increasing up to 50–200 pg/ml (25). These high levels of circulating vasopressin are necessary to elicit a vasopressor response. Activation of the renin-angiotensin system and circulating angiotensin 2 may also directly stimulate the release of vasopressin.

The development of cysts in PKD is accompanied by a urinary-concentrating defect that raises plasma osmolality and by activation of the renin-angiotensin system, both contributing to a moderate increase in production and release of vasopressin. In heart failure the vasopressin response is also moderate, in part because the baroreceptor tonic inhibitory activity is reduced in the aortic arc and carotid sinus but increased in the left atrium. The circulating vasopressin levels in heart failure are usually lower than 10 pg/ml (26–28). However, these levels may be high enough to contribute to cardiac myocyte hypertrophy and cardiac remodeling because V1aR is upregulated in the failing heart and transgenic overexpression of V1aR in mice causes cardiomyopathy (29, 30).

VAPTANS AND AQUARETICS

Aquaretics are vaptans that act on V2R and include dual V1aR/V2R and selective V2R antagonists. Beyond their ability to increase free water clearance and correct hyponatremia, aquaretics have attracted attention for the treatment of congestive heart failure and more recently PKD. They have a broad spectrum of selectivity and potency (**Table 1**) (2, 4, 31–33). Lixivaptan and satavaptan

Table 1 Dual V1a/V2 and selective V2receptor antagonists

	Conivaptan (YM-087)	Mozavaptan (OPC-31260)	Tolvaptan (OPC-41061)	Lixivaptan (VPA-985)	Satavaptan (SR121463)
Selectivity index (V2R/V1aR)	0.15	10	29	100	112
Ki (nmol/L) for V2R	1.11	25.4	0.43	0.60	4.1
Administration route	Oral/intravenous	Oral	Oral	Oral	Oral
Metabolism	Hepatic (CYP3A4)	Hepatic (CYP3A4)	Hepatic (CYP3A4)	Hepatic (CYP3A4)	Hepatic (CYP3A4, CYP2D6)
Pharmaceutical company	Yamanouchi Astellas	Otsuka	Otsuka	Wyeth-Ayerst Cardiokine	Sanofi Aventis

are the most selective, and conivaptan and mozavaptan are the least. Tolvaptan and lixivaptan are the most potent and mozavaptan the least.

RATIONALE FOR THE USE OF VAPTANS IN HEART FAILURE

There is a solid rationale for the use of both V2R and V1aR antagonists in heart failure. V2R antagonists may reduce water and salt retention and left ventricular preload, reduce diuretic requirement and adverse effects from diuretics, reduce cardiac V1aR expression, correct hyponatremia, reduce cardiomyocyte senescence, and possibly afford renal protection. V1aR antagonists may reduce left ventricular afterload and cardiomyocyte hypertrophy. However, V2R antagonists moderately increase the circulating levels of vasopressin and may exert detrimental effects mediated by unprotected V1aRs, and V1aR antagonists may exert antidiuretic and antinatriuretic effects.

PRECLINICAL STUDIES IN HEART FAILURE

The acute effects of vaptans on heart failure have been studied in humans with congestive heart failure and in dogs with heart failure induced by rapid ventricular pacing. The V1aR antagonist OPC-21268 significantly reduced blood pressure and increased cardiac output, and the V2R antagonist mozavaptan reduced the plasma concentration of atrial natriuretic peptide and enhanced the effects of OPC-21268 on blood pressure and cardiac output (34). The dual V1aR/V2R antagonist conivaptan reduced right atrial and pulmonary artery wedge pressures and enhanced the natriuretic effect of furosemide (35, 36). Like furosemide, the V2R antagonist tolvaptan lowered right atrial and pulmonary artery wedge pressures, but without inducing potentially detrimental increases in circulating levels of plasma renin activity, norepinephrine, and vasopressin (37–39).

