



Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Corticosteroid-related adverse events in patients with giant cell arteritis: A claims-based analysis^{☆, ☆☆☆}



Michael S. Broder, MD, MSHS^a, Khaled Sarsour, PhD, MPH^{b,*}, Eunice Chang, PhD^a, Neil Collinson, PhD^c, Katie Tuckwell, PhD^c, Pavel Napalkov, