AJKD
Original Investigation

Allopurinol and Progression of CKD and Cardiovascular Events: Long-term Follow-up of a Randomized Clinical Trial

Marian Goicoechea, MD, PhD, Soledad Garcia de Vinuesa, MD, Ursula Verdalles, MD, Eduardo Verde, MD, Nicolas Macias, MD, Alba Santos, MD, Ana Pérez de Jose, MD, PhD, Santiago Cedeño, MD, Tania Linares, MD, and Jose Luño, MD, PhD

Background: Asymptomatic hyperuricemia increases renal and cardiovascular (CV) risk. We previously conducted a 2-year, single-blind, randomized, controlled trial of allopurinol treatment that showed improved estimated glomerular filtration rate and reduced CV risk.

Study Design: Post hoc analysis of a long-term follow-up after completion of the 2-year trial.

Setting & Participants: 113 participants (57 in the allopurinol group and 56 in the control group) initially followed up for 2 years and 107 participants followed up to 5 additional years.

Intervention: Continuation of allopurinol treatment, 100 mg/d, or standard treatment.

Outcome: Renal event (defined as starting dialysis therapy and/or doubling serum creatinine and/or ≥50% decrease in estimated estimated glomerular filtration rate) and CV events (defined as myocardial infarction, coronary revascularization or angina pectoris, congestive heart failure, cerebrovascular disease, and peripheral vascular disease).

Results: During initial follow-up, there were 2 renal and 7 CV events in the allopurinol group compared with 6 renal and 15 CV events in the control group. In the long-term follow-up period, 12 of 56 participants taking allopurinol stopped treatment and 10 of 51 control participants received allopurinol. During long-term follow-up, an additional 7 and 9 participants in the allopurinol group experienced a renal or CV event, respectively, and an additional 18 and 8 participants in the control group experienced a renal or CV event, respectively. Thus, during the initial and long-term follow-up (median, 84 months), 9 patients in the allopurinol group had a renal event compared with 24 patients in the control group (HR, 0.32; 95% CI, 0.15-0.69; $P = 0.004$; adjusted for age, sex, baseline kidney function, uric acid level, and renin-angiotensin-aldosterone system blockers). Overall, 16 patients treated with allopurinol experienced CV events compared with 23 in the control group (HR, 0.43; 95% CI, 0.21-0.88; $P = 0.02$; adjusted for age, sex, and baseline kidney function).

Limitations: Small sample size, single center, not double blind, post hoc follow-up and analysis.

Conclusions: Long-term treatment with allopurinol may slow the rate of progression of kidney disease and reduce CV risk.

Am J Kidney Dis. 65(4):543-549.

INDEX WORDS: Chronic kidney disease (CKD) progression; allopurinol treatment; hyperuricemia; uric acid concentration; cardiovascular (CV) risk; renal disease.

Editorial, p. 525

In a randomized study published in 2010, we demonstrated that treatment with allopurinol prevents progressive declines in glomerular filtration rate (GFR) in patients with chronic kidney disease (CKD).[1] In that study, 113 patients were randomly assigned to treatment with allopurinol or their standard medication (control group) and were followed up for 2 years. The main results were as follows: (1) treatment with allopurinol reduced levels of inflammatory markers and risk of hospitalization, (2) treatment with allopurinol decreased the risk of cardiovascular events in 71% of patients, (3) estimated GFR (eGFR) increased 1.2 mL/min/1.73 m^2 in the allopurinol treatment group and decreased 3.4 mL/min/1.73 m^2 in the control treatment group ($P = 0.02$), and (4) allopurinol led to a 47% reduction in progression of CKD (defined as a decrease in eGFR > 0.2 mL/min/1.73 m^2 per month).

Recent epidemiologic studies have shown a relationship between uric acid level and progression of kidney disease[2-6]; however, to our knowledge, no data have been published about the effect of decreasing uric acid levels with allopurinol on long-term progression of kidney disease.

We report a post hoc analysis of our previous study, including long-term follow-up for 5 additional years. Our aim was to determine whether continued lowering of serum uric acid levels with allopurinol

From the Department of Nephrology, Hospital General Universitario Gregorio Marañón, Madrid, Spain.

Received August 20, 2014. Accepted in revised form November 2, 2014. Originally published online January 13, 2015.

Address correspondence to Marian Goicoechea, MD, PhD, Department of Nephrology, Hospital General Universitario Gregorio Marañón, C/Dr Esquerdo 46, 28007 Madrid, Spain. E-mail: marian.goicoechea@gmail.com

0272-6386
http://dx.doi.org/10.1053/j.ajkd.2014.11.016

could maintain the positive effect of allopurinol on slowing progression of kidney disease.

METHODS

Study Design

The design of the previous randomized controlled trial (RCT) has been described elsewhere.[1] Briefly, 113 patients with eGFRs < 60 mL/min/1.73 m^2, stable clinical condition (no hospitalizations or cardiovascular events within the 3 months before screening), and stable kidney function were randomly assigned according to a computer-generated list to continue with their standard treatment (control group) or to treatment with allopurinol at 100 mg/d. The dosage of antihypertensive drugs, lipid-lowering agents, and antiplatelet drugs was continued with adjustment according to the individual patient's clinical condition. Participants were followed up for a mean of 23.4 ± 7.8 (standard deviation) months. The end points analyzed were as follows: (1) hospitalizations, (2) cardiovascular events (defined as myocardial infarction, coronary revascularization or angina pectoris, congestive heart failure, cerebrovascular disease, and peripheral vascular disease), (3) end-stage renal disease requiring dialysis therapy, and (4) mortality.

