Risk of cerebrovascular disease associated with the use of glucocorticoids in patients with incident rheumatoid arthritis: a population-based study

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ABSTRACT

Objectives: To determine the effect of glucocorticoids (GC) on the risk of cerebrovascular accidents (CVA) in patients with rheumatoid arthritis (RA).

Methods: A population-based cohort study was carried out using administrative health data on 7051 individuals with RA onset between 1997 and 2001 and no exposure to GC before RA onset. Follow-up was until 2006. GC exposure was defined in four ways: current use (yes/no), current dose (mg/day), cumulative dose (grams) and cumulative duration of use (years). All were used as time-dependent variables updated monthly. CVA were ascertained using hospitalisation and vital statistics data. Transient ischaemic attacks were not considered as CVA. Cox regression models adjusting for demographics, cardiovascular drug use, propensity scores and RA characteristics were used.

Results: The mean age of the cohort was 56 years and 66% were women. Over 6 years' mean follow-up (43 355 person-years), 178 incident CVA cases were identified. GC current use was not associated with a significant increase in the risk of CVA (HR=1.41, 95% CI 0.84 to 2.37). Similarly, the models that accounted for daily dose (HR=1.07, 95% CI 0.94 to 1.21 for each 5 mg increase in the daily dose), cumulative duration of use (HR=1.1, 95% CI 0.94 to 1.32 for each year accumulated in the past) and total cumulative dose (HR=1.04, 95% CI 0.99 to 1.08 per gram accumulated in the past) were also not significantly associated with CVA.

Conclusions: This large population-based study indicates that GC use is not associated with an increased risk of CVA in cases with RA.

Introduction

In the past decade, research has demonstrated that patients with rheumatoid arthritis (RA) have an increased risk for cardiovascular disease (CVD).[1–3] Overall, there is a 50% increased risk of cardio- vascular death in patients with RA compared with the general population.[2] Some studies,[1 4] but not al, have suggested that patients with RA have an increased risk of stroke.[5–7]

RA itself or uncontrolled inflammation might have a direct effect on the endothelium and pre- dispose patients to accelerated atherosclerosis.[8 9] In addition, the increased risk of cerebrovascular accidents (CVA) may be due to the effects of drugs used to treat RA, particularly glucocorticoids (GC).[10] Theoretically, GC could modulate the risk of CVA via their deleterious effects on lipids, blood pressure, glucose tolerance, atherosclerosis and coagulation.[11–13] Alternatively, GC may have protective effects mediated by their anti-inflammatory and antiproliferative actions in the endothelial wall, especially at low doses.[14–16]

Despite the wide use of GC in RA, little is known about the association between GC and risk of CVA in RA, as results across studies are inconsistent. Wei *et al*[17] found that GC are associated with an increased risk of CVA in a population-based cohort of GC users, which included those with inflammatory arthritis. However, two case–control studies in patients with RA found no statistically significant association between GC use and CVA.[18 19]

The purpose of our study was to determine the association between GC use and risk of CVA in patients with RA. We used a population-based incident cohort of patients with RA and

performed a comprehensive assessment of the putative associations between several aspects of GC exposure and risk of CVA.

MATERIALS AND METHODS

Study sample and data

We used data from a previously established population-based RA cohort for the province of British Columbia.[20] Our RA case definition has been previously published.[20]

Administrative billing data for reimbursement of doctor visits by the Ministry of Health allowed identification of all cases with a first diagnosis of RA between January 1997 and December 2001 and without a prior diagnosis of RA from January 1990 onwards (earliest available data). Follow-up was until March 2006. We excluded all patients with RA who had received oral GC before the first RA diagnostic code (index date) and those who had had a CVA before the index date.

