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The Effects of Colchicine on Risk of Cardiovascular Events and Mortality Among Patients with Gout: A Cohort Study Using Electronic Medical Records Linked with Medicare Claims

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Abstract

Background—Colchicine may have beneficial effects on cardiovascular (CV) disease, but there are sparse data on its CV effect among patients with gout. We examined the potential association between colchicine and CV risk and all-cause mortality in gout.

Methods—The analyses used data from an electronic medical record (EMR) database linked with Medicare claims (2006–2011). To be eligible for the study cohort, subjects must have had a diagnosis of gout in the EMR and Medicare claims. New users of colchicine were identified and followed-up from the first colchicine dispensing date. Non-users had no evidence of colchicine prescriptions during the study period and were matched to users on the start of follow-up, age, and gender. Both groups were followed for the primary outcome, a composite of myocardial infarction (MI), stroke or transient ischemic attack (TIA). We calculated hazard ratios (HRs) in Cox regression, adjusting for potential confounders.

Results—We matched 501 users with an equal number of non-users with a median follow-up of 16.5 months. During follow-up, 28 primary CV events were observed among users and 82 among non-users. Incidence rates per 1,000 person-years were 35.6 for users and 81.8 for non-users. After full adjustment, colchicine use was associated with a 49% lower risk (HR 0.51, 95% CI 0.30 – 0.88) in the primary CV outcome as well as a 73% reduction in all-cause mortality (HR 0.27, 95% CI 0.17 – 0.43).

Conclusion—Colchicine use was associated with a reduced risk of a CV event among patients with gout.

Keywords

Gout; Colchicine; Cardiovascular Disease; Epidemiology

INTRODUCTION

Atherosclerosis is a multifactorial disease with strong inflammatory underpinnings.[1, 2] Several current trials are testing various immunomodulatory agents for primary and secondary CV prevention, including methotrexate, canakinumab, and colchicine.[3] These agents modulate IL-1, IL-6 and TNF, which are involved in CV risk in epidemiologic studies, as well as *in vitro* and animal models.[4, 5] One open-label trial previously found that colchicine use may have been effective in secondary CV prevention, however this trial did not conceal subjects and providers to treatment assignment.[6] An observational study among patients with gout found no change in risk with colchicine, but users were only required to have had one prescription and relatively few events were noted in the colchicine group. [7]

Colchicine, originally derived from the plant *Colchicum*, had its medicinal value recognized several thousand years ago and has been used for gout for at least several hundred years.[8] It down-regulates inflammation through blocking microtubule spindle formation, disrupting inflammasome function, inhibiting cytokine production, and hindering neutrophil chemotaxis.[9] These mechanism spurred investigators to examine its potential benefits in the secondary prevention of CV events in the general population and among certain sub-groups; it has been found to confer protection from recurrent pericarditis and post-pericardotomy atrial fibrillation.[10, 11]

While colchicine may confer lower risk for a second CV event in the general population, there are sparse data in gout where colchicine may also be indicated for disease control, treatment and/or prevention. One study showed a reduced prevalence of MI among colchicine users compared with non-users.[12] This prior analysis included a large sample, but several limitations hinder interpretation: there was no adjustment for any potential confounders and colchicine use was of unclear duration. Since gout and hyperuricemia are associated with an increased CV risk,[13–15] it is important to consider whether colchicine might have value as a CV prevention measure in gout patients.

We examined previously collected data to determine the association between the risk of CV events and colchicine use among a cohort of patients with gout. We tested the hypothesis that colchicine use would be associated with reduced CV risk, using a rich dataset that includes information from an EMR linked with Medicare claims. This dataset provides drug prescribing, pharmacy filling, diagnoses, hospitalizations, and laboratory data on a large cohort of gout patients.

METHODS

Study cohort and design

We derived our study cohort from a database with information from the Brigham and Women's Hospital EMR linked with Medicare pharmacy and health care claims. The linked database was created by first finding subjects seen at Brigham and Women's Hospital with a diagnosis of gout noted in the EMR. We then linked Medicare data from the Center for Medicare and Medicaid Services, including Parts A (hospital insurance), B (medical/

outpatient insurance) and D (drug insurance) for 2006–2011, for all gout subjects found in the EMR who were Medicare eligible. A review of the EMR looking for gout diagnoses in 100 subjects found that our cohort definition had a 99% positive predictive value (PPV) using the physician diagnosis as the gold standard.

