AJKD

Original Investigation

Efficacy of Febuxostat for Slowing the GFR Decline in Patients With CKD and Asymptomatic Hyperuricemia: A 6-Month, Double-Blind, Randomized, Placebo-Controlled Trial

Dipankar Sircar, MD, DM,[1] Soumya Chatterjee, MD,[2] Rajesh Waikhom, MD, DM,[3] Vishal Golay, MD, DM,[1] Arpita Raychaudhury, MD, DM,[1] Suparna Chatterjee, MD,[2] and Rajendra Pandey, MD, DM[1]

Background: Hyperuricemia is a putative risk factor for the progression of chronic kidney disease (CKD). We hypothesized that control of asymptomatic hyperuricemia may slow disease progression in CKD.

Study Design: This was a single-center, double-blind, randomized, parallel-group, placebo-controlled study.

Setting & Participants: Eligible participants were adults from Eastern India aged 18 to 65 years with CKD stages 3 and 4, with asymptomatic hyperuricemia.

Intervention: The intervention group received febuxostat, 40 mg, once daily for 6 months, while the placebo group received placebo; both groups were followed up for 6 months.

Outcomes: The primary outcome was the proportion of patients showing a >10% decline in estimated glomerular filtration rate (eGFR) from baseline in the febuxostat and placebo groups. Secondary outcomes included changes in eGFRs in the 2 groups from baseline and at the end of the study period.

Results: 45 patients in the febuxostat group and 48 in the placebo group were analyzed. Mean eGFR in the febuxostat group showed a nonsignificant increase from 31.5 ± 13.6 (SD) to 33.7 ± 16.6 mL/min/1.73 m^2 at 6 months. With placebo, mean eGFR decreased from a baseline of 32.6 ± 11.6 to 28.2 ± 11.5 mL/min/1.73 m^2 ($P = 0.003$). The difference between groups was 6.5 (95% CI, 0.08-12.81) mL/min/1.73 m^2 at 6 months ($P = 0.05$). 17 of 45 (38%) participants in the febuxostat group had a >10% decline in eGFR over baseline compared with 26 of 48 (54%) from the placebo group ($P < 0.004$).

Limitations: Limitations of this study included small numbers of patients and short follow-up, and ~10% of the randomly assigned population dropped out prior to completion.

Conclusions: Febuxostat slowed the decline in eGFR in CKD stages 3 and 4 compared to placebo.

Am J Kidney Dis. ■(■):■-■. © *2015 by the National Kidney Foundation, Inc.*

INDEX WORDS: Chronic kidney disease (CKD); hyperuricemia; uric acid; disease progression; febuxostat; xanthine oxidase inhibitor; renal function; estimated glomerular filtration rate (eGFR); randomized controlled trial (RCT).

Chronic kidney disease (CKD) has traditionally been considered to be an irreversible process, and patients who have it are often expected to experience a progressively worsening course. The rate of disease progression varies with the cause, and various therapeutic interventions, such as control of hypertension and proteinuria, have been shown to decrease it.

Hyperuricemia has been associated with adverse outcomes in CKD. Hyperuricemia has been linked to macrovascular heart disease in diabetic CKD.[1] High uric acid levels have been reported to be associated with increased rates of decline in glomerular filtration rate (GFR) in cross-sectional studies.[2,3]

Febuxostat is a xanthine oxidase inhibitor shown to be efficacious in hyperuricemia and gout.[4] It does not require dose modification in patients with kidney failure. Therapy with febuxostat has been shown to prevent renal damage in 5/6 nephrectomized rats.[5] The xanthine reductase inhibitor allopurinol has been shown to be effective in reducing lipid accumulation and atherosclerosis in apolipoprotein E (ApoE) knockout mice.[6] One randomized controlled trial has demonstrated the efficacy of allopurinol in reducing the rate of decline in GFR in patients with CKD with estimated GFRs (eGFRs) < 60 mL/min/1.73 m^2.[7] In this context, we hypothesized that febuxostat might retard the progression of kidney disease in patients with CKD and hyperuricemia.

The aims of the study were to determine the efficacy of febuxostat compared to placebo for slowing eGFR decline in patients with CKD stages 3 and 4 (eGFR, 15-60 mL/min/1.73 m^2) and asymptomatic

From the Departments of [1]Nephrology and [2]Pharmacology, Institute of Postgraduate Medical Education and Research (IPGMER), Kolkata; and [3]Department of Nephrology, Jawaharlal Nehru Institute of Medical Sciences, Imphal, Manipur, India.

Received August 25, 2014. Accepted in revised form May 7, 2015.

Trial registration: Clinical Trials Registry−India; study number: CTRI/2014/08/004853.

Address correspondence to Dipankar Sircar, MD, DM, 118/3B, B.L.Tala Road, Kolkata 700060, India. E-mail: deepsircar@gmail.com

0272-6386

http://dx.doi.org/10.1053/j.ajkd.2015.05.017

hyperuricemia (uric acid ≥ 7 mg/dL) and to compare the incidence of adverse cardiovascular events (myocardial infarction, cerebrovascular events, and heart failure), death, and hospitalization rates between the 2 groups. We also planned to compare treatment-associated emergent adverse events between the febuxostat and placebo groups and evaluate the reduction in serum uric acid levels in both groups.

METHODS

This was a single-center, double-blind, randomized, parallel-group, placebo-controlled study conducted in Eastern India. The study was approved by the IPGMER Research Oversight Committee (approval number Inst/IEC/1305). The participants gave written informed consent in accordance with the principles of the Declaration of Helsinki.

Eligible participants were patients of both sexes aged 18 to 65 years with eGFRs of 15 to 60 mL/min/1.73 m^2 (as calculated with the 4-variable MDRD [Modification of Diet in Renal Disease] Study equation). All had serum uric acid levels ≥ 7 mg/dL. Exclusion criteria were requirement of medication (excluding diuretics) or conditions that may increase uric acid levels, such as disorders of primary uric acid metabolism. Patients with autosomal dominant polycystic kidney disease were also excluded,[8] as well as those with pregnancy, lactation, and symptomatic hyperuricemia or gout.

The study was carried out in a government tertiary-care center in Kolkata, in Eastern India. This is a primary referral center for kidney disease from West Bengal. Total study duration was 18 months; patients were recruited from February 2012 through January 2013 and follow-up of the last patient ended in July 2013.

Patients randomly assigned to the study drug febuxostat received 40-mg tablets to be taken once daily after breakfast. Patients randomly assigned to placebo received tablets to be taken at the same time. Both groups received antihypertensive medication, including angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, unless there was a specific contraindication. Diuretics were administered as clinically indicated. Drugs and placebo were continued throughout the study period. Patients were evaluated at baseline and every 3 months for history, physical examination, assessment of any adverse events or end points, serum creatinine levels, uric acid levels, urine examination, and any other tests as needed by the treating clinician. Every patient had at least 3 serum creatinine measurements over the 6-month period. The intervention period and follow-up duration were at least 6 months for each patient.

The primary outcome was the proportion of patients showing a ≥10% decline in eGFR from baseline in the febuxostat and placebo populations.[9]

Secondary outcome measures were changes in eGFR in the 2 groups from baseline and at the end of the study period, cardiovascular events (myocardial infarction, stroke, or heart failure), death due to any cause, development of CKD stage 5 (eGFR decrease to <15 mL/min/1.73 m^2), changes in uric acid levels in the 2 populations, and development of any drug-related adverse events. Cardiovascular events were defined by hospital admissions with the diagnosis being reached with appropriate clinical and laboratory criteria.

The proportion of patients with a ≥10% decline in eGFR between the febuxostat and placebo groups was used as the primary efficacy variable for sample-size calculation. If it is hypothesized that this rate is 25% in the placebo group with an effect size of 20%, we calculated that we would need to recruit 49 individuals in each group with an equal allocation ratio to be able to reject the null hypothesis with power of 80% and type I error probability of 0.05. We have used an uncorrected χ^2 statistic to evaluate this null hypothesis. However, we proposed to recruit 54 individuals per group assuming a 10% dropout rate in order to achieve the desired sample size.

A computer-generated random-number table was used for allocation of individuals to the study drug and placebo in a 1:1 ratio.

Febuxostat and placebo were provided as white tablets identical in appearance and taste and were prepackaged in identical bottles. Allocation concealment was done by sealed sequentially numbered opaque envelopes. They were consecutively numbered and bottles were given out according to the number allocated to the participant. The investigator was blinded to the allotment as the procedure was carried out by a third person.

A modified intention-to-treat analysis was performed for efficacy and safety data. Individuals who attended the baseline and at least 2 postbaseline follow-up visits were considered for analysis. Summary statistics of numeric variables were expressed as mean ± standard deviation, and categorical data, as proportion. Baseline variables were compared between groups to detect any variability at baseline. To determine differences between groups of categorical data (eg, proportion with ≥10% decline in eGFR or proportion with cardiovascular adverse events), Fisher exact test or Pearson χ^2 test were used as applicable. Between-group comparison of numeric parametric data was done by unpaired t test. Within-group repeated-measure parametric data were compared for statistical significance using repeated-measure analysis of variance. The 95% confidence interval (CI) of the difference between mean values was determined and $P < 0.05$ was considered statistically significant.

RESULTS

Two hundred five patients were screened for initial enrolment (Fig 1) based on elevated uric acid values in previous laboratory reports. Fifty-four patients were enrolled in each arm, of whom 45 in the febuxostat group and 48 in the placebo group completed at least 2 visits and were available for analysis. Two individuals from the febuxostat group and 3 from the placebo

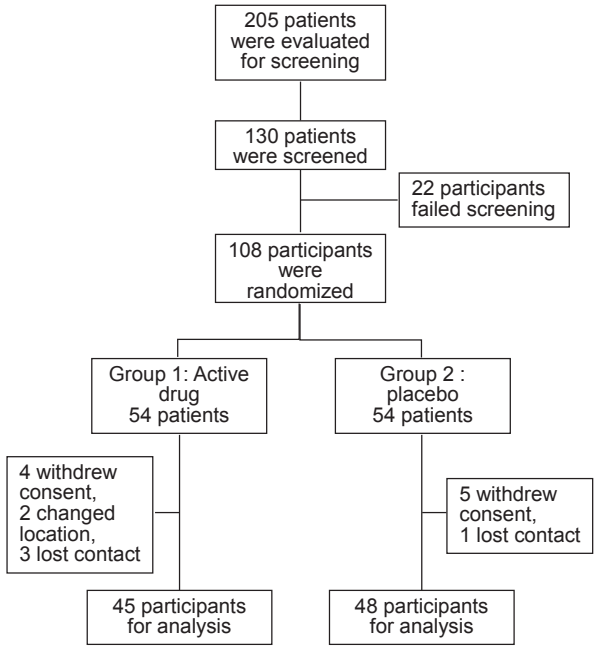

Figure 1. Flow diagram of single-center trial evaluating febuxostat in comparison to placebo in asymptomatic hyperuricemia in individuals with chronic kidney disease stages 3 to 4.