For each RA case, we obtained data from the Ministry of Health databases on all provincially funded health services used. These included data on all visits to doctors, all investigations and all hospitalisations from January 1990 to March 2006, and all prescription drugs dispensed by pharmacists for all cases from January 1996 to March 2006 regardless of the source of funding. We obtained information on date and cause of death from vital statistics data. The Ministry of Health provided the linkage for their databases and no personal identifying information was provided to the investigators. All procedures were compliant with the British

Columbia Freedom of Information and Privacy Protection Act. The study received ethics approval from the University of British Columbia.

Assessment of exposure to oral GC

All patients who received one or more prescriptions for oral GC during their follow-up were identified as GC users. We calculated GC doses as prednisone equivalents based on accepted standards.[21] Data were available on drug name, start date, dose, number of pills and days for each dispensed prescription. We used these data to construct four time-dependent measures of GC exposure: current use (yes/no), current dose (mg/day), total cumulative dose (grams) and total cumulative use (years), which were updated monthly. First, we calculated the daily GC dose between the beginning and the end of each dispensed GC prescription, by dividing the total quantity of dispensed drug by the number of days for each prescription. Then, we obtained the time-dependent measure of past cumulative dose by summing all doses from all past prescriptions until the given day of follow-up. We calculated past cumulative duration of use by summing the duration of all prescriptions. For prescriptions overlapping for <7 days, we assumed the individual had refilled early and completed the first prescription before starting the second.[22 23]

Representation of cumulative dose and duration

In addition to the traditional method that considers the lifetime past cumulative exposure measures (duration of use and dose) equally, regardless of recency of use, we used a novel time-dependent method proposed by Abrahamowicz *et al*[24] to evalu- ate if weighting for recency of use

would improve the prediction of CVA. This method assumes that more recent exposure has a greater influence on risk outcome than more remote exposure.

Outcome assessment

The primary outcome was the first CVA event occurring during the follow-up. We identified CVA events from hospitalisation separation data (ICD-9 codes: 431, 434 and 436). We defined death from CVA based on the death certificate diagnostic codes, including out of hospital deaths (ICD-10 codes: I60, I61, I63, I64). Transient ischaemic attacks were not included in the out- come because of the poor reliability of the ICD-9 codes for this entity.[25]

Assessment of covariates

Factors known to influence CVA risk that were available in the administrative databases were selected a priori and were included as fixed-in-time covariates measured at the index date in multivariate time-dependent Cox regression analyses.[26] These included age, gender and comorbidities based on diagnostic codes from all outpatient doctor and hospital visits from January 1990 to the index date, using a modification of the Charlson comorbidity index developed for administrative data (excluding RA, chronic obstructive pulmonary disease (COPD) and CVA).[27 28]

We also assessed exposure to the following drugs over the year preceding the index date: antihypertensive agents (β and α blockers, calcium channel blockers, angiotensin receptor blockers, angiotensin-converting enzyme inhibitors), lipid-lowering drugs (statins and fibrates), other cardiovascular drugs (diuretics, anti- arrhythmic agents, anticoagulants and nitrates), diabetes drugs

(insulin and oral hypoglycaemic agents), hormone replacement therapy and oral contraceptives. Aspirin use was not ascertained because this drug is available over the counter.

We used the following markers as surrogates of disease severity: whether the patient ever visited a rheumatologist for their RA, number of visits to the doctor (RA-related visits to family doctors and all visits to rheumatologists) for each person-year of follow-up and use of disease-modifying antirheumatic drugs (DMARDs). DMARD use was categorised as an ordinal variable: no-DMARD use (group 1); sulfasalazine and antimalarial agents (group 2); methotrexate or intramuscular gold (group 3); leflunomide, ciclosporin A, azathioprine, cyclophosphamide, chloram-bucil or mycophenolate mofetil (group 4) and biological agents (group 5). These categories were mutually exclusive and we used the highest rank ever attained during the follow-up. We assumed that patients with at least one visit to a rheumatologist, patients with more doctor visits per person-year of follow-up and patients with a higher DMARD ranking (eg, biological agents vs antimalarial agents) were those with more severe dis- ease. Finally, we also calculated patient's current use of methotrexate, cyclo-oxygenase-2 (COX-2) inhibitors and non-steroidal anti inflammatory drugs as time-dependent covariates.