From this linked study database, subject's use of colchicine was identified in Medicare Part D claims. All subjects with at least 90-days of Medicare claims who also had no colchicine prescriptions during these 90-days became eligible for our new user cohort. Subjects who then began using colchicine were categorized as new users and subjects who did not start colchicine at any time were categorized as non-users.

Non-users were matched 1:1 to users based on age (± 5 years), gender, and index date. The index date (i.e., start of follow-up) for the new users was the first date of filling a colchicine prescription. The index date for non-users was the date of a Medicare claim for any visit matched to the index date of colchicine users. Thus, this study was designed as a matched cohort analysis of patients with gout who were new users of colchicine versus non-users.

This study was approved by the Partners Healthcare Institutional Review Board.

Colchicine use

New use of colchicine was the exposure of interest. The primary analysis examined the period from the index date through the last available colchicine dosage based on the number of colchicine pills filled. New users of colchicine were then censored from the analysis 60-days after the end of the exposure period in the primary analyses. Other censoring events included death, lack of Medicare data, or the end of follow-up (December 31, 2011).

Several variations on this exposure definition were considered in secondary analyses. First, we examined CV risk among colchicine users only. Exposure was categorized based on quartiles of colchicine pills used during follow-up, and risk between quartiles was compared. We hypothesized that greater exposure (higher quartile) would be associated with reductions in CV risk. Second, new users' exposure period continued beyond their last available dosage, mimicking an intention to treat analysis. We hypothesized that the potential CV preventive benefits observed with colchicine would wane in the intention to treat analysis.

Cardiovascular outcomes

All CV outcomes were defined using the Medicare claims data to avoid missing outcomes that might have occurred outside of Brigham and Women's Hospital. The primary outcome was defined as the first of any of the following events: MI, stroke, or TIA. These were defined using well-established algorithms in the claims data (see Appendix Table); each has positive predictive values $> 85\%$. [16–18] Two secondary outcome were examined: first, the primary events plus re-vascularization procedures, such as percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) [19, 20], and second, all-cause death.

Covariates

Variables potentially related to the use of colchicine and known CV risk factors were assessed using data from the 90 days prior to the start of follow up. Demographics were determined from the EMR as was body mass index (BMI) and tobacco use. Since BMI and tobacco use had substantial missing data, categories were formed as follows: BMI (according to CDC category) – -1 = missing, 0 = <18.5 kg/m², 1 = 18.5–24.9 kg/m², 2 = 25–29.9 kg/m², 3 = ≥30 kg/m²; and smoking – -1 = missing, 0 = non-smoker, 1 = ever smoker. Cardiovascular risk factors, such as history of CV events or re-vascularization, heart failure, hypertension, diabetes, hyperlipidemia, and chronic kidney disease (CKD) were all determined based on Medicare claims. Relevant medications, assessed using the Medicare Part D claims, consisted of statins, beta-blockers, ACE inhibitors, angiotensin receptor blockers, diuretics, calcium channel blockers, non-steroidal anti-inflammatory drugs, selective COX-2 inhibitors (coxibs), oral steroids, allopurinol, and febuxostat. The EMR medication list was used as the source of aspirin information. Finally, we examined the EMR for the uric acid level closest to but not after the index date. These were available in approximately one-quarter of subjects and analyzed in secondary analyses.

Statistical analyses

After assembling the matched cohorts, baseline characteristics were compared across colchicine users and non-users. The incidence rates for primary and secondary outcomes were estimated for each group, as well as the 95% CIs. The incidence rate ratio was calculated as the incidence rate among colchicine users divided by the incidence rate among non-users.

