RHEUMATOLOGY

Rheumatology 2015;54:2145–2150
doi:10.1093/rheumatology/kev246
Advance Access publication 12 July 2015

Concise report

Effect of allopurinol on all-cause mortality in adults with incident gout: propensity score–matched landmark analysis

Chang-Fu Kuo[1,2], Matthew J. Grainge[3], Christian Mallen[4], Weiya Zhang[1] and Michael Doherty[1]

Abstract

Objective. To examine the association between allopurinol use and all-cause mortality for patients with incident gout.

Methods. We compared all-cause mortality in incident gout patients who received allopurinol for at least 6 months within the exposure window (1 year or 3 years) with those who did not, using the UK Clinical Practice Research Data-link. Landmark analysis was used to account for immortal time bias and propensity score matching was used to control for potential effects of known confounders.

Results. Of 23 332 incident gout patients identified, the propensity score–matched cohorts contained 1016 patients exposed to allopurinol on the date 1 year from diagnosis (landmark date) and 1016 allopurinol non-users. Over a median follow-up period of 10 years after the landmark date, there were 437 allopurinol users and 443 allopurinol non-users who died during follow-up. Allopurinol users and non-users had similar risk for all-cause mortality (hazard ratio 0.99; 95% CI 0.87, 1.12). In the 3-year landmark analysis, 3519 allopurinol users (1280 died) were compared with 3519 non-users (1265 died). The hazard ratio for all-cause mortality was 1.01 (95% CI 0.92, 1.09).

Conclusion. This propensity score–matched landmark analysis in a population of incident gout patients in the UK primary care setting found a neutral effect on the risk of all-cause mortality. Our study provides reassurance about the prescription of allopurinol for gout patients early in their disease course to prevent untoward consequences of chronic uncontrolled hyperuricaemia. However, whether higher than the commonly used dose of allopurinol could influence mortality remains to be determined.

Key words: gout, allopurinol, mortality, propensity score, landmark analysis.

CLINICAL SCIENCE

Rheumatology key messages

- Allopurinol is the most commonly used urate-lowering agent for long-term management of chronic gout.
- Allopurinol use in the early course of gout did not increase mortality.
- The influence of higher doses of allopurinol on gout patient mortality requires further study.

Introduction

Gout is the most common inflammatory arthritis, with a rising worldwide prevalence [1]. The hallmark of initial gout presentation is acute arthritis, but patients eventually experience unremitting arthritis and joint deformity, and tophus deposition may develop with long-standing hyperuricaemia [2]. Patients with gout suffer not only arthritis but also cardiovascular, renal, metabolic and other comorbidities [3]. Collectively, gout and associated comorbidities lead to reduced overall survival [4].

[1]Division of Rheumatology, Orthopaedics and Dermatology, School of Medicine, University of Nottingham, Nottingham, UK, [2]Division of Rheumatology, Allergy and Immunology, Chang Gung Memorial Hospital, Taoyuan, Taiwan, [3]Division of Epidemiology and Public Health, School of Medicine, University of Nottingham, Nottingham and [4]Arthritis Research UK Primary Care Centre, Keele University, Keele, UK

Submitted 26 January 2015; revised version accepted 29 May 2015

Correspondence to: Weiya Zhang, Academic Rheumatology, Clinical Sciences Building, City Hospital, Nottingham NG5 1PB, UK.
E-mail: weiya.zhang@nottingham.ac.uk

Allopurinol, with its primary mechanism of inhibiting the activity of xanthine oxidase, is currently the first-line urate-lowering treatment recommended in European guidelines for gout. However, only around one-third of gout patients receive allopurinol in the UK [5], and those are mainly on a fixed dose of 300 mg, which is probably insufficient for most patents. This is despite its reasonable safety profile and probable additional beneficial effects on chronic diseases such as hypertension, heart failure and stroke [6].