Statistical analysis

For every case in the cohort, we calculated the person-time from the index date to the last healthcare service use, CVA date or March 2006, whichever came first. Rates per person-year for CVA were calculated for GC use and non-use (including non- use periods for GC users).

To control for confounding by indication, wherein GC would be given to patients with more severe disease and/or less adverse cardiovascular profiles, we used propensity scores (PS) to control for the observed differences between GC users and non-users.[29 30] We calculated PS using a multivariate logistic regression model that included all covariates described above as independent variables (gender, age, antihypertensive agents, lipid-lowering drugs, other CV drugs, diabetes drugs, hormone replacement therapy, oral contraceptives, angina, COPD, Charlson's index, having seen a rheumatologist, number of visits to a doctor and DMARD ranking). To this end, for each case we estimated a PS indicating the likelihood of receiving at least one GC prescription during the follow-up. Each GC user was matched for calendar time, age and sex with a non-GC user at the time of the first GC prescription in order to assign a date for calculating PS for each non-GC user. As recommended,[31] we assessed the predictive ability of the PS to distinguish GC users from non-users and we found that the c statistic was 0.82. We summarised the balance achieved on the PS between GC users and non-users by grouping subjects into PS quintiles. Our examination indicated residual imbalance on some covariates (gender, use of anti- hypertensive drugs, diabetes, use of other cardiovascular drugs, Charlson's index; having seen a rheumatologist, presence of angina and COPD). Therefore, we included imbalanced covariates in addition to PS quintiles in all Cox models.[32]

We used five separate multivariate Cox proportional hazards regression models[26] to estimate the risk of CVA, each representing the effects of GC using a different time-dependent measure of GC exposure. All models adjusted for PS, imbalanced covariates

in the PS (all entered as fixed-in-time covariates); cur- rent use of methotrexate, COX-2 inhibitors and non-steroidal anti-inflammatory drugs, represented by binary (yes/no) time-dependent covariates updated every month. The Akaike information criterion was used to compare the predictive ability among the models.[33 34]

Analyses were performed with SAS software version 9. For all HRs, we calculated 95% CI. All p values are two sided.

RESULTS

Study sample

The cohort included 7051 incident RA cases. During follow-up 2844 cases (40%) were prescribed GC. Table 1 summarises the baseline characteristics of the cohort. Overall, GC users were older, had more comorbidity and used more drugs than non-GC users. For the entire cohort, the overall follow-up was 43 355 person-years; the number of person-years of GC use and non-GC use periods (including non-use periods for GC users) was 3139 and 40 216 person-years, respectively.

GC use and incidence of CVA

Overall, GC users spent 17% of their follow-up time on GC with a median dose of 13.6 mg/day and a median duration per GC course of 43 days. During follow-up we identified 178 CVA, of which 61 (34%) were fatal. The CVA incidence rate was 4.1 per 1000 person-years in the RA cohort, 6.6 during GC exposure and 3.9 during non-GC exposure.

Effect of GC exposure

Table 2 shows the results of all Cox models assessing the effects of different GC exposure measures on risk of CVA. Model 1 corresponds to the simplest time-dependent model that rep- resents current use (yes/no) and ignores dose and duration of exposure. In this model, GC current use was not associated with a significant increase in the risk of CVA (HR=1.41, 95% CI 0.84 to 2.37). Model 2 accounts for current daily dose only and indicated that current dose was not significantly associated with CVA (HR=1.07, 95% CI 0.94 to 1.21). Again, models 3 and 4 indicate that cumulative duration of use and cumulative dose were not significantly associated with an increased risk of CVA. Furthermore, accounting for recency of use (6-month weighted models) did not improve the model's fit to data (higher or equal Akaike information criterion values than unweighted models) or identify a statistically significant association between GC use and CVA.

DISCUSSION

This large population-based study of an incident RA cohort evaluated whether the risk of CVA is increased with oral GC treatment. Our results showed that GC exposure was not associated with an increased risk of CVA.

The highest point estimate for CVA risk was 41%. Although this could be considered of some clinical significance, this estimate was for the crudest exposure measure (yes/no), which ignores

dose and duration. The point estimates of less crude exposure measures were very small and none reached statistical significance, even in the models that adjusted for recency of use.

We previously found a consistent association between GC and myocardial infarction using the same GC exposure measures as in this study.[35]

The immediate effects of GC that might mediate increased cardiovascular risk, such as CVA and myocardial infarction, include the interaction of GC with the vascular wall, endothelial and vascular smooth muscle, and GC-mediated enhancement of vascular contractility.[36] There is evidence that the effects of GC on endothelial cells may vary depending on the vascular bed considered.[37–40] In general, cells from different vascular beds display certain common qualities, but each subtype is uniquely adapted to meet the demands of the underlying tissue.[37] In an elegant study, Förster *et al*[40] demonstrated that GC receptor status and GC responsivity differ between endothelial cells from various vascular beds, including cells from the brain and the heart. The permeability response to GC has important implications because the principal functions of the endothelium (eg, the control of haemostasis, vasomotor tone, cell and nutrient trafficking, barrier functions and angiogenesis) are differentially regulated between different sites of the vascular tree and from one moment to the next.[41] These differential effects are further supported by data from several clinical trials showing that GC may benefit brain endothelium after acute CVA, but offer no protection for heart endothelium after acute myocardial infarction.[42–44]

An alternative explanation for the lack of statistically significant associations in our study may be lack of power due to an insufficient number of CVA events or because the period of observation was too short to allow the potential pathophysiological process to induce a significant

risk. In order to test this possibility, we calculated a post hoc power analysis and we found that our study had 86% power to detect a significant HR of at least 1.5. The highest HR from our study was 1.4 and the power for this HR was 70%. Another possibility might be non- linear associations; however, when we grouped daily dose (<7.5, 7.5–12.5 and >12.5 mg/day) and cumulative dose in tertiles, no significant associations were seen.

The risk of CVA associated with the use of GC in patients with RA has been assessed recently.[17–19] Souverein *et al*[18] in a population based nested case–control study from the General Practice Research Database identified 3656 cases with CVA and matched them with 3676 controls. They found that current GC use (in the past 3 months) was associated with a decreased risk for CVA (adjusted OR=0.91, 95% CI 0.84 to 0.99). However, when the analysis was restricted to patients who had RA (n=1515) as the underlying condition for receiving GC, the association was neither protective nor significant (OR=1.23, 95% CI 0.92 to 1.64).

Nadareishvili *et al*[19] in a case–control study of 41 cases with incident ischaemic stroke in patients with RA from the National Data Bank for Rheumatic Diseases, found that GC use (yes/no) was not significantly associated with CVA (adjusted OR =1.75, 95% CI 0.87 to 3.53). Of interest, the author found no evidence for an association of CVA with diabetes, smoking or obesity.

In comparison with these studies, our study used a substantially larger population, with a median follow-up of 6 years. A unique characteristic of our study is the inclusion of incident RA cases with no use of GC before RA onset, allowing us to

evaluate GC use over the entire disease course. We also used data from dispensed rather than prescribed drugs. Finally, our study is the first to explore the importance of current dose versus cumulative duration of use by including the two time-dependent exposure measures in the same model.

Our results have important implications for people with RA and their treating doctors, when weighing the risks and benefits of using GC to treat RA. It seems that the use of GC in RA is clearly something of a clinical balancing act, the key to which would seem to be judicious timing and duration.[45] Detailed information about long-term GC side effects is scarce and clinicians need evidence on this issue.