To estimate the relative risk of the primary and secondary outcomes, we constructed Cox proportional hazards models with colchicine use entered as the exposure of interest. All covariates were considered potential confounders and were tested in models sequentially adjusted for more covariates: Model 1 – age, gender, and race; Model 2 – Model 1 + history of CV disease, diabetes, hypertension, statin use, aspirin use, anti-hypertensive use, smoking and BMI; and Model 3 – Model 2 + non-steroidal anti-inflammatory drugs or coxibs, oral steroids, allopurinol, and CKD or end stage renal disease. These steps were repeated for the secondary outcomes. Secondary analyses (duration and intention to treat) were run in similar Cox regression models.

The proportional hazard assumptions were tested adding an interaction term of exposure and time to the model. The proportional hazards assumption was not violated and the p-value for interaction was 0.64.

All analyses were run using SAS (Cary, NC), version 9.4.

RESULTS

From the 3,952 patients with gout according to the EMR who also had Medicare data linkable, we found 655 potential subjects with a first prescription for colchicine after 90-days in the cohort. From this group, 501 (76.5% of 655) patients could be matched to non-users based on age, gender, and index date.

Baseline characteristics of these two matched groups were compared (see Table 1). Subjects were on average 72–73 years of age and approximately 2/3 were men. The majority of subjects identified themselves as White. The two groups were similar in many respects: similar prevalence of known CV disease, heart failure, diabetes, CKD and aspirin use. However, prevalence of hypertension and use of statins, allopurinol, non-steroidal anti-inflammatory drugs, and steroids was higher in the colchicine users. Additionally, colchicine users had a higher mean BMI.

Median follow-up overall was 1.31 years, but was longer in the non-user group (1.56 years) compared with the users (0.95 years). The incidence rates for the primary outcome components (MI, stroke, and TIA) were lower among colchicine users versus non-users (see Table 2). However, incidence rates for re-vascularization procedures (PCI and CABG) were similar. All-cause mortality was higher for non-users compared with colchicine users. The Kaplan-Meier survival plots are shown for primary and secondary outcomes in Figure 1 and demonstrate that the event free survival diverged early and remained different over several years of follow-up.

The adjusted risk of CV outcomes associated with colchicine use was significantly reduced in all models (see Figure 2). After full adjustment, colchicine use was associated with a 49% lower risk (HR 0.51, 95% CI 0.30 – 0.88, $p = 0.016$) in the primary CV outcome. The analyses of the secondary CV composite outcome demonstrated a trend towards a reduced risk, but the HRs were less dramatic (see lower half of Figure 2). Primary analyses using all-cause mortality as the outcome also demonstrated a lower risk among users of colchicine (HR 0.27, 95% CI 0.17 – 0.43, $p < 0.0001$).

Sensitivity analyses examined whether duration of colchicine use was associated with a gradient in CV risk. As shown in Figure 3, the lowest hazard ratios were observed for the group using colchicine for 90 days or less in analyses for the primary and secondary outcomes.

We repeated the analyses using an intention to treat approach. These showed a less dramatic protective effect, but a statistically significant reduction in risk of CV outcomes for colchicine users (see Appendix Figure, upper panel). Further sensitivity analyses among patients with serum uric acid levels ($n = 278$) demonstrated a similar trend as the primary analyses (see Appendix Figure, lower panel).

DISCUSSION

Control of traditional CV risk factors has significantly reduced risk of events as measured at the population level. However, specific patient populations, such as gout and rheumatoid arthritis, experience abnormally high CV risk likely because of systemic inflammation.[1] There is growing interest in the use of immune-modulatory agents to reduce CV risk.[3] However, these trials are focused on the general population and not on these subgroups. Using a robust observational dataset, we found that patients with gout who used colchicine experienced fewer CV events and a lower all-cause mortality than non-users.

While there is a strong biologic basis for these findings and trial data supporting a similar beneficial effect of colchicine,[6] these findings should be interpreted cautiously. Observational drug studies are limited by non-random assignment of patients to a given treatment. While Table 1 suggests that the two groups had many similarities, there were important differences that suggest colchicine may have been preferentially prescribed to patients more willing to use medications (e.g., higher rates of statins, anti-hypertensive drugs, allopurinol, non-steroidal anti-inflammatory drugs, and steroids). In addition, the increased all-cause mortality observed in non-users may suggest that providers were less likely to use colchicine in sicker patients. Even though we adjusted for many potential confounders, residual confounding is impossible to rule-out. The lack of a clear gradient of effect according to duration of use (Figure 3) could be seen as evidence against a causal relationship. The use of an observational study database also may introduce misclassification of exposure: patients prescribed colchicine who did not use it or those without any recent prescriptions who may have used samples or old prescriptions. Misclassification of outcomes is also possible (e.g., prior history of MI mis-interpreted as acute MI) but the claims-based algorithms have a positive predictive value > 85% (see Appendix Table 1). No information was included on gout attacks or duration of gout; this may have introduced confounding.