Despite generally being well tolerated, allopurinol has been associated with Steven–Johnson syndrome and toxic epidermal necrolysis [7], which is potentially life threatening. Although rare, this serious adverse event has become one of the barriers to prescription of allopurinol for gout [8]. Whether the balance of these potential benefits and risks can translate to any influence on survival in gout patients remains unclear. Therefore, we undertook this study to assess the association between allopurinol use and long-term mortality in patients with gout using the UK Clinical Practice Research Data-link (CPRD).

Methods

Data source

The CPRD is an anonymized database containing prospectively collected medical records from ~12 million individuals in the UK. The database has been validated for many diagnoses [9]. The database contains comprehensive information on patient demographics, date of death, lifestyle factors, medical diagnoses, results of laboratory tests and examinations, and medications prescribed. In addition, the CPRD is also linked to external data sources that provide information on secondary care admissions, mortality and specific disease audits. The study was approved by the Trent Multi-centre Research Ethics Committee and the Independent Scientific Advisory Committee.

Cohort

We used READ codes to identify incident gout patients in the CPRD between 1995 and 1999. To be eligible as incident gout patients, participants had to be older than 20 years of age, have no evidence of gout or prescription for urate-lowering treatment (mostly allopurinol) prior to the time of diagnosis (index date) and have at least 1-year registration prior to index date. The case definition was based on physician diagnosis, using 18 Read codes indicative of incident gout [10]. The validity of a gout diagnosis in the CPRD has been demonstrated previously [11].

Exposure

We classified patients by exposure to allopurinol. A minimum of 6 months prescription of allopurinol was required for assignment of allopurinol exposure. The prescription of allopurinol largely lags behind the time of first diagnosis [5]. Therefore, the completion of 6 months of allopurinol therapy in relation to the date of gout diagnosis is likely to vary considerably from person to person. In this study, we utilized a landmark analysis to examine the effect of allopurinol exposure on all-cause mortality [12]. In a landmark analysis, a fixed time after cohort entry was selected *a priori* for conducting survival analysis. Only patients alive at the date of the landmark were included in the analysis, and treatment assignment was based on exposure prior to the landmark date. Exposure was only evaluated between the index date and the landmark time point (exposure window), and the outcome was then evaluated from this landmark time point. Two landmark time points were determined *a priori* in this study, specifically at 1 and at 3 years after initial gout diagnosis (supplementary Fig. S1A, available at *Rheumatology* Online). Exposure status was assigned for patients who were alive at the landmark dates.

Covariates

Covariates included patient characteristics, lifestyle factors, 17 categories of comorbidity and drug treatments (supplementary data, section on covariates, available at *Rheumatology* Online). Only general practitioner records occurring within the 5-year period before initial diagnosis of gout were used to evaluate comorbidities and drug treatment.

Outcomes

Patients were followed up until the date of death, transfer out from a participating CPRD practice, or 31 December 2013, whichever was earliest (supplementary Fig. S1B, available at *Rheumatology* Online). Mortality and date of death were assessed using the main CPRD database. We have undertaken a validation study comparing death recordings in the CPRD and National Death Registry and found the sensitivity, specificity, positive predictive value and negative predictive value of a CPRD-recorded death to be 0.99, 0.99, 0.93 and 1.00, respectively (supplementary Table S1, available at *Rheumatology* Online) [5].

Statistical analysis

We utilized propensity score–matching methods to account for confounding by indication [13]. The propensity score for allopurinol use represents the probability that a patient is prescribed ($\geqslant$6 months) allopurinol treatment. We used logistic regression models to determine a propensity score for receiving at least 6 months allopurinol during the exposure window (supplementary data, section on propensity score adjustment analysis, available at *Rheumatology* Online). In our primary analysis we matched the allopurinol-exposed patients to unexposed patients in a ratio of 1 to 1, based on the logit of the propensity score using callipers of width equal to 0.2 of the S.D. of the logit of the propensity score. Kaplan–Meier plots were used to estimate the cumulative probability of survival. The hazard ratio for mortality was determined using the Cox proportional hazards model. As a sensitivity analysis, we included the entire cohort and adjusted for the raw propensity score (supplementary data, section on propensity score adjustment analysis, available at

Rheumatology Online). All statistical analyses were performed using SAS statistical software, version 9.3.

