Case–control study examining the association between allopurinol use and ischemic cerebrovascular disease

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ABSTRACT

Few studies focus on the relationship between allopurinol and ischemic cerebrovascular disease. The goal of the study was to investigate the association of long-term therapy of allopurinol with the first-time attack of ischemic cerebrovascular disease in Taiwan. We performed a case–control study using the database of the Taiwan National Health Insurance Program. The case group included 14,937 subjects aged 20–84 years with the first-time attack of ischemic cerebrovascular disease from 2000 to 2013. The control group included 14,937 sex-matched and age-matched subjects aged 20–84 years without any type of cerebrovascular disease. Ever use of allopurinol was defined as subjects who had at least a prescription for allopurinol before the index date. The OR and the 95% CI for ischemic cerebrovascular disease associated with allopurinol use were measured by the multivariable logistic regression model. The adjusted OR of ischemic cerebrovascular disease was 0.992 (95% CI 0.989 to 0.996) for subjects with increasing cumulative duration of allopurinol use for every 1 month, compared with never use. In a further analysis, the adjusted OR of ischemic cerebrovascular disease was 0.74 (95% CI 0.57 to 0.96) for cumulative duration of allopurinol use >3 years, compared with never use. Our findings suggest that lone-term therapy of allopurinol >3 years is associated with decreased risk of the first-time attack of ischemic cerebrovascular disease, compared with no allopurinol therapy.

Significance of this study

What is already known about this subject?
- Hyperuricemia correlates with increased risk of cerebrovascular disease.
- Allopurinol use correlates with reduced risk of overall cerebrovascular disease.

What are the new findings?
- Lone-term therapy of allopurinol >3 years is associated with decreased risk of the first-time attack of ischemic cerebrovascular disease, compared with no allopurinol therapy.

How might these results change the focus of research or clinical practice?
- Further real-world data can answer whether allopurinol use has the beneficial effects on primary prevention of ischemic cerebrovascular disease among people with hyperuricemia.

INTRODUCTION

As well known, hyperuricemia is associated with increased risk of gout. In addition, a large number of epidemiologic studies and meta-analysis have shown that hyperuricemia correlates with increased risk of cerebrovascular disease.[1–5] Allopurinol is widely used to reduce serum uric acid. Few studies investigate the effects of lowering serum uric acid on the risk of cerebrovascular disease. One cohort study showed that allopurinol use correlated with reduced risk of overall cerebrovascular disease (HR 0.91, 95% CI 0.83 to 0.99),[6] but the other cohort study showed that allopurinol use was not statistically associated with the risk of overall cerebrovascular disease (HR 1.18, 95% CI 0.95 to 1.47).[7] Current data from observational studies remain to be conflicting.

Cerebrovascular disease ranked the fourth leading cause of total deaths in Taiwan in 2016 (11,846 deaths due to cerebrovascular disease, 6.87% of total deaths).[8] The prevalence of hyperuricemia was high in Taiwan, 39.4% in men and 17.4% in women.[9] Little is known about the effects of allopurinol use on the risk of ischemic cerebrovascular disease in Taiwan. If the association of allopurinol use with ischemic cerebrovascular disease really exits, more evidence can be given to this issue. A population-based case–control study was performed to investigate the following questions: (1)Is there an association of allopurinol use with ischemic cerebrovascular disease? (2) Is there a duration-dependent effect of allopurinol use?

METHODS

Study design and data source

The design and data source of the study were adapted from previous studies.[10–12] A case–control study was performed to analyze the database of the Taiwan National Health Insurance Program. The program was launched in March

1995 and has covered 99.6% of 23 million people living in the independent country of Taiwan.[13 14]

Study subjects

The case group included subjects aged 20–84 years with the first-time attack of ischemic cerebrovascular disease from 2000 to 2013. Ischemic cerebrovascular disease included ischemic infarction and transient ischemic attack based on International Classification of Diseases, Ninth Revision, Clinical Modification (codes 433, 434, and 435). We defined the date of diagnosing ischemic cerebrovascular disease as the index date. A random number was appointed for each subject without any type of cerebrovascular disease by generating random numbers between 0 and 1 which were equally distributed. The control group consisted of subjects without any type of cerebrovascular disease who were randomly selected. The case group and the control group were matched for 1:1 ratio and also matched for sex, age (every 5-year interval), comorbidities, and the year of the index date. That is, the enrollment date for the control group was matched for the same year of the case group, but the month and the day were randomly appointed. These statistical criteria were *used in* previous studies.[15 16]

Allopurinol exposure

The definition of allopurinol exposure was adapted from previous studies.[17–19] Ever use of allopurinol was defined as subjects who had at least a prescription for allopurinol before the index date. Never use of allopurinol was defined as subjects who did not have a prescription for allopurinol before the index date.