Several strengths of these analyses are worth noting. The study database included a robust set of covariates, including cardiovascular risk factors, CKD, and gout-related variables and treatments. The new user design employed is considered state of the art in drug epidemiology and allows one to define the start of follow-up at the start of treatment.[21] The gout definition had a very high positive predictive value, suggesting little misclassification in the cohort. In addition, the secondary analyses were consistent with a true effect of the colchicine and not confounding.

The use of the linked EMR plus Medicare claims is unusual and a possible strength. There are other research groups that have pursued similar linkages between databases collected for different reasons,[22] however little actual research has been conducted on such linked databases. A recent study used a large carotid artery stenting registry linked with Medicare claims.[23] This prior work had to rely on a deterministic linkage without personal identifiers. We were able to use an insurance identification number to make a similar deterministic linkage because the gout patients we included are patients at our medical center. The linkage with the EMR allowed us to include laboratory, tobacco use and BMI data, not typically available in claims data. Such analyses in linked databases will become more common with increasing availability of data from EMRs and registries.

Most patients with gout do not receive long-term colchicine, as it is indicated for acute attacks or while initiating uric-acid lowering treatments.[9] However, some patients with frequent attacks use it long-term. These results, along with those from prior studies, suggest that long-term colchicine may provide CV risk protection among patients with gout with and without known CVD, a group known to experience a 30–60% increased risk of CV events. [15] While based on hypothesis, results from this study may be considered hypothesis-generating for a formal test of whether colchicine reduces CV risk in the setting of a randomized controlled trial.

The CV risk profile of gout patients demonstrates a higher prevalence of hypertension, diabetes, insulin resistance, obesity, and the metabolic syndrome.[24–26] Several studies have examined whether the hyperuricemia underpinning gout might be a contributor to CV risk. While epidemiologic data suggest that lower uric acid levels associate with lower risk, [13] this has not been shown in a randomized controlled trial. Colchicine does not lower uric acid. If it is found to reduce CV risk in future randomized controlled trials, this would likely be through its immunomodulatory effects.

CONCLUSION

In conclusion, we found that new use of colchicine was associated with a lower CV risk among patients with gout. While we are unable to confirm a causal link in a non-randomized observational study, this study provides justification for a randomized controlled trial of colchicine to reduce CV risk among gout patients. Such a trial might focus on secondary CV prevention. Since CV disease affects approximately 7–14% of the estimated 8 million adults in the US with gout,[24–26] and colchicine is a drug familiar to these patients, this study has strong feasibility and should be considered.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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A.

B.

C. Kaplan-Meier Survival for All-Cause Mortality

Figure 1.

Kaplan-Meier Survival Plots Comparing Colchicine New Users to Non-Users. Panel A compares colchicine users to non-users for the primary outcome (a composite of MI, stroke and TIA). Panel B compares colchicine users to non-users for the secondary CV outcome (a composite of MI, stroke, TIA, PCI and CABG). Panel C compares colchicine users to non-users for the secondary all-cause mortality outcome. Time axis is in years.

Figure 2.

Forest Plot Demonstrating Adjusted Cox Proportional Hazard Ratios (95% CI) Comparing Colchicine New Users with Non-Users. The upper panel shows results for the primary CV outcome. Results for the secondary composite CV outcome and all-cause mortality are demonstrated on the bottom of the figure.

Notes: Model 1 -- Age, gender and race adjusted only ; Model 2 -- Model 1 + history of CV disease, diabetes, hypertension, statin use, aspirin use, anti-hypertensive use, smoking and BMI; and Model 3 -- Model 2 + non-steroidal anti-inflammatory drugs or coxibs, oral steroids, allopurinol, and CKD or ESRD.