Results

Study population

Between January 1995 and December 1999, we identified 23 332 incident gout patients [men: 17 197 (73.91%)]. Due to transferring out or death, 1385 patients were excluded from the 1-year landmark analysis and 3783 patients were excluded from the 3-year landmark analysis (supplementary Fig. S1A, available at *Rheumatology* Online). Supplementary Table S2, available at *Rheumatology* Online, summarizes and compares baseline characteristics between included and excluded patients in the 1-year and 3-year landmark analyses. In general, those excluded were older and had a higher Charlson comorbidity index. These differences were similar in the 1-year and 3-year landmark analyses.

Matching

For the 1-year landmark analysis, we included 21 947 patients who were alive at 1 year from initial diagnosis of gout. Among them, 1016 patients had at least 6 months of allopurinol prescription. No significant differences were found in variables included in the propensity score calculation between allopurinol users and non-users after matching, confirming the success of our matching (Table 1). Supplementary Table S3, available at *Rheumatology* Online, shows the comparison of variables between allopurinol users and non-users in the 3-year landmark analysis.

Outcomes after matching

As shown in Table 2, a total of 880 patients in the 1-year landmark analysis and 2546 patients in the 3-year landmark analysis died during the follow-up period. No significant difference was found for overall mortality rate between allopurinol users and non-users in either the 1-year or the 3 year landmark analysis. There was no difference in survival based on Kaplan–Meier estimates between allopurinol users and non-users in either the 1-year (log-rank test $P = 0.84$) or the 3-year landmark analysis (log-rank test $P = 0.94$) (supplementary Fig. S2, available at *Rheumatology* Online). Hazard ratios for all-cause mortality were 0.99 (95% CI 0.87, 1.12) in the 1-year landmark analysis and 1.01 (95% CI 0.92, 1.09) in the 3-year landmark analysis.

Discussion

This population-based study of incident gout patients found that having at least 6 months use of allopurinol within either 1 year or 3 years from initial diagnosis was associated with neither a beneficial nor an adverse effect on the long-term risk of all-cause mortality in patients who survived to the date of the landmark time point. Our study suggests that concern over an increased mortality risk from taking allopurinol is unfounded. Given the many established clinical benefits of allopurinol, such a neutral effect on all-cause mortality supports the use of allopurinol early in the course of gout to prevent long-term complications secondary to chronic hyperuricaemia.

This study used a well-defined population of incident gout patients to determine whether allopurinol treatment influences all-cause mortality. However, the date of allopurinol prescription largely lags behind the initial diagnosis of gout [10]. Using diagnosis date as an index date to start the follow-up for a delayed treatment in a cohort study is prone to immortal time bias, which could confer a spurious survival advantage to the treatment group [14]. A landmark analysis, as in our study, has been devised to avoid this [12]. Another important factor that could influence comparison of survival function between patients exposed and those not exposed to allopurinol is confounding by indication, which is the result of non-random allocation of treatment assignment. General practitioners tended to prescribe allopurinol for patients of more advanced age, more comorbidity and more polypharmacy, who already have higher mortality. Therefore, an unadjusted model demonstrated a higher mortality risk in the allopurinol exposure group. To minimize this bias, we used propensity score matching to balance the probability of being prescribed allopurinol in our exposure window. Analyses based on both methods produced the same neutral influence of allopurinol on long-term risk of all-cause mortality.

Several previous studies have attempted to measure the influence of allopurinol treatment on mortality, but have reported conflicting results [15–19]. These studies in general ignored or only in part considered immortal time bias and confounding by indication. Immortal time bias generally causes spurious inflation of the beneficial treatment effect due to the guaranteed period of survival in the treatment group by design. Conversely, confounding by indication generally favours the unexposed group, because treated patients tend to have a poorer prognosis. For example, Málek *et al*. [15] reported poorer survival in allopurinol-treated patients in a cohort of acute heart failure patients hospitalized in specialized heart centres, but noted that allopurinol was an identifier of high-risk patients who obviously had a particularly bad prognosis.

Immortal time bias is more difficult to identify than confounding by indication. For example, Luk *et al*. [17] reported that allopurinol use was associated with a beneficial effect on mortality in a hyperuricaemic population by comparing survival of users and non-users. However, allopurinol users commenced follow-up from the time of incident allopurinol use, at which time they had survived from the date of first documentation of hyperuricaemia, whereas the follow-up of non-users could have been as early as the date of first documentation of hyperuricaemia. Although they matched the index date between users and non-users, it did not mean that they matched the time from diagnosis of hyperuricaemia to the index date between the two groups. Allopurinol users were still more likely to have a spurious survival advantage because by design they had to survive to the date of first allopurinol

Table 1 Comparison of patients exposed or not exposed to allopurinol within 1 year of initial diagnosis of gout before and after matching

	Exposure groups before matching			Exposure groups after matching		
	Allopurinol users ($n = 1016$)	Allopurinol non-users ($n = 20\,931$)	*P*-value	Allopurinol users ($n = 1016$)	Allopurinol non-users ($n = 1016$)	*P*-value
Age, median (interquartile range), years	66 (56–74)	61 (49–73)	<0.001	66 (55–75)	66 (56–74)	0.87
Gender						
Men	665 (65.45)	15 611 (74.58)	<0.001	665 (65.45)	655 (64.47)	0.64
Women	351 (34.55)	5320 (25.42)		351 (34.55)	361 (35.53)	
BMI, kg/m^2						
<18.5	2 (0.20)	144 (0.69)	<0.001	2 (0.20)	2 (0.20)	0.89
18.5–24.9	206 (20.28)	4472 (21.37)		206 (20.28)	223 (21.95)	
25.0–29.9	375 (36.97)	8161 (38.99)		375 (36.97)	351 (34.55)	
⩾30	352 (34.65)	5537 (26.45)		352 (34.65)	357 (35.14)	
Unknown	81 (7.97)	2617 (12.50		81 (7.97)	83 (8.17)	
Smoking						
Non-smoker	132 (12.99)	2391 (11.42)	<0.001	132 (12.99)	135 (13.29)	0.72
Current smoker	96 (9.45)	1708 (8.16)		96 (9.45)	112 (11.02)	
Ex-smoker	638 (62.80)	12 421(59.34)		638 (62.80)	613 (60.33)	
Unknown	150 (14.76	4411 (21.07)		150 (14.76	156 (15.35)	
Alcohol consumption, units/week						
Never/ex-drinker	158 (15.55)	2141 (10.23)	<0.001	158 (15.55)	167 (16.44)	0.80
Current 1–9	435 (42.81)	7986 (38.15)		435 (42.81)	444 (43.70)	
Current ⩾10	211 (20.77)	5070 (24.22)		211 (20.77)	188 (18.50)	
Unknown	212 (20.87)	5734 (27.39)		212 (20.87)	217 (21.36)	
Charlson comorbidity index						
0	600 (59.06)	14 975 (71.54)	<0.001	600 (59.06)	591 (58.17)	0.84
1–2	330 (32.48)	5054 (24.15)		330 (32.48)	341 (33.56)	
3–4	82 (8.07)	865 (4.13)		82 (8.07)	81 (7.97)	
⩾4	4 (0.39)	37 (0.18)		4 (0.39)	3 (0.30)	
Medications						
Aspirin	295 (29.04)	3455 (16.51)	<0.001	295 (29.04)	296 (29.13)	0.96
Statin	94 (9.25)	892 (4.23)	<0.001	94 (9.25)	86 (8.46)	0.53
Diuretics	622 (61.22)	7401 (35.36)	<0.001	622 (61.22)	617 (60.73)	0.82
Insulin	10 (0.98)	93 (0.44)	0.01	10 (0.98)	15 (1.48)	0.31
NSAID	773 (76.08)	15 272 (72.96)	0.03	773 (76.08)	789 (77.36)	0.50

Values are number (percentage) unless described otherwise.

