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Original Investigation

Tolvaptan and Kidney Pain in Patients With Autosomal Dominant Polycystic Kidney Disease: Secondary Analysis From a Randomized Controlled Trial

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Background: Kidney pain is a common complication in patients with autosomal dominant polycystic kidney disease (ADPKD), and data from the TEMPO 3:4 trial suggested that tolvaptan, a vasopressin V2 receptor antagonist, may have a positive effect on kidney pain in this patient group. Because pain is difficult to measure, the incidence of kidney pain leading to objective medical interventions was used in the present study to assess pain.

Study Design: Secondary analysis from a randomized controlled trial.

Setting & Participants: Patients with ADPKD with preserved kidney function.

Intervention: Tolvaptan or placebo.

Outcomes: Kidney pain events defined by objective medical interventions.

Measurements: Kidney pain events were recorded and independently adjudicated. Incidence of a first kidney pain event was assessed overall and categorized into 5 subgroups according to severity.

Results: Of 1,445 participating patients (48.4% women; mean age, 39 ± 7 [SD] years; mean estimated glomerular filtration rate, 81 ± 22 mL/min/1.73 m^2; median total kidney volume, 1,692 [IQR, 750-7,555] mL), 50.9% reported a history of kidney pain at baseline. History of urinary tract infections, kidney stones, or hematuria (all $P < 0.001$) and female sex ($P < 0.001$) were significantly associated with history of kidney pain. Tolvaptan use resulted in a significantly lower incidence of kidney pain events when compared to placebo: 10.1% versus 16.8% ($P < 0.001$), with a risk reduction of 36% (HR, 0.64; 95% CI, 0.48-0.86). The reduction in pain event incidence by tolvaptan was found in all groups irrespective of pain severity and was independent of predisposing factors (P for interaction > 0.05). The effect of tolvaptan was explained at least in part by a decrease in incidence of urinary tract infections, kidney stones, and hematuria when compared to placebo.

Limitations: Trial has specific inclusion criteria for total kidney volume and kidney function.

Conclusions: Tolvaptan decreased the incidence of kidney pain events independent of patient characteristics predisposing for kidney pain and possibly in part due to reductions in ADPKD-related complications.

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INDEX WORDS: Autosomal dominant polycystic kidney disease (ADPKD); pain; tolvaptan; vasopressin; acute kidney pain event; TEMPO (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes) 3:4; pain severity; analgesic.

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[*]A full list of the TEMPO 3:4 Investigators is given in the Supplemental Appendix of Torres et al.[5]

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Pain is a common complication in patients with autosomal dominant polycystic kidney disease (ADPKD). It is a symptom that is often reported early in the disease course and that sometimes can be severe and difficult to manage and adversely affect a patient's quality of life.[1-3] Acute pain in patients with ADPKD can be caused by cyst hemorrhage, infection, and kidney stones, which are often accompanied by hematuria. When pain is present longer than 4 to 6 weeks, it is typically classified as chronic pain, which has a reported prevalence as high as 60%.[4]

The TEMPO (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes) 3:4 trial demonstrated the renoprotective effects of tolvaptan treatment in a randomized controlled clinical trial setting.[5] During 3 years' follow-up, tolvaptan, a vasopressin V2 receptor antagonist, reduced the annual rate of growth in total kidney volume (TKV) from 5.5% to 2.8% ($P < 0.001$) and the annual rate of estimated glomerular filtration rate (eGFR) decline from −3.70 to −2.72 mL/min/1.73 m^2 ($P < 0.001$) compared to placebo.[5] This trial also demonstrated a reduction in clinical progression as assessed by its key secondary composite end point through a reduction of ADPKD-related clinical events. This outcome was driven by 2 components of the composite: time to decline in kidney function and time to clinically significant kidney pain events.[5]

In the present study, we explored this last finding more closely. We characterized what constituted a "clinically significant kidney pain event" by objectively examining the intensity of medical interventions used to define them. We also investigated the association of ADPKD clinical characteristics (such as history of kidney pain, infection, kidney stones, or hematuria at baseline) with the incidence of acute kidney pain events during the 3-year trial. Furthermore, we analyzed the effect of tolvaptan use on incidence of kidney pain events and explored whether new pain events were associated with baseline patient characteristics and the possible mechanisms by which tolvaptan reduced their incidence.