Primary CV outcome was a composite of MI, stroke and TIA. Secondary CV outcome also included revascularization, such as PCI and CABG.

Figure 3. Fully adjusted Cox Proportional Hazard Ratios (95% CI) Comparing Colchicine New Users with Non-users by Duration of Use.

Table 1

Baseline Characteristics of Colchicine New Users and Matched Non-Users

	Colchicine users N=501	Non-users N=501	P value
<i>Mean ± SD or %</i>			
Age, years	72.2 ± 10.6	73.0 ± 12.3	0.29
Female gender	36.3	36.3	0.99
Race			0.006
White	69.6	78.4	
Black	20.4	16.0	
Hispanic	6.2	2.8	
Other	3.8	2.8	
Prior MI	3.2	5.0	0.15
Prior Stroke	2.6	3.2	0.57
Prior TIA	1.4	2.4	0.25
Prior CABG	1.4	1.8	0.61
Prior PCI	5.8	4.8	0.48
Known CV disease *	12.0	13.2	0.57
Prior heart failure	10.2	11.0	0.68
Diabetes	39.3	35.7	0.24
Hypertension	76.5	28.1	<0.0001
Statin use	49.7	15.6	<0.0001
Aspirin use	40.7	39.7	0.75
Smoking			0.0005
Never	37.9	38.8	
Ever	62.1	61.2	
BMI	31.0 ± 6.4	29.4 ± 5.6	0.007
Chronic kidney disease	41.7	42.9	0.70
End-stage renal disease	12.2	17.4	0.02
Uric acid, mg/dl †	8.4 ± 2.8	7.1 ± 2.9	0.003
Other Medications			
Number of anti-hypertensive drugs			<0.0001

	Colchicine users N=501	Non-users N=501	P value
0	23.8	74.9	
1	27.5	9.8	
2	30.5	7.8	
3	13.8	6.0	
4+	4.4	1.6	
Allopurinol	41.9	16.0	<0.0001
NSAIDs or coxibs	41.9	9.0	<0.0001
Oral steroids	41.9	12.4	<0.0001

* Any of the above: CVD, MI, stroke, TIA, CABG, or PCI.

[†] Available on 278 subjects.

NSAIDs, non-steroidal anti-inflammatory drugs. BMI, body mass index. Missing data: smoking status was missing for 224 colchicine users and 286 non-users; BMI was missing for 262 colchicine users and 280 non-users.

P-values were calculated using a Student's t-test for continuous variables, Wilcoxon-Mann-Whitney test for ordinal variables, and a Kruskal-Wallis test for dichotomous variables.

Table 2

Cardiovascular Event Rates Among Colchicine New Users and Non-Users

	Colchicine users N=501			Non-users N=501			
	N events	Person- years	Incidence rate (95% CI)	N events	Person- years	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
MI	18	793	22.7 (11.3 – 34.1)	45	1,039	43.3 (27.2 – 58.9)	0.52 (0.29–0.92)
Stroke	9	809	11.1 (3.1 – 19.2)	35	1,057	33.1 (19.4 – 46.8)	0.34 (0.14–0.71)
TIA	6	816	7.4 (0.8 – 13.9)	10	1,071	9.3 (2.0 – 16.7)	0.79 (0.24–2.39)
Primary CV outcome	28	786	35.6 (19.4 – 51.9)	82	1,002	81.8 (57.8 – 105.8)	0.44 (0.27–0.68)
CABG	7	809	8.6 (1.6 – 15.7)	3	1,077	2.8 (0–6.8)	3.11 (0.71–18.62)
PCI	26	774	33.6 (19.8 – 47.4)	34	1,045	32.5 (19.0 – 46.1)	1.03 (0.59–1.78)
Secondary CV outcome	49	753	65.1 (46.2 – 84.0)	103	979	105.2 (81.7 – 128.7)	0.62 (0.43–0.88)
All-cause mortality	43	818	52.6 (36.9 – 68.3)	103	1,083	95.1 (69.4 – 120.8)	0.55 (0.39–0.79)

Incidence rate per 1,000 person-years.