Congestive heart failure was diagnosed by x-ray examination (pulmonary edema) and echocardiogram (left ventricular dysfunction). Patients with congestive heart failure were considered symptomatic and in New York Heart Association class II to IV with left ventricular ejection fraction ≤ 45%. Patients were considered to have cerebrovascular disease when they had a history of ischemic or hemorrhagic stroke, transient ischemic attack (verified using computed tomography), or carotid artery stenosis > 70% (verified using Doppler ultrasound). The diagnosis of peripheral vascular disease was based on the presence of intermittent claudication, angiography or ultrasonography proven stenosis of the major arteries of the lower limbs, and ulcers caused by atherosclerotic disease or by surgery.

When the initial study finished, patients returned to community- or hospital-based nephrology care, with no attempt to maintain previously randomly assigned therapy; any changes in their treatment during the long-term follow-up period were made by their attending physicians. For the post hoc study, we redefined progression of kidney disease (renal event) as initiating dialysis therapy and/or doubling serum creatinine level and/or ≥50% decrease in eGFR. Cardiovascular events were defined as in the initial study. A compound outcome was analyzed as cardiovascular and/or renal event.

The same independent researcher (M.G.) assessed renal and cardiovascular events from the clinical history. The researcher obtained full documentation on all putative outcomes from hospitals. The researcher did not know whether the patient belonged to the allopurinol group or the control group.

Follow-up Assessment

Serum creatinine, uric acid, daily urinary protein excretion, hemoglobin, and C-reactive protein were monitored at least yearly after the trial. The isotope-dilution mass spectrometry–traceable 4-variable MDRD (Modification of Diet in Renal Disease) Study equation was used to estimate GFR. Routine clinical and biochemical variables were measured on autoanalyzers using standardized methods. High-sensitivity C-reactive protein in plasma was measured using a latex-based turbidimetric immunoassay on a Hitachi analyzer (Sigma Chemical Co). Daily urinary albumin excretion was measured using an immunonephelometric method.

Statistical Analysis

Statistical analysis was performed by intention to treat. All statistical analyses were performed using IBM SPSS, version 21.0 (IBM Corp) for Windows XP. Values are expressed as mean ± standard deviation or median with interquartile range. Categorical data were compared using χ^2 test; continuous variables, using *t* test. Two-way analysis of variance (ANOVA) was used to examine the influence of 2 different categorical independent variables on 1 dependent variable. Kaplan-Meier curves and log-rank test were used to analyze renal and cardiovascular survival. Cox proportional hazard models were used to evaluate the risk of cardiovascular events and progression of kidney disease, and results were adjusted for several covariates. Age, sex, and baseline kidney function were entered into the model as potential confounding covariates. Univariate Cox regression was used to determine which covariates should be introduced in the multivariable model. Statistical significance is defined as 2-tailed $P < 0.05$.

RESULTS

Patient Flow

Baseline characteristics, previous cardiovascular diseases, concomitant medication, and laboratory parameters have been described elsewhere[1] and are listed in Table 1. In the original study, 113 participants (57 in the allopurinol group and 56 in the control group) initially were followed up for 2 years. In the long-term follow-up reported here, 107 participants were followed up to 5 additional years (56 in the allopurinol group because 1 patient was lost to follow-up and 51 in the control group because 3 patients were lost to follow-up and 2 patients died). Overall median follow-up was 84 (interquartile range, 54-84) months from time of randomization. A patient flow chart (initial and post hoc study) is shown in Fig 1A and B.

During the long-term follow-up, 10 patients from the control group received allopurinol. Two patients in the allopurinol group stopped treatment during the RCT phase owing to gastrointestinal symptoms and 12 additional patients stopped treatment during the long-term follow-up owing to unknown cause.

Progression of Kidney Disease

After a median follow-up of 84 months, serum uric acid levels were significantly decreased in the allopurinol group, from 7.8 ± 2.1 to 6.6 ± 1.5 mg/dL ($P = 0.04$), but were unchanged throughout the study in the control group (baseline, 7.3 ± 1.6 mg/dL; 84 months, 7.1 ± 1.35 mg/dL). eGFRs in the allopurinol and control groups decreased by 6.5 ± 1.6 and 13.3 ± 5.0 mL/min/1.73 m^2, respectively, after 84 months ($P = 0.001$). eGFRs decreased over time ($P = 0.001$), and this decrease differed significantly between groups ($P = 0.001$; 2-way ANOVA). Follow-up averages of uric acid and eGFR values during the RCT and long-term follow-up are shown in Table S1.

In a post hoc analysis of the initial study, a renal event (initiating dialysis therapy and/or doubling serum creatinine and/or ≥50% decrease in eGFR)