Rheumatology 2009;48:804–806
Advance Access publication 15 May 2009
doi:10.1093/rheumatology/kep069

Concise Report

Allopurinol and mortality in hyperuricaemic patients

Andrew J. Luk[1], Gregory P. Levin[2], Elya E. Moore[3], Xiao-Hua Zhou[1], Bryan R. Kestenbaum[4] and Hyon K. Choi[5]

Objectives. While studies have suggested that gout and hyperuricaemia are associated with the risk of premature death, none has investigated the role of urate-lowering therapy on this critical outcome. We examined the impact of allopurinol, the most commonly used urate-lowering drug, on the risk of mortality in hyperuricaemic patients.

Methods. From a population of hyperuricaemic veterans of [serum urate level >416 μmol/l (7.0 mg/dl)] at least 40 years of age, we compared the risk of death between incident allopurinol users ($n = 2483$) and non-users ($n = 7441$). We estimated the multivariate mortality hazard ratio (HR) of allopurinol use with Cox proportional hazards models.

Results. Of the 9924 veterans (males, 98% and mean age 62.7 years), 1021 died during the follow-up. Patients who began treatment with allopurinol had worse prognostic factors for mortality, including higher BMI and comorbidities. After adjusting for baseline urate levels, allopurinol treatment was associated with a lower risk of all-cause mortality (HR 0.78; 95% CI 0.67, 0.91). Further adjustment with other prognostic factors did not appreciably alter this estimate (HR 0.77; 95% CI 0.65, 0.91). The mean change from baseline in serum urate within the allopurinol group was −111 μmol/l (−1.86 mg/dl). Adjusting for baseline urate level, allopurinol users had a 40 μmol/l (0.68 mg/dl) lower follow-up serum urate value than controls (95% CI −0.55, −0.81).

Conclusion. Our findings indicate that allopurinol treatment may provide a survival benefit among patients with hyperuricaemia.

Key words: Allopurinol, Mortality, Hyperuricaemia, Gout.

Introduction

Hyperuricaemia, the culprit of gout pathogenesis, is associated with cardiovascular disease (CVD) in humans, although whether it is an independent risk factor with a pathogenic role in CVD or only a marker for associated CVD risk factors, such as insulin resistance, obesity, diuretic use, hypertension and renal disease, remains unclear [1–3]. Recently, large-scale epidemiological studies found that individuals with gout have a higher risk of premature death [1, 4, 5]. For example, compared with men without gout, men with gout had a 28% increased risk of death, independent of other mortality risk factors [1]. Furthermore, an extension study of a large clinical trial found that a diagnosis of gout accompanied by hyperuricaemia is associated with increased risk of all-cause mortality that arises largely from an increased risk of CVD mortality [4]. While these data suggest that gout and hyperuricaemia increase the risk of death, no study has investigated the role of urate-lowering therapy on mortality. We performed a cohort study of hyperuricaemic patients enrolled in veterans affairs (VA) medical centres in the Pacific Northwest, to ascertain if allopurinol, the most commonly used urate-lowering agent, was associated with a decreased risk of mortality.

Methods

Study population

We used the VA Consumer Health Information and Performance Sets (CHIPS) database, which maintains data on demographics, diagnostic codes, vital status, prescriptions, healthcare utilization, laboratory tests and medical procedures for all outpatient and inpatient VA patient encounters [6, 7]. The source population consists of veterans ⩾40 years of age within the Northwest Veterans Integrated Service Network (a collection of eight VA facilities located in Washington State, Idaho, Oregon and Alaska) [6, 7]. From this source population, a hyperuricaemic population was selected, defined as having at least one outpatient serum urate level >416 μmol/l (7.0 mg/dl) between the years 2000 and 2007. Subjects were excluded if they had an estimated glomerular filtration rate (GFR) of <30 ml/min (estimated according to the Modification of Diet in Renal Disease Equation), prior dialysis or renal/organ transplantation, or history of malignancy.

We then defined a cohort of hyperuricaemic subjects treated with allopurinol (allopurinol group) on the basis of (i) incident allopurinol use between 1 January 2000 and 31 December 2007 and (ii) an outpatient serum urate level >416 μmol/l (7.0 mg/dl) within 1 year prior to allopurinol initiation. Three non-allopurinol-treated control subjects were identified for each allopurinol user, on the basis of (i) being alive and at-risk at the time the allopurinol-treated subject initiated allopurinol (index time) and (ii) having hyperuricaemia (as defined above) during the previous year.

The Institutional Review Board of the University of Washington approved this study and waived informed consent.

Statistical analyses

The primary outcome of interest was all-cause mortality. Both allopurinol and control subjects began accruing risk time beginning with the time of incident allopurinol use in the allopurinol group and index time in the control group, and were followed until death, study closure or no further contact with the VA for 18 consecutive months.

Cox proportional hazards models, with robust standard errors, were used to estimate the independent association between allopurinol exposure and the risk of death. Multivariate models adjusted for demographics (age, race and gender), BMI,

[1]Veterans Affairs Puget Sound Health Care System, [2]Department of Biostatistics, [3]Department of Epidemiology, [4]Department of Medicine, University of Washington, Seattle, WA, USA and [5]Department of Medicine, Division of Rheumatology, University of British Columbia, Arthritis Research Centre of Canada, Vancouver, Canada.

Submitted 18 December 2008; revised version accepted 6 March 2009.

Correspondence to: Hyon K. Choi, Department of Medicine, Division of Rheumatology, University of British Columbia, Arthritis Research Centre of Canada, 895 West 10th Avenue, Vancouver, BC V5Z 1L7, Canada.
E-mail: hchoi@arthritisresearch.ca

comorbidities (as defined by ICD-9 CM codes for hypertension, diabetes and CVD), healthcare utilization (as defined by number of previous primary care or internal medicine visits at baseline), use of cardiovascular and other medications [statins, fibrates, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), β-blockers, calcium channel blockers, low-dose aspirin, NSAIDs, loop diuretics, hydrochlorothiazide (HCTZ) and losartan], baseline serum levels of urate, cholesterol, albumin and baseline GFR. The multivariate models also adjusted for the Charlson index [8], which is a composite index of diagnoses that includes myocardial infarction, congestive heart failure (CHF), peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, peptic ulcer disease, liver disease, diabetes with complications, renal disease, cancer and AIDS/HIV. Multivariate models were stratified by individual VA site.

In order to approximate the 'intent-to-treat' design of a clinical trial, subjects were analysed according to whether or not they initiated allopurinol use at study baseline, regardless of whether they stopped or started allopurinol during follow-up. As a sensitivity analysis, we used an 'as-treated' model, where control subjects were censored upon initiation of allopurinol use.

The association between allopurinol use and follow-up serum urate level was assessed using linear regression, adjusting for baseline urate level. Follow-up serum urate level was defined as the latest outpatient measurement in the first 6 months of follow-up after allopurinol initiation. The groups were also compared with respect to the mean change between baseline and follow-up serum urate levels. All analyses were performed using Stata 9.2 software (STATA Corp., College Station, TX, USA; 2007).

Results

The cohort consisted of 9924 veterans, with 2483 subjects in the allopurinol group and 7441 in the control group. There were 745 deaths in the control group and 276 deaths in the allopurinol group during 23 903 person-years of follow-up. The cohort comprised almost entirely of males (98%), and the majority of subjects with race recorded were white (88%) (Table 1). The mean age was 62.7 years, with a range from 40 to 93 years. Compared with the control cohort, the allopurinol group had a higher BMI and an increased prevalence of hypertension, CVD and diabetes, along with an overall greater burden of comorbidities, as defined by the Charlson index (Table 1). The number of primary care or internal medicine visits, along with the use of cardiovascular medications, especially loop and thiazide diuretics, were also higher in the allopurinol cohort. Notably, 83% of the allopurinol users had a gout diagnosis, compared with 20% of the control group, suggesting that allopurinol was mainly used to prevent gout attacks. The allopurinol group had a higher baseline urate level than the control group [535 μmol/l (9.0 mg/dl) *vs* 488 μmol/l (8.2 mg/dl)] and a lower GFR (69.8 *vs* 75.1).

Mean follow-up serum urate levels were 428 and 446 μmol/l (7.2 and 7.5 mg/dl) in the allopurinol and control groups, respectively. Adjusting for baseline urate level, allopurinol users had a 40 μmol/l (0.68 mg/dl) lower follow-up serum urate value than controls [95% CI -33, -48 μmol/l (-0.55, -0.81 mg/dl)]. The mean change from baseline in serum urate within the allopurinol group was -111 μmol/l (-1.86 mg/dl).

After adjusting for baseline urate levels, allopurinol treatment was associated with a lower risk of all-cause mortality [hazard ratio (HR) 0.78; 95% CI 0.67, 0.91)] (Table 2). Further stepwise adjustment for potential confounders such as demographics, comorbidities, healthcare utilization, cardiovascular and other medications and baseline cholesterol, albumin and GFR did not appreciably alter the HR (0.77; 95% CI 0.65, 0.91) (Table 2). Results from an as-treated model were slightly stronger (HR 0.73; 95% CI 0.62, 0.86).

Table 1. Baseline characteristics according to incident allopurinol use

	Control group ($n=7441$)	Allopurinol group ($n=2483$)
Demographics		
Age, mean ± S.D., years	62.3 ± 11.4	64.2 ± 11.1
Race, %		
Caucasian	88	88
African–American	8	9
Other	3	4
Male, %	98	99
Measures of comorbidity		
BMI, mean ± S.D.	31.6 ± 6.0	32.5 ± 6.3
Hypertension, %	70	81
CVD, %	15	18
Diabetes, %	24	28
Gout, %	20	83
Charlson index, mean ± S.D.	0.7 ± 1.3	1.2 ± 1.5
No. of previous primary care or internal medicine visits, %		
0	6	2
1–2	28	21
3–7	48	50
8+	18	26
Medications, %		
Statins	38	44
Fibrates	5	8
ACE inhibitors	38	49
ARBs	6	9
β-Blockers	33	46
Calcium channel blockers	18	26
Aspirin	17	21
NSAIDs	25	50
Loop diuretics	14	26
HCTZ	26	34
Losartan	2	3
Insulin	5	7
Baseline laboratory measurements		
Urate, mean ± S.D., μmol/l	488 ± 59	535 ± 83
Cholesterol, mean ± S.D., mmol/l	5.09 ± 1.12	5.02 ± 1.09
GFR, mean ± S.D., ml/min/1.73 m^2	75.1 ± 20.0	69.8 ± 21.2
Albumin, mean ± S.D., g/l	43 ± 4	43 ± 4

Table 2. HRs for all-cause death comparing allopurinol users with controls

	Control group	Allopurinol group
Number of deaths from all causes	745	276
HRs (95% CI)		
Adjusting for baseline urate level	1.0 (referent)	0.78 (0.67, 0.91)
+ Age, race, BMI, sex	1.0 (referent)	0.79 (0.68, 0.92)
+ Comborbidities, health care utilization	1.0 (referent)	0.74 (0.63, 0.87)
+ Cardiovascular and other medications	1.0 (referent)	0.74 (0.63, 0.87)
+ Baseline cholesterol, albumin, GFR	1.0 (referent)	0.77 (0.65, 0.91)

The variables are added at every level of the iteration.

Discussion

In this large cohort study of hyperuricaemic veterans, we found that the use of allopurinol was associated with a 23% lower mortality rate. This association was independent of age, sex, race, BMI, relevant comorbidities, healthcare utilization, use of cardiovascular and other medications, serum levels of urate, cholesterol, albumin and GFR. The magnitude of the risk reduction is comparable with that of established cardiovascular drugs, such as ACE inhibitors, ARBs and β-blockers [9]. Furthermore, this level of risk reduction could substantially reduce the risk of premature death due to gout reported in the literature (a 9–28% risk increase [1, 4]). To our knowledge, this is the first study to show a survival benefit of allopurinol, the most commonly used urate-lowering agent.

It remains unclear if the survival benefit is entirely due to the urate-lowering effect of allopurinol, or to other beneficial effects of the drug [10–14]. For example, the effect of allopurinol or its metabolite oxypurinol on cardiovascular function has been tested in a number of studies [11–18]. When endothelial function was

measured by changes in arterial response using various methods, allopurinol or oxypurinol was shown to improve endothelial function in patients with hypertension, type II diabetes and dyslipidaemia, in smokers, in hyperuricaemic patients with elevated cardiovascular risk and in patients with established coronary artery disease, compared with controls [12, 14–16]. Similarly, trials of xanthine oxidase (XO) inhibition in CHF showed improvement in endothelial function and myocardial efficiency and lowered B-type natriuretic peptide concentrations [11, 13, 17, 18]. In some studies, a single dose of allopurinol or oxypurinol was used, suggesting that the mechanism of action is XO inhibition rather than the urate-lowering effect. Due to allopurinol's action on both urate levels and XO activity, low-cost, generally good side-effect profile and its extensive history of use, it is considered to be the urate-lowering agent of choice for clinical trials of potential cardiovascular risk reduction [9].

Several potential limitations of our study deserve comment. We could not examine if the observed survival benefit associated with allopurinol use reflects a decline in cardiovascular death, because information on specific cause of death is not available in the CHIPS database. However, because the excess mortality risk observed among gout patients was due to increased cardiovascular death [1, 4], the potential survival benefit due to allopurinol would likely come from preventing excess cardiovascular death. Nevertheless, this explanation calls for direct confirmation in future studies examining specific cause of death. In a pharmacoepidemiological study such as ours, confounding by indication may bias the results. Indeed, allopurinol users had worse mortality risk profile including higher adiposity, a greater burden of comorbidities, higher baseline serum urate and lower GFR. Thus, these individuals would have been at greater mortality risk than non-allopurinol-treated hyperuricaemic patients. Any residual confounding by indication beyond our multivariate adjustment would likely have biased the association towards the null, making our estimates conservative. The veteran population is generally considered at high risk for cardiovascular mortality by virtue of the high prevalence of risk factors such as older age, male gender, metabolic syndrome and hyperuricaemia; thus, the generalizability of our findings to a younger, healthier population with more women is not clear, and will need to be studied. Finally, our study was observational; thus, we cannot rule out the possibility that unmeasured factors might contribute to the observed associations.