Comorbidities

The comorbidities which could be potentially associated with ischemic cerebrovascular disease were *adapted from* previous studies, including alcohol-related disease, atrial fibrillation, chronic kidney disease, chronic obstructive pulmonary disease, coronary artery disease, diabetes mellitus, hyperlipidemia, as well as hypertension.[20 21]

Statistical analysis

In the beginning, we compared the distributions of demographic status, allopurinol use, and comorbidities between the case group and the control group by using the X^2 test for categorical variables, and the t-test for continuous variables. Next step, all variables were included in a univariable logistic regression model. Variables which were found to be statistically significant in a univariable logistic regression model were further included in a multivariable logistic regression model. The OR and the 95% CI for ischemic cerebrovascular disease associated with allopurinol use were measured. Last, we performed the analyses about the duration-dependent and dose-dependent relationship of allopurinol use on the risk of ischemic cerebrovascular disease. All analyses were performed by the SAS statistical software (V.9.2; SAS Institute). The results were considered statistically significant when two-tailed p values were <0.05.

RESULTS

Basic information of the study population

There were 14,937 subjects with ischemic cerebrovascular disease in the case group and 14,937 subjects without

Table 1 Basic information between cases with ischemic cerebrovascular disease and matched controls

	Cases with ischemic cerebrovascular disease n=14,937		Matched controls n=14,937		
Variable	n	(%)	n	(%)	p Values*
Sex					0.61
Female	6676	(44.7)	6720	(45.0)	
Male	8261	(55.3)	8217	(55.0)	
Age group (y)					0.66
20–39	523	(3.5)	499	(3.34)	
40–64	6019	(40.3)	6071	(40.64)	
65–84	8395	(56.2)	8367	(56.02)	
Age (y), mean±SD†	65.6±12.4		64.6±12.0		<0.001
Ever use of allopurinol	1989	(13.3)	1842	(12.3)	0.01
Cumulative duration of allopurinol exposure (mo), median/IQR (Q1–Q3)†	1.50 (0.40–7.00)		2.00 (0.47–8.73)		0.002
Comorbidities*					
Alcohol-related disease	672	(4.5)	717	(4.8)	0.22
Atrial fibrillation	538	(3.6)	495	(3.3)	0.17
Chronic kidney disease	434	(9.6)	1434	(9.6)	0.99
Chronic obstructive pulmonary disease	4464	(29.9)	4438	(29.7)	0.74
Coronary artery disease	7446	(49.9)	7456	(49.9)	0.91
Diabetes mellitus	2826	(18.9)	2878	(19.3)	0.44
Hyperlipidemia	5716	(38.3)	5696	(38.1)	0.81
Hypertension	11 603	(77.7)	11 591	(77.6)	0.87

Data are shown as the number of subjects in each group with percentages given in parentheses.
*X^2 test comparing cases with ischemic cerebrovascular disease and matched controls.
†*t*-test comparing cases with ischemic cerebrovascular disease and matched controls.

Table 2 Association between ischemic cerebrovascular disease and cumulative duration of allopurinol use

Variable	Case number/control number	Crude OR	(95% CI)	Adjusted OR*	(95% CI)
Never use of allopurinol as a reference	12 948/13 095	1.00	(Reference)	1.00	(Reference)
Cumulative duration of allopurinol use (increase in use duration for every 1 mo)	1989/1842	0.993	(0.989 to 0.997)	0.992	(0.989 to 0.996)
Cumulative duration of allopurinol use (y)					
<1	1652/1468	1.14	(1.06 to 1.23)	1.12	(1.04 to 1.21)
1–3	238/242	1.00	(0.83 to 1.19)	0.97	(0.81 to 1.16)
>3	99/132	0.76	(0.58 to 0.99)	0.74	(0.57 to 0.96)

*Variables which were found to be statistically significant in a univariable logistic regression model were further tested by a multivariable logistic regression model. Only age could be included for adjustment.

any type of cerebrovascular disease in the control group (table 1). The mean ages (SD) were 65.6 (12.4) years in the case group and 64.6 (12.0) years in the control group. Because the age matching was done by groups with large age range, statistical significance was noted in mean age (t-test, $p<0.001$). The cumulative duration for allopurinol exposure for the case group was shorter than the duration for the control group, with statistical significance (t-test, $p=0.002$). Due to the matched case–control study design, there was no significant difference in comorbidities between the case group and the control group (X^2 test, $p>0.05$). The case group had a higher proportion of ever use of allopurinol than the control group (13.3% vs 12.3%, X^2 test, $p=0.01$).