Table 2 Comparison of patients exposed or not exposed to allopurinol within 3 years of initial diagnosis of gout before and after matching

	1-year landmark analysis			3-year landmark cohort		
	Allopurinol users ($n = 3540$)	Allopurinol non-users ($n = 16\,009$)	*P*-value	Allopurinol users ($n = 3519$)	Allopurinol non-users ($n = 3519$)	*P*-value
Follow-up, median (interquartile range), years[a]	10 (5–14)	10 (4–15)	0.72	9 (4–12)	10 (5–13)	0.25
Death	437 (43.01)	443 (43.60)	0.79	1281 (36.40)	1265 (35.95)	0.69
Mortality, died (%)						
1 year from landmark	41 (4.07)	44 (4.37)	0.84	133 (3.82)	147 (4.22)	0.94
2 year from landmark	74 (7.40)	85 (8.52)		269 (7.84)	291 (8.48)	
5 year from landmark	189 (19.64)	204 (21.19)		629 (19.08)	639 (19.30)	
10 year from landmark	340 (37.61)	348 (38.31)		1088 (35.22)	1084 (35.01)	

Values are number (percentage) unless described otherwise. [a]Since the time point of landmark.

use in order to be assigned as cases. The more recent study by Dubreuil *et al.* [19], using The UK Health Improvement Network (THIN) database, also reported a beneficial survival effect related to allopurinol use. Their conclusions possibly suffered from immortal time bias, because the necessity of allopurinol users to survive from cohort entry (date of hyperuricaemia) to allopurinol prescription was not required for non-users. Therefore, without tackling immortal time bias by design (such as using landmark analysis) or explicitly modelling the timing of exposure (such as using time-dependent methods), a biased estimate can inevitably occur.

There are potential limitations to this study. First, there is possible misclassification bias because the identification of gout patients was based on diagnoses made by general practitioners, rather than according to classification criteria or to the gold standard of urate crystal identification. However, the validity of gout diagnosis in the CPRD has been investigated and found to be high [11]. Second, the use of landmarks at 1 year and 3 years means that our finding that allopurinol confers a neutral effect on all-cause mortality only applies to patients who are alive at these two landmarks time points. Third, the dose of allopurinol used in primary care in the UK is predominantly $<$300 mg/day [20], and it is possible that higher doses may be required to obtain a beneficial effect on cardiovascular and renal outcomes. Ideally, a randomized controlled trial is required to address this.

In conclusion, this propensity score–matched landmark analysis in a population of incident gout patients in the UK primary care setting found a neutral effect on the risk of all-cause mortality from a minimal 6-month allopurinol use at 1 year and at 3 years after initial diagnosis of gout. Our study provides reassurance concerning the prescription of allopurinol in gout patients early in their disease course to prevent untoward consequences of chronic uncontrolled hyperuricaemia.

Acknowledgements

This work was funded by the National Science Council of Taiwan (project 103-2314-B-182A-070-MY2) and Chang Gung Memorial Hospital (project CMRPG3A0624) and supported by the University of Nottingham for methodological assistance. The sponsors of the study had no role in design and conduct of the study; collection, management, analysis and interpretation of the data; and preparation, review, or approval of the manuscript. C.D.M. is funded by the National Institute for Health Research (NIHR) Collaborations for Leadership in Applied Health Research and Care West Midlands, the NIHR School for Primary Care Research and a NIHR Research Professorship in General Practice (NIHR-RP-2014-04-026). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. C.F.K. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. C.F.K., W.Z. and M.D. conceived and designed the study. C.F.K. and W.Z. obtained the funding and acquired the data. C.F.K., M.J.G. and W.Z. performed and supervised the statistical analysis. C.F.K., M.J.G., C.M., W.Z. and M.D. analysed and interpreted the data. C.F.K. and W.Z. drafted the manuscript. All authors contributed to the critical revision of the manuscript for important intellectual content. W.Z., M.J.G. and M.D. supervised the study. M.D. is the guarantor.