In conclusion, this cohort study of veterans suggests that allopurinol use may provide a survival benefit in hyperuricaemic patients. While this first large-scale study on the topic is encouraging, it remains premature to advocate the use of allopurinol for cardiovascular prophylaxis. Nonetheless, our findings provide justification for further prospective studies of urate-lowering therapy for the prevention of premature death in hyperuricaemic patients.

Rheumatology key message

- Allopurinol treatment may provide a survival benefit among patients with hyperuricaemia.

Acknowledgements

H.K.C. holds the Mary Pack Arthritis Society of Canada Chair in Rheumatology. The views expressed in this abstract are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs. This was an investigator-initiated research project funded by Takeda Pharmaceuticals North America, Inc. The funding source had no role in the study design, data collection, analysis or interpretation of the data in this manuscript.

Funding: Supported by a grant from Takeda Pharmaceuticals North America, Inc.

Disclosure statement: H.K.C. served on the advisory board for Takeda and Savient Pharmaceuticals. All other authors have declared no conflicts of interest.

References

1 Choi HK, Curhan G. Independent impact of gout on mortality and risk for coronary heart disease. Circulation 2007;116:894–900.
2 Oparil S, Zaman MA, Calhoun DA. Pathogenesis of hypertension. Ann Intern Med 2003;139:761–6.
3 Johnson RJ, Kang DH, Feig D *et al.* Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? Hypertension 2003;41:1183–90.
4 Krishnan E, Svendsen K, Neaton JD, Grandits G, Kuller LH. Long-term cardiovascular mortality among middle-aged men with gout. Arch Intern Med 2008;168:1104–10.
5 Cohen SD, Kimmel PL, Neff R, Agodoa L, Abbott KC. Association of incident gout and mortality in dialysis patients. J Am Soc Nephrol 2008;19:2204–10.
6 Au DH, Udris EM, Fan VS, Curtis JR, McDonell MB, Fihn SD. Risk of mortality and heart failure exacerbations associated with inhaled beta-adrenoceptor agonists among patients with known left ventricular systolic dysfunction. Chest 2003;123:1964–9.
7 Maynard C, Chapko MK. Data resources in the Department of Veterans Affairs. Diabetes Care 2004;27(Suppl. 2):B22–6.
8 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.
9 Dawson J, Quinn T, Walters M. Uric acid reduction: a new paradigm in the management of cardiovascular risk? Curr Med Chem 2007;14:1879–86.
10 George J, Carr E, Davies J, Belch JJ, Struthers A. High-dose allopurinol improves endothelial function by profoundly reducing vascular oxidative stress and not by lowering uric acid. Circulation 2006;114:2508–16.
11 Farquharson CA, Butler R, Hill A, Belch JJ, Struthers AD. Allopurinol improves endothelial dysfunction in chronic heart failure. Circulation 2002;106:221–6.
12 Butler R, Morris AD, Belch JJ, Hill A, Struthers AD. Allopurinol normalizes endothelial dysfunction in type 2 diabetics with mild hypertension. Hypertension 2000;35:746–51.
13 Doehner W, Schoene N, Rauchhaus M *et al.* Effects of xanthine oxidase inhibition with allopurinol on endothelial function and peripheral blood flow in hyperuricemic patients with chronic heart failure: results from 2 placebo-controlled studies. Circulation 2002;105:2619–24.
14 Guthikonda S, Sinkey C, Barenz T, Haynes WG. Xanthine oxidase inhibition reverses endothelial dysfunction in heavy smokers. Circulation 2003;107:416–21.
15 Cardillo C, Kilcoyne CM, Cannon RO 3rd, Quyyumi AA, Panza JA. Xanthine oxidase inhibition with oxypurinol improves endothelial vasodilator function in hypercholesterolemic but not in hypertensive patients. Hypertension 1997;30:57–63.
16 Mercuro G, Vitale C, Cerquetani E *et al.* Effect of hyperuricemia upon endothelial function in patients at increased cardiovascular risk. Am J Cardiol 2004;94:932–5.
17 Cappola TP, Kass DA, Nelson GS *et al.* Allopurinol improves myocardial efficiency in patients with idiopathic dilated cardiomyopathy. Circulation 2001;104:2407–11.
18 Gavin AD, Struthers AD. Allopurinol reduces B-type natriuretic peptide concentrations and haemoglobin but does not alter exercise capacity in chronic heart failure. Heart 2005;91:749–53.