The effects of more prolonged administration of V2R antagonists have been studied in rat models of congestive heart failure. Tolvaptan increased urine output without increasing urine sodium excretion, plasma renin activity, or plasma aldosterone, but it had no effect on cardiac remodeling, cardiac function, or survival in a model of autoimmune myocarditis (40, 41). Tolvaptan alone or in combination with furosemide, but not furosemide alone, reduced end-diastolic and end-systolic volumes, increased the left ventricular ejection fraction, and decreased (*a*) the plasma concentration of atrial natriuretic peptide, (*b*) the cardiac expression of V1aR, and (*c*) fibrosis in a model of heart failure following myocardial infarction (42, 43). Similar results, as well as a

Table 2 Randomized clinical trials of aquaretics for heart failure

Drug (Study) Year	Duration dose	Inclusion criteria	Primary and secondary outcomes	Post hoc analysis
Tolvaptan (METEOR)	1 year 30 mg QD	NYHA II-III (LVEF ≤ 30%)	No difference in LVEDV or PROs at 1 year	Improved hospital-free survival
Tolvaptan (ACTIV) 2004	60 days 30–60 mg QD	Hospitalization for HF (LVEF ≤ 30%)	Short-term: More weight loss at day 1 Long-term: No difference in mortality, hospitalization, or unscheduled visits	Improved survival in patients with more renal dysfunction or congestion
Tolvaptan (EVEREST) 2007	≥60 days (median follow-up 9.9 mo) 30 mg QD	Hospitalization for HF (LVEF ≤ 40%)	Short-term: Lower weight at discharge; less dyspnea on day 1 Long-term: No difference in mortality or CV death/HF hospitalization	Lower CV morbidity and mortality after discharge in patients with PNa^+ ≤130 mEq/L
Lixivaptan (BALANCE) 2012	60 days 50–100 mg QD or BID	Hospitalization for HF (PNa^+ 120–135)	Short-term: Higher PNa^+ day 7 Long-term: No difference in hospital-free survival	None

Abbreviations: BID, twice daily; CV, cardiovascular; HF, heart failure; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic pressure; PRO, patient-reported outcomes; QD, daily; PNa^+, plasma sodium.

renoprotective effect and improved survival, were obtained in a Dahl salt hypertensive model of heart failure (44, 45).

RANDOMIZED CLINICAL TRIALS IN HEART FAILURE

Compared to the results of preclinical trials, the outcomes of randomized clinical trials in humans have been disappointing (**Table 2**). Although some short-term outcomes were favorable to aquaretics, long-term outcomes showed no improvement in mortality or hospitalization rates (46–50). Improved hospital-free survival (reported by the METEOR trial) (46) and survival benefits in subgroups of patients with more renal dysfunction, severe congestion or severe hyponatremia [reported by ACTIV (51, 52) and EVEREST (53, 54)] were observed in post hoc analyses of clinical trials of tolvaptan. However, an early imbalance in mortality with lixivaptan compared to placebo (15 versus 4 sudden deaths in the first 10 days) in the BALANCE clinical trial raised concerns about the safety of lixivaptan in patients with acute heart failure and hyponatremia (50, 55). A post-marketing analysis of tolvaptan in Japan, which included 1,053 of 1,840 registered patients, showed a sustained increase in urine output, reduction in body weight, and increase in plasma sodium, without a significant change in serum creatinine despite high baseline serum creatinine concentrations (56). These effects were accompanied by reductions in edema, dyspnea, pulmonary congestion, and jugular vein distension.