Potential limitations of our study include those inherent to observational studies based on administrative data. Uncertainty about diagnostic accuracy is the main limitation of studies identifying cases from administrative databases. To counter this, we used one of the strictest published RA case definitions,[20] based on a previously published definition with a positive predictive value of 0.92[46 47] with additional exclusion criteria, yielding a prevalence rate of 0.76%, consistent with rates in other adult populations.[48] The outcome CVA was also assessed using administrative data. Privacy protection laws prevent access to medical records to confirm diagnoses. However, validation studies for CVA in Canada and other parts of the world have shown a positive predictive value >90%.[25 49 50] A major methodological concern in observational studies assessing effects of drug exposures is confounding by indication, whereby more severe cases are more likely to receive GC and may be at a higher risk for CVD. We attempted to control for confounding by indication bias by using PS.[30 51 52] Because of residual imbalance within PS

quintiles in some of the variables used to calculate the PS, we included these variables as covariates in the final model, in addition to the PS, as suggested.[32] Although we adjusted for all known risk factors for CVA available in our administrative data, our results might still have been affected by unknown or unmeasured confounders (eg, markers of disease severity, smoking) and this should be kept in mind when interpreting our results.

In this study, we were able to adjust for recency of GC expo- sure using a 6-month time window in the weight function. This time window was chosen based on results from previous studies suggesting that only recent GC exposure was associated with an increased risk of CVD.[17 18 53 54] This method has been proposed as a more efficient modelling of time-varying exposures, where outcomes are rare and associations weak. Lack of significance despite the use of this novel method supports the lack of association between GC and CVA.

In conclusion, data from this population-based study did not support a statistically significant increase in the risk of CVA associated with GC exposure. Further studies are needed with larger cohorts with longer follow-up, to confirm if our negative results were due to insufficient power, or whether the risk is truly null, and GC exert a differential effect on the vasculature of the brain and the heart.

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Competing interests:

JAA-Z held doctoral and fellowship awards for this research from the Canadian Arthritis Network/the Arthritis Society of Canada, the Canadian Institutes of Health Research, the Michael Smith Foundation for Health Research and the Mexican Institute for Social Security (IMSS) and CONACyT-Mexico. JAA-Z is currently the British Columbia Lupus Society Scholar and a Canadian Arthritis Network/the Arthritis Society of Canada Scholar. M-PS held a doctoral award from the Canadian Institutes of Health Research, DL is the Nancy and Peter Paul Saunders Scholar and holds an investigator award from the Arthritis Society of Canada.

Ethics

Ethics approval obtained from the University of British Columbia.

Provenance and peer review

Not commissioned; externally peer reviewed.

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Table 1 Baseline characteristics of the incident rheumatoid arthritis cohort