Association between ischemic cerebrovascular disease and cumulative duration of allopurinol use

The multivariable logistic regression model showed that the adjusted OR of ischemic cerebrovascular disease was 0.992 (95% CI 0.989 to 0.996) for subjects with increasing cumulative duration of allopurinol use for every 1 month, compared with never use. In a further analysis, the adjusted ORs of ischemic cerebrovascular disease were 1.12 (95% CI 1.04 to 1.21) for cumulative duration of allopurinol use <1 year, 0.97 (95% CI 0.81 to 1.16) for 1–3 years, and 0.74 (95% CI 0.57 to 0.96) for >3 years, respectively, compared with never use (table 2).

Association between ischemic cerebrovascular disease and cumulative dosage of allopurinol use among subjects with long-term therapy of allopurinol >3 years

Among subjects with cumulative duration of allopurinol use >3 years, the adjusted OR of ischemic cerebrovascular disease was 1.10 (95% CI 0.78 to 1.55) for subjects with increasing cumulative dosage of allopurinol use for every 50 mg, compared with never use (table 3). The dose-dependent effect of allopurinol use on the risk of ischemic cerebrovascular disease did not reach statistical significance.

DISCUSSION

We noted that long-term therapy of allopurinol >3 years was associated with decreased odds of ischemic cerebrovascular disease, compared with no allopurinol therapy. There was a duration-dependent effect of allopurinol use on the risk reduction of ischemic cerebrovascular disease. These findings were compatible with previous cohort studies showing that allopurinol use was associated with risk reduction of ischemic cerebrovascular disease.[6 22] The risk would be further decreased for those with long duration of allopurinol use.[6]

The underlying mechanisms about the association of allopurinol use with ischemic cerebrovascular disease cannot be examined in our observational study. A randomized, double-blind, placebo-controlled study showed that allopurinol use could reduce the central blood pressure and the carotid intima-media thickness among subjects with recent ischemic cerebrovascular disease.[23] This at least partially explains that allopurinol use has the beneficial effects on ischemic cerebrovascular disease. In addition, allopurinol use can improve endothelial function,[24 25] which could also have the beneficial effects on ischemic cerebrovascular disease.

Some limitations should be discussed. First, the large sample size of our study can provide statistical significance for a point estimate that is very vulnerable to being influenced by methodological decisions, such as a case–control study design. Further real-world data can answer whether allopurinol use has the beneficial effects on primary prevention of ischemic cerebrovascular disease among people with hyperuricemia. Second, due to the limitation of the database studied, the status of cigarette smoking was not recorded. We included chronic obstructive pulmonary disease and coronary artery disease as a surrogate. Third, the cumulative duration for allopurinol exposure for the case group was shorter than the duration for the control group. The time-window bias found in a case–control

Table 3 Association between ischemic cerebrovascular disease and cumulative dosage of allopurinol use among subjects with long-term therapy of allopurinol >3 y

Variable	Case number/control number	Crude OR	(95% CI)	Adjusted OR*	(95% CI)
Never use of allopurinol as a reference	12 948/13 095	1.00	(Reference)	1.00	(Reference)
Cumulative dosage of allopurinol use (increase in dosage for every 50 mg)	99/132	1.10	(0.78 to 1.55)	1.10	(0.78 to 1.55)

*Variables which were found to be statistically significant in a univariable logistic regression model were further tested by a multivariable logistic regression model. Only age could be included for adjustment.

study potentially existed. Interpretation of our data should be cautious. Despite the above limitations, this is the first population-based case–control study to investigate the association of allopurinol use with the first-time attack of ischemic cerebrovascular disease in Taiwan.

Our findings suggest that lone-term therapy of allopurinol >3 years is associated with decreased risk of the first-time attack of ischemic cerebrovascular disease, compared with no allopurinol therapy.

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Patient consent Not required.

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