Several factors may account for the inconsistent results of preclinical and randomized clinical trials of aquaretics in heart failure. It may be that V2R antagonists do not improve long-term outcomes because they fail to amend the complex physiopathology of heart failure. It is also possible that the randomized clinical trials have not adequately tested the potential of aquaretics in this condition. Doses of medication may need to be individualized, possibly using small split daily doses. Maybe only the patients with more severe heart failure, hyponatremia, and renal

Table 3 Approved indications for aquaretics in adults

Drug	United States (FDA)	European Union (EMA) indications	Japan (PMDA)
Tolvaptan	Hypervolemic or euvolemic hyponatremia (≤125 mEq/L or symptomatic and resistant) in SIADH and heart failure. No more than 30 days.	Hyponatremia secondary to SIADH	Volume overload resistant to diuretics in heart failure Fluid retention resistant to diuretics in hepatic cirrhosis ADPKD patients with large and rapidly increasing kidney volumes
Conivaptan	Hypervolemic or euvolemic hyponatremia in hospitalized patients	None	None
Mozavaptan	None	None	Hyponatremia in paraneoplastic SIADH

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; EMA, European Medicines Agency; FDA, US Food and Drug Administration; PMDA, Pharmaceuticals and Medical Devices Agency; SIADH, syndrome of inappropriate antidiuretic hormone.

dysfunction are likely to benefit, or maybe balanced or combined V1aR/V2R antagonists rather than a V2R-selective antagonists should be used. More and differently designed clinical trials are warranted, but it is uncertain that adequate funding to conduct these additional trials will become available.

Tolvaptan is currently approved for heart failure patients with hypervolemic or euvolemic hyponatremia (≤125 mEq/L or symptomatic and resistant) in the United States and for heart failure patients with volume overload resistant to diuretics in Japan. Recently, the US Food and Drug Administration (FDA) recommended limiting the use of tolvaptan to 30 days because of liver function test abnormalities in patients enrolled in a clinical trial of tolvaptan for autosomal dominant polycystic kidney disease (ADPKD), despite the absence of such abnormalities in clinical trials of tolvaptan for hyponatremia or in post-marketing data. Conivaptan is approved for hypervolemic or euvolemic hyponatremia in hospitalized patients. In September 2012, a Cardiovascular and Renal Advisory Panel of the FDA reviewed the results of the BALANCE study and unanimously opposed approval of lixivaptan for acute decompensated heart failure (50). Approved indications for aquaretics in adult patients are summarized in **Table 3**.

RATIONALE FOR AQUARETICS IN POLYCYSTIC KIDNEY DISEASE

A large body of evidence indicates that dysregulation of calcium and cAMP signaling plays a central role in PKD (17). Renal levels of cAMP are consistently elevated in animal models of PKD (57–61), possibly owing to activation of calcium-inhibitable adenylyl cyclase 6 and inhibition of calcium/calmodulin-dependent phosphodiesterase 1 (also increasing the levels of guanosine-3′,5′-cyclic monophosphate, cGMP) and cGMP-inhibitable PDE3 (58, 62). Indeed, the severity of the disease in orthologous models in rodents is attenuated by knocking down adenylyl cyclase 6 (63) and increased by knocking down PDE3A (64). Upregulation of cAMP/PKA signaling within the context of PKD promotes cell proliferation in a Src-, Ras-, B-raf-, MAPK-, and mTOR-dependent manner. It also promotes chloride-driven fluid secretion, mediated by cystic fibrosis transmembrane conductance regulator, and possibly a STAT3-directed inflammatory microenvironment (65).

ADPKD: autosomal dominant polycystic kidney disease

The central role of cAMP provides a strong rationale for strategies to lower its levels in cystic tissues. Blocking the effect of vasopressin on the V2R is particularly appealing because V2Rs are almost exclusively located on collecting ducts, connecting tubules, and thick ascending limbs of

Henle (66, 67), the main sites of cystogenesis, thus minimizing off-target toxicities. Vasopressin is the major GsPCR agonist responsible for most cAMP generation in freshly isolated collecting ducts (68). The kidneys are continuously exposed to the tonic action of vasopressin to avoid dehydration. This exposure is further enhanced in PKD owing to a concentrating defect distal to cAMP generation and PKA activation. Cyst development is markedly inhibited in PCK rats lacking circulating vasopressin (generated by crosses of PCK and Brattleboro rats), an effect reversed by the administration of the V2R agonist 1-deamino-8-d-arginine vasopressin (dDAVP) (69). Suppression of vasopressin by high water intake sufficient to achieve a 3.5-fold increase in urine output attenuates the progression of PKD in the PCK rat (70).

