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Original Investigation

Rationale and Design of the TEMPO (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes) 3-4 Study

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Background: Current management of autosomal dominant polycystic kidney disease (ADPKD) is focused on treating disease complications, not on slowing cyst development or preventing progression to kidney failure. Tolvaptan, a selective vasopressin V2 (vasopressin 2) receptor antagonist, has been proved to inhibit kidney cyst growth and preserve kidney function in multiple animal models of polycystic kidney disease. The TEMPO (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes) 3-4 Study will examine the long-term effectiveness and safety of tolvaptan in patients with ADPKD. We report baseline characteristics and revised power calculations for the trial.

Study Design: A prospective, 3-year, multicenter, double-blind, placebo-controlled trial of tolvaptan, a selective V2 receptor antagonist. Primary outcome is total kidney volume percentage of change from baseline for tolvaptan relative to placebo. Secondary outcome parameters include time to ADPKD-associated complications (kidney function decrease, blood pressure control, renal pain, and albuminuria) and safety end points.

Setting & Participants: This trial includes patients with ADPKD with relatively preserved kidney function (baseline estimated creatinine clearance ≥60 mL/min), aged 50 years or younger, and with total kidney volume measured using magnetic resonance imaging ≥750 mL.

Intervention: Administration of placebo or tolvaptan, dose titrated to tolerance.

Outcomes: Number of subjects enrolled and baseline characteristics.

Measurements: Total kidney volume, kidney function, albuminuria, kidney pain, and vital signs.

Results: 1,445 patients with ADPKD were enrolled between March 2007 and January 2009. Preliminary baseline median total kidney volume was 1.46 L, and estimated creatinine clearance was 105 ± 34 mL/min. A prespecified blinded sample-size recalculation at two-thirds enrollment confirmed the likely power of the study to detect 20% differences from placebo in the primary and key secondary end points at $P < 0.05$.

Limitations: This is a preselected ADPKD population chosen for its risk of progression to kidney failure and may not represent the general ADPKD population. If study results are positive with regard to the primary end point, positive effects on other secondary clinical outcomes will be required to assess overall benefit.

Conclusions: This randomized trial is the largest clinical study of a proposed ADPKD intervention to date. It targets patients with ADPKD with early disease who are projected to have rapid cyst growth and accelerated outcomes. Blockade of vasopressin V2 receptor is hypothesized to inhibit cyst growth, thereby delaying additional adverse clinical outcomes.

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Autosomal dominant polycystic kidney disease (ADPKD) is the most common kidney hereditary disease (caused in most cases by a mutation in the *PKD1* or *PKD2* gene[1,2]). ADPKD is a systemic disorder characterized by progressive cyst formation in both kidneys, with progressive kidney enlargement often leading to end-stage renal disease. Other kidney symptoms include pain, hypertension, gross hematuria, nephrolithiasis, and mild albuminuria. Current therapies are directed toward limiting morbidity and mortality from complications of ADPKD,[3] but not specifically targeting the inhibition of cyst formation.

Although kidney failure is the most feared consequence of the disease, glomerular filtration rate (GFR) is a poor marker of disease severity and progression in early phases of the disease. GFR remains intact during a prolonged period (typically decades) through compensatory hyperfiltration, but ultimately decreases sharply thereafter. Gradual anatomic distortion likely parallels the loss of functioning glomeruli.[4] The Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) showed that total kidney volume at entry into the study predicted future kidney function deterioration and identified a potential method for study of therapies targeted at inhibition of cyst formation.[5] Therefore, in early ADPKD, total kidney volume is likely to be a more sensitive marker of disease progression than kidney function.

Improved knowledge of genetic, molecular, and cellular mechanisms underlying cyst formation in ADPKD has resulted in the discovery of potentially effective therapeutic targets.[6] Vasopressin, acting on vasopressin 2 (V2) receptors, increases intracellular cAMP (cyclic adenosine monophosphate) in distal nephron segments and collecting ducts, promoting chloride-driven fluid secretion. cAMP also stimulates B-RAF/MEK/extracellular signal–regulated signaling, mitogenesis, and proliferation of polycystic kidney epithelial cells or wild-type kidney epithelial cells under experimental conditions of calcium deprivation.[7,8] Localization of the V2 receptors in the distal nephron and collecting duct[9] corresponds to the main site of cystogenesis in autosomal recessive polycystic kidney disease (ARPKD) and arguably in ADPKD,[10] and increased circulating levels of vasopressin in animal models[11,12] and patients with ADPKD[13,14] provided the rationale for experimental studies with vasopressin V2 receptor antagonists. The vasopressin V2 receptor antagonist OPC-31260 inhibited cyst formation in animal models for ARPKD, nephronophthisis,[11] and ADPKD.[12] Tolvaptan, another vasopressin V2 receptor antagonist with high potency and selectivity for human vasopressin V2 receptor, proved effective in a rat model for ARPKD.[15] Moreover, genetic elimination of arginine vasopressin in this model yielded animals relative free of cysts unless an exogenous V2 receptor agonist was administered.[16]

Tolvaptan induces free-water clearance and is approved by the US Food and Drug Administration for hypervolemic and euvolemic hyponatremia and the European Medicines Agency for hyponatremia associated with syndrome of inappropriate secretion of antidiuretic hormone. These approvals were based on studies of the efficacy and safety of this vasopressin V2 receptor antagonist in hyponatremia.[17-19] Phase 2 studies in patients with ADPKD showed that split-dose administration of tolvaptan was more effective than a single dose in achieving sustained suppression of vasopressin action, evidenced by 24-hour urine osmolality decrease to $<$300 mOsm/L.[20] A phase 2 open-label trial in 46 and 17 patients with ADPKD investigating the long-term safety, tolerability, and efficacy of split-dose regimens has completed 3 years of treatment and is ongoing in the United States[21] and Japan,[22] respectively.

Based on promising results in animal models and early clinical studies with respect to efficacy and safety, we have designed and initiated a large clinical trial to examine the effectiveness of tolvaptan in patients at relatively early stages of ADPKD.

METHODS

Study Population

Patients with ADPKD (diagnosis based on Ravine criteria[23]) aged 18-50 years with estimated creatinine clearance (eCCr) using the Cockcroft-Gault[24] equation $>$60 mL/min and measured total kidney volume (sum of right and left kidney volumes) $>$750 mL using magnetic resonance (MR) imaging (MRI) were eligible for study-participation. Detailed study inclusion and exclusion criteria are listed in Box 1.

Study Design and Setting

The TEMPO (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes) 3-4 study was designed as a multicenter, double-blind, placebo-controlled, parallel-arm trial in patients with ADPKD. Patients were enrolled worldwide (North and South America, Europe, Japan, and Australia). After determining eligibility (Box 1), patients were randomly assigned with stratification to 1 of 2 treatment groups (2:1 ratio of tolvaptan to placebo). Stratification factors include baseline hypertension (present or absent), eCCr ($\geq$80 or $<$80 mL/min), and total kidney volume ($\geq$1,000 or $<$1,000 mL). Hypertension is defined as systolic blood pressure $>$139 mm Hg and/or diastolic blood pressure $>$89 mm Hg or use of antihypertensive treatment.

Figure 1 schematically represents the trial design. Three split-dose regimens of oral tolvaptan and matching placebo are