Characteristics	All cases (n=7051)	Exposed (n=2844)	Unexposed (N=4207)	p Value*
Gender				
Women	4683 (66)	1981 (70)	2702 (64)	<0.001
Men	2368 (34)	863 (30)	1505 (36)	<0.001
Mean age (SD)	56 (18)	57 (17)	54 (18)	<0.001
CV drugs use†	1343 (19)	612 (22)	731 (17)	<0.001
Antihypertensive drugs	1212 (17)	553 (19)	611 (15), 659 (16)	<0.001
ACE inhibitors	620 (9)	288 (10)	332 (8)	0.001
β Blockers	543 (8)	252 (9)	291 (7)	0.002
α Blockers	74 (1)	37 (1)	37 (1)	NS
Calcium channel blockers	194 (3)	94 (3)	100 (2)	0.01
ARB	67 (1)	28 (1)	39 (1)	NS
Other CV drugs†	1111 (16)	515 (18)	596 (14)	<0.001
Cardiac glycosides	152 (2)	58 (2)	94 (2)	NS
Diuretics	861 (12)	406 (14)	455 (11)	<0.001
Antiarrhythmic agents	33 (0.5)	16 (0.6)	17 (0.4)	NS
Anticoagulants	108 (2)	42 (1)	66 (2)	NS
Nitrates	241 (3)	107 (4)	134 (3)	NS
Diabetes drugs†	268 (4)	110 (4)	158 (4)	NS
HRT†	728 (10)	323 (11)	405 (10)	0.02
Oral contraceptives†	186 (3)	79 (3)	107 (3)	NS
Lipid-lowering-drugs†				
Fibrates	43 (0.6)	16 (0.6)	27 (0.6)	NS
Statins	366 (5)	179 (6)	187 (4)	<0.001
NSAIDs during follow-up				
No NSAIDs	1308 (19)	355 (12)	953 (23)	<0.001
Traditional NSAIDs	2834 (40)	1089 (38)	1745 (41)	<0.001
COX-2	2909 (41)	1400 (49)	1509 (36)	<0.001
DMARD use				
No DMARDs	4357 (62)	1039 (37)	3318 (79)	<0.001
Non-MTX DMARDs‡	1075 (15)	588 (21)	487 (12)	<0.001
MTX	1619 (23)	1217 (43)	402 (10)	<0.001
Biological agents	229 (3)	206 (7)	23 (0.5)	<0.001
Seen by a rheumatologist	2906 (41)	1563 (55)	1343 (32)	
Charlson index, mean (SD)†	1.0 (2)	1.1 (2)	0.9 (1)	NS
Angina†	1434 (20)	639 (22)	795 (19)	<0.001
COPD†	2014 (29)	896 (32)	1118 (27)	<0.001

Unless otherwise indicated, values represent number (%).
*Comparing exposed to glucocorticoids with never exposed to glucocorticoids.
†From 1990 to rheumatoid arthritis onset.
‡Traditional DMARDs, excluding methotrexate (MTX).
ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease;
CV, cardiovascular; DMARDs, disease-modifying antirheumatic drugs; HRT, hormone replacement therapy; MTX, methotrexate; NS, not significant; NSAIDs, non-steroidal anti-inflammatory drugs.

Table 2 Unadjusted and adjusted Cox regression models assessing the effects of the different GC exposure measures on the risk of CVA

Model	GC exposure (unit)	Univariate RR (95% CI)	p Value	Multivariate* HR (95% CI)	p Value
1	Current use (yes/no)	1.68 (1.06 to 2.68)	0.03	1.41 (0.84 to 2.37)	NS
2	Current mean daily dose (5 mg)	1.11 (0.99 to 1.23)	NS	1.07 (0.94 to 1.21)	NS
3	Total cumulative duration of use (year)	1.18 (1.02 to 1.35)	<0.02	1.11 (0.94 to 1.32)	NS
4	Total past cumulative dose (1 g)	1.06 (1.02 to 1.10)	<0.001	1.04 (0.99 to 1.08)	NS
5	Current daily dose (5 mg) + cumulative duration (year)	1.08 (0.95 to 1.23) 1.15 (0.99 to 1.29)	NS NS	1.05 (0.92 to 1.20) 1.10 (0.92 to 1.31)	NS

Model 1 includes a binary (yes/no) time-dependent representation of the current use. Model 2 includes a continuous time-dependent representation of the current daily dose. Model 3 includes a continuous time-dependent representation of cumulative duration.
Model 4 includes a continuous time-dependent representation of cumulative dose. Model 5 includes both time-dependent variables for cumulative duration of use and current dose.
*Adjusted for propensity score, unbalanced covariates (age, gender, hypertension, statins, diabetes, angina, chronic obstructive pulmonary disease, other cardiovascular drugs use, Charlson index, having seen a rheumatologist for rheumatoid arthritis, number of visits to a doctor per year), current use of COX-2 inhibitors, methotrexate and non-steroidal anti-inflammatory drugs.
CVA, cerebrovascular accidents; GC, glucocorticoids; NS, not significant.