PRECLINICAL STUDIES OF V2 RECEPTOR ANTAGONISTS IN ADPKD

V2R antagonists (mozavaptan and/or tolvaptan) attenuate the progression of PKD in cpk mice (71) and in rodent models of nephronophthisis (pcy mice) (58, 72), autosomal recessive polycystic kidney disease (ARPKD; PCK rats) (58, 73), ADPKD-1 (kidney-specific inducible *Pkd1* knockout and $Pkd1^{RC/RC}$ mice), and ADPKD-2 ($Pkd2^{-}$/WS25 mice) (74–76). Low concentrations of tolvaptan also inhibit vasopressin-induced chloride secretion and decrease in vitro cyst growth of human ADPKD cells (77).

CLINICAL TRIALS OF V2R ANTAGONISTS IN ADPKD

Small clinical trials were initially conducted to ascertain the safety and pharmacokinetics of tolvaptan in adult patients with ADPKD and relatively preserved renal function (78). Twice-daily administration was found to be necessary to block V2R activation throughout a 24-h period as reflected by sustained urine hypotonicity. A phase II open-label uncontrolled three-year clinical trial was then conducted to ascertain long-term safety and tolerability (79). Patients were randomized to 45/15 mg or 60/30 mg daily doses chosen after an analysis of efficacy (defined as Uosm persistently <300 mOsm/kg in 70% and 77% of patients, respectively) and self-reported tolerability (for the rest of life in 96% and 61% of patients, respectively) during the titration phase. Changes in kidney volume (determined by magnetic resonance imaging, MRI) and estimated glomerular filtration rate (eGFR) were compared to historical controls from the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) and the Modification of Diet in Renal Disease (MDRD) studies. Rates of increase in kidney volume (1.7 versus 5.8%) and decline in eGFR (−0.71 versus −2.1 ml/min per 1.73 m^2 per year) were significantly less in the tolvaptan-treated patients than in the historical controls. Limitations of the study were the small number of patients and the utilization of noncontemporary controls with unmatched ethnicities.

Slight elevations in serum creatinine, rapidly reversible after cessation of drug administration, were observed in the phase II clinical trials. To better understand the acute effects of tolvaptan on renal function, 20 ADPKD patients were studied before and after a regimen of split-dose tolvaptan (45/15 mg daily) for one week (80). Tolvaptan-induced aquaresis was accompanied by an 8.6% reduction in iothalamate clearance and a 13.0% increase in serum uric acid, without a significant change in renal blood flow. Post hoc blinded analysis of renal MRIs showed that tolvaptan induced a 3.1% reduction in kidney volume, as well as a reduction in the volume of individual cysts. A similar study of 27 patients at various stages of chronic kidney disease (group A: >60, group B: 30–60, and group C: <30 ml/min per 1.73 m^2) showed reversible 6.5%, 7.0%, and (not significant) 3.0% reductions in GFR and 6.7%, 16.2%, and 4.7% increases in serum uric acid in groups A, B, and C, respectively, without significant changes in ^{131}I-hippuran clearance, after administration of tolvaptan (up-titrated to 90/30 mg/day, if tolerated) for three weeks (81).

RANDOMIZED CONTROLLED TRIAL OF TOLVAPTAN IN ADPKD

A phase III multicenter randomized double-blind placebo-controlled parallel-arm trial of tolvaptan in ADPKD (TEMPO, Tolvaptan Efficacy and Safety in Management of ADPKD and its Outcomes, 3:4; NCT00428948), conducted at 129 sites in 15 countries, included 1,145 ADPKD subjects with progressive disease reflected by kidney volumes of at least 750 ml at a relatively young age (between 18 and 50 years), but still with preserved renal function (estimated creatinine clearance >60 ml/min) (82, 83). Participants were randomized 2:1 to tolvaptan or placebo. Split 45/15 mg doses of study drug were up-titrated at weekly intervals to 60/30 and 90/30 mg, if tolerated. The maximal tolerated dose was maintained for three years. Serum creatinine and laboratory parameters were measured every four months, and renal MRIs were obtained yearly. Participants were instructed to drink enough water to prevent thirst. Twenty-three percent of tolvaptan-treated subjects withdrew from the trial, 15% owing to adverse events, including aquaresis-related symptoms in 8%. The corresponding percentages in the placebo group were 14%, 5%, and 0.4%.

The analysis of the primary endpoint showed that tolvaptan reduced the rate of kidney growth by 50%, from 5.5% to 2.8% per year (**Figure 4*a***). A "mixed model for repeated measures" sensitivity analysis showed that the treatment effect of tolvaptan was greatest from baseline to year 1 but that it was also significant from year 1 to year 2 and from year 2 to year 3, resulting in an increasing separation in kidney volume between the groups over time (**Figure 4*b***). The analysis of the key composite secondary endpoint of time to development or progression of multiple clinical events (25% reductions in reciprocal serum creatinine, severe kidney pain, and categorical changes in blood pressure status and urine albumin excretion) showed fewer clinical events for tolvaptan, compared to placebo with a hazard ratio of 0.87. This positive result was driven by favorable effects on kidney function decline (61% lower risk) and kidney pain (36% lower risk) (**Figure 4*c***). The administration of tolvaptan also reduced the rate of decline of reciprocal serum creatinine, from 3.81 to 2.61 per year ($p < 0.001$) (**Figure 4*d***).

Frequencies of adverse events and serious adverse events were similar in both groups. Adverse events related to aquaresis were significantly more common in the tolvaptan group, whereas adverse events related to ADPKD, such as kidney pain, hematuria, and urinary tract infection, were more common in the placebo group. Increases in serum sodium and uric acid were more frequently seen in tolvaptan-treated subjects. Unexpectedly, elevations of serum alanine and/or aspartate aminotransferases over three times the upper limit of normal in at least one visit were observed in 4.7% of tolvaptan-treated patients compared to 1.7% of placebo-treated patients. These led to the discontinuation of the study medication in 1.8% of tolvaptan- and 0.2% of placebo-treated patients. In two of the tolvaptan-treated patients, the elevations of liver enzymes and bilirubin met the Hy's law criteria, implying a 10% risk of irreversible liver damage (84). Liver function tests returned to normal after discontinuation of tolvaptan in all patients.

REVIEW OF TOLVAPTAN INDICATION FOR POLYCYSTIC KIDNEY DISEASE BY REGULATORY AGENCIES

Tolvaptan was approved in March 2014 by the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan for the suppression of progression of ADPKD in patients with a high kidney volume and a rapid rate of increase. The labeling notes that the administration of tolvaptan should be conducted under the supervision of a physician with sufficient knowledge of ADPKD and only to patients for whom potential benefits are considered to outweigh potential risks. Patients taking tolvaptan should have easy access to and be able to tolerate water. Levels of plasma sodium and uric acid require monitoring, and liver function should be monitored closely (monthly) during therapy.

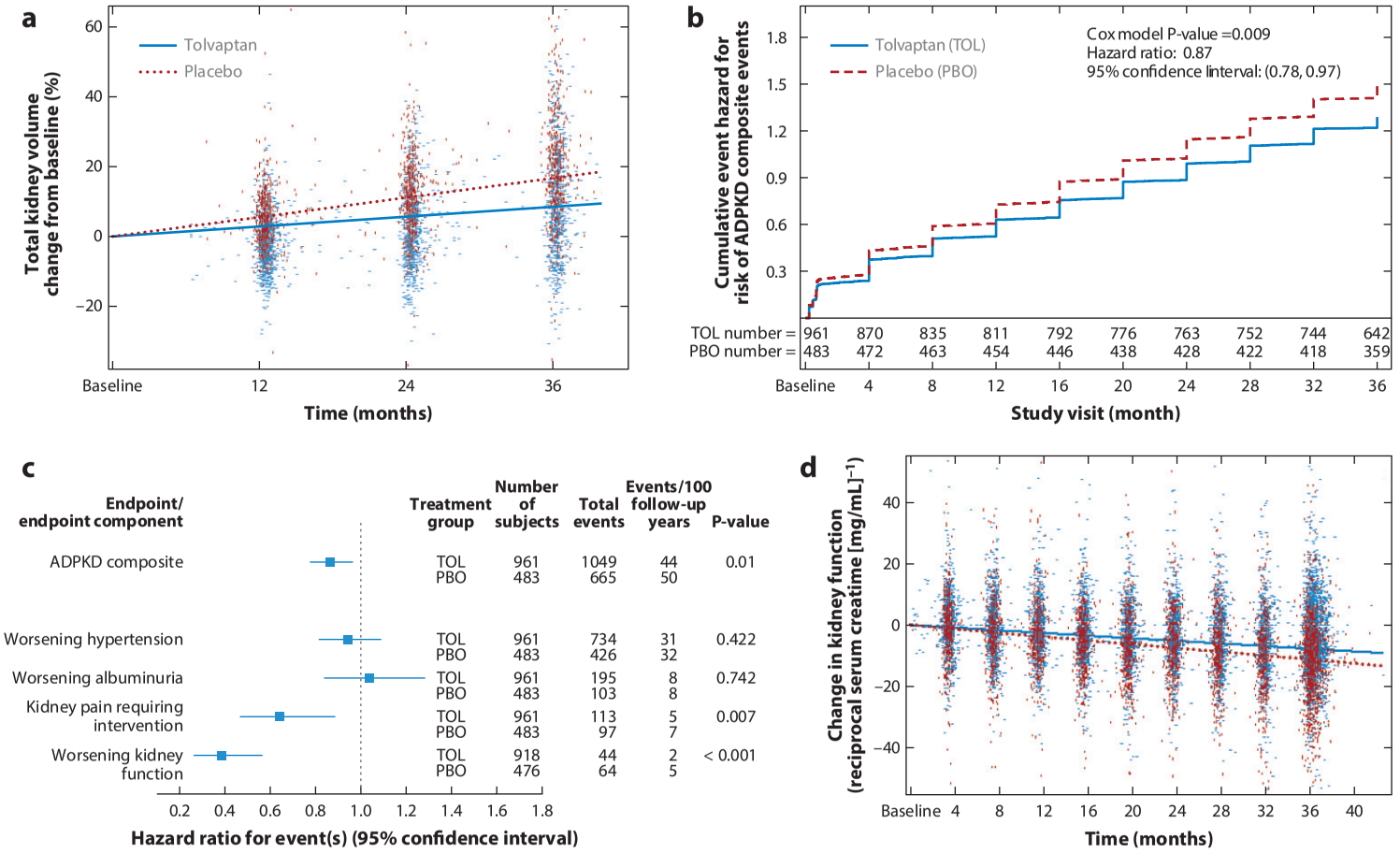

Figure 4

Effects of tolvaptan on primary and secondary endpoints in the TEMPO 3:4 clinical trial. (*a*) Changes in total kidney volume in the intent-to-treat population during the three-year treatment period. Tolvaptan reduced the rate of kidney growth from 5.5% to 2.8% per year ($p < 0.001$). (*b*) Hazard ratios for the secondary composite endpoint of ADPKD-related events. There were fewer events per 100 person-years of follow-up in the tolvaptan group than in the placebo group, with a hazard ratio of 0.87 (95% CI 0.78–0.97). (*c*) Hazard ratios for the composite secondary endpoint and its components. Horizontal bars indicate 95% confidence intervals. (*d*) Changes in kidney function estimated with the use of the reciprocal of the serum creatinine level in the intent-to-treat population during the treatment period. Tolvaptan reduced the on-treatment rate of decline of reciprocal serum creatinine from 3.81 to 2.61 per year ($p < 0.001$). Abbreviation: ADPKD, autosomal dominant polycystic kidney disease. From Reference 83 with permission.

In August 2013, the FDA issued a complete response letter (CRL) regarding the new drug application for the use of tolvaptan in the treatment of adult patients with rapidly progressing ADPKD. The FDA issues CRLs to convey that their initial review of an application is complete but that they cannot approve the application in its present form and request additional information. In its letter to Otsuka, the maker of tolvaptan, the FDA requested additional data to further evaluate the efficacy and safety of the drug in patients with ADPKD. Concerns raised at the August 5, 2013, meeting of the FDA's Cardiovascular and Renal Drugs Advisory Committee (85) included (*a*) not accepting total kidney volume as an established surrogate, (*b*) the uncertainty introduced by missing data and a post-treatment baseline for the key secondary endpoint, and (*c*) the "small" 1 ml/min per 1.73 m^2 per year (33%) improvement in renal function decline. The FDA also questioned whether the net benefit would be positive, since improvements in kidney cyst growth or renal function decline might not persist and the sponsor's strategy to reduce the risk of irreversible liver injury through frequent monitoring was unproven.

Applications for approval of tolvaptan for the treatment of ADPKD are currently under review by the European Medicines Agency (EMA) and Health Canada.

BEYOND TEMPO

Many questions remain about the potential use of tolvaptan even in countries where this drug is or may eventually be approved for the treatment of PKD. Treatments for ADPKD are more likely to be effective if started early, but patients with mild disease do not progress to renal failure and do not need treatment. Therefore, algorithms will be necessary to identify the patients who will benefit from treatment at relatively early stages of the disease (86). Optimal dosage is likely to be variable from patient to patient, and tools to monitor the response to therapy will be needed. Modified release formulations may be better tolerated and more efficient. Whether dual V1aR/V2R antagonists or combinations of V2R and V1aR antagonists are more or less effective than selective V2R antagonists deserves study. Combinations of V2R antagonists with other effective therapies should also be considered. For example, the combination of tolvaptan and the somatostatin analog pasireotide has been shown to be more effective than either drug alone in a *Pkd1* mouse model (76).

Finally, several studies have shown that blockade of vasopressin action on the kidney may be renoprotective in chronic kidney disease in general (87). Vasopressin acting on V2R contributes to hyperfiltration, albuminuria, glomerulosclerosis, tubular hypertrophy, and interstitial fibrosis. Genetic, physiologic, or pharmacologic downregulation of vasopressin signaling delays disease progression in preclinical models of renal mass reduction and diabetic nephropathy (88–92). Consistent with a beneficial effect of suppression of vasopressin signaling, epidemiologic studies have shown an association between increased hydration and a reduced risk for chronic kidney disease (93–96).

SUMMARY

The vaptans are orally bioavailable vasopressin antagonists devoid of agonistic activity. Those acting on V2R (aquaretics) very effectively increase free water clearance. Despite a solid rationale and encouraging preclinical testing, aquaretics have not improved clinical outcomes in randomized clinical trials for heart failure. Additional clinical trials with select population targets, more flexible dosing schedules, and possibly different drug type (balanced V1aR/V2R antagonism) may be warranted. Aquaretics are promising for the treatment of ADPKD and have been approved in

Japan for this indication. More studies are needed to better define their long-term safety and efficacy and optimize their utilization.

DISCLOSURE STATEMENT

Dr. Torres is an investigator and chairs the Steering Committee for clinical trials of tolvaptan in ADPKD sponsored by Otsuka Pharmaceuticals and has received research support from Otsuka Pharmaceuticals.

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