METHODS

Study Design and Patients

The present study was performed as a post hoc exploratory analysis of the TEMPO 3:4 trial, a prospective, blinded, randomized, placebo-controlled trial in patients with diagnosed ADPKD (ClinicalTrials.gov study number NCT00428948). Patients were enrolled at 129 sites worldwide during January 2007 to January 2009. Inclusion criteria were age 18 to 50 years with a diagnosis of ADPKD, TKV measured by magnetic resonance imaging ≥ 750 mL, and creatinine clearance estimated by the Cockcroft-Gault formula ≥60 mL/min. Exclusion criteria included, among others, concomitant illnesses likely to confound end point assessments, such as diabetes mellitus, and prior kidney surgery. The institutional review board or ethics committee at each site approved the protocol. Written informed consent was obtained from all participants. Details of the study protocol[6] and the primary study results[5] have been published previously. This report has been prepared in accordance with the CONSORT (Consolidated Standards of Reporting Trials) 2010 Statement.[7]

Study Treatment

Patients were randomly assigned to receive tolvaptan or placebo (2:1). Tolvaptan dosing was started at 45 mg AM/15 mg PM (daily split dose) and increased weekly to 60/30 mg and 90/30 mg if tolerated. Patients remained on the highest tolerated dose for 36 months.

Study Assessments and Definitions

Evaluations were performed at baseline, every 4 months during treatment, and twice for 2 to 6 weeks after completion of treatment at 36 months and included interviews, examinations, vital sign measurements, and blood and trough spot morning urine samples. TKV was assessed using standardized kidney magnetic resonance imaging at baseline and months 12, 24, and 36 or at early withdrawal. In addition, height-adjusted TKV was calculated as TKV in milliliters divided by height in meters. Serum creatinine level was reported to 2 decimal points and used to estimate GFR (applying the CKD-EPI [Chronic Kidney Disease Epidemiology Collaboration] equation).[8]

At baseline, a standardized interview was performed to gather information about demographic characteristics and medical history, including information for prior kidney pain. Incidence of acute kidney pain during follow-up was a component of the composite secondary efficacy end point, which assessed kidney pain events requiring medical intervention and that required documentation of clinical signs and symptoms that pain was kidney related (ie, flank tenderness or evidence of cystic expansion or hemorrhage). The investigator's clinical judgment was required to arbitrate whether the level of pain met the definition of end point, which required clinically significant kidney pain necessitating pharmacologic treatment or invasive intervention. Pain was a priori categorized according to the intensity of intervention into 5 groups: mild, prescription of acetaminophen; moderate, prescription of other non-narcotic analgesics; moderately severe, prescription of non-narcotic analgesic and limitation in physical activity; severe, prescription of narcotic analgesics; most severe, need for hospitalization and/or invasive intervention. Events were assessed by an independent adjudication committee blinded for treatment allocation. Finally, the incidence of urinary tract infection, kidney stones, and hematuria was assessed as a composite score and separately. Of note, the initial TEMPO 3:4 trial publication provided data for these events only when reported as (serious) adverse events, whereas in the present study, all clinically significant pain-related adverse events are taken into account.

Study Outcomes

The primary end point in this study was the effect of tolvaptan use on incidence of acute kidney pain events compared to placebo. Second, we investigated: (1) the association of ADPKD clinical characteristics (such as history of kidney pain, infection, kidney stones, or hematuria at baseline) with the incidence of acute kidney pain events during the 3-year trial, (2) whether new acute kidney pain events were associated with baseline patient characteristics, and (3) the possible mechanisms by which tolvaptan reduced their incidence.

Statistical Analyses

Baseline characteristics were calculated for participants with and without a history of kidney pain separately. Normally distributed variables are expressed as mean ± standard deviation,

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