Funding: This work was funded by the National Science Council of Taiwan (project 103-2314-B-182A-070-MY2) and Chang Gung Memorial Hospital (project CMRPG3A0624).

Disclosure statement: M.D. reports personal fees for *ad hoc* advisory activities for gout and osteoarthritis for AstraZeneca, Menarini, Nordic Biosciences, Novartis and Pfizer. All other authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* Online.

References

1 Roddy E, Zhang W, Doherty M. The changing epidemiology of gout. Nat Clin Pract Rheumatol 2007;3:443–9.

2 Zhang W, Doherty M, Pascual E *et al*. EULAR evidence based recommendations for gout. Part I: Diagnosis. Report of a task force of the Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2006;65:1301–11.

3 Kuo CF, Grainge MJ, Mallen C, Zhang W, Doherty M. Comorbidities in patients with gout prior to and following diagnosis: case-control study. Ann Rheum Dis 2014; Advance Access published 14 November 2014, doi: 10.1136/annrheumdis-2014-206410.

4 Kuo CF, Yu KH, See LC *et al*. Elevated risk of mortality among gout patients: a comparison with the national population in Taiwan. Joint Bone Spine 2011;78:577–80.

5 Kuo CF, Grainge MJ, Mallen C, Zhang W, Doherty M. Eligibility for and prescription of urate-lowering treatment in patients with incident gout in England. JAMA 2014;312:2684–6.

6 Kelkar A, Kuo A, Frishman WH. Allopurinol as a cardiovascular drug. Cardiol Rev 2011;19:265–71.

7 Halevy S, Ghislain PD, Mockenhaupt M *et al*. Allopurinol is the most common cause of Stevens–Johnson syndrome and toxic epidermal necrolysis in Europe and Israel. J Am Acad Dermatol 2008;58:25–32.

8 Doherty M, Jansen TL, Nuki G *et al*. Gout: why is this curable disease so seldom cured? Ann Rheum Dis 2012;71:1765–70.

9 Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. Br J Clin Pharmacol 2010;69:4–14.

10 Kuo CF, Grainge MJ, Mallen C, Zhang W, Doherty M. Rising burden of gout in the UK but continuing suboptimal

management: a nationwide population study. Ann Rheum Dis 2015;74:661–7.

11 Meier CR, Jick H. Omeprazole, other antiulcer drugs and newly diagnosed gout. Br J Clin Pharmacol 1997;44:175–8.

12 Dafni U. Landmark analysis at the 25-year landmark point. Circ Cardiovasc Qual Outcomes 2011;4:363–71.

13 Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika 1983;70:41–55.

14 Weiss GB, Bunce H III, Hokanson JA. Comparing survival of responders and nonresponders after treatment: a potential source of confusion in interpreting cancer clinical trials. Control Clin Trials 1983;4:43–52.

15 Malek F, Ostadal P, Parenica J *et al*. Uric acid, allopurinol therapy, and mortality in patients with acute heart failure—results of the Acute HEart FAilure Database registry. J Crit Care 2012;27:737 e11–24.

16 Wu AH, Ghali JK, Neuberg GW *et al*. Uric acid level and allopurinol use as risk markers of mortality and morbidity in systolic heart failure. Am Heart J 2010;160:928–33.

17 Luk AJ, Levin GP, Moore EE *et al*. Allopurinol and mortality in hyperuricaemic patients. Rheumatology 2009;48:804–6.

18 Struthers AD, Donnan PT, Lindsay P *et al*. Effect of allopurinol on mortality and hospitalisations in chronic heart failure: a retrospective cohort study. Heart 2002;87:229–34.

19 Dubreuil M, Zhu Y, Zhang Y *et al*. Allopurinol initiation and all-cause mortality in the general population. Ann Rheum Dis 2015;74:1368–72.

20 Roddy E, Mallen CD, Hider SL, Jordan KP. Prescription and comorbidity screening following consultation for acute gout in primary care. Rheumatology 2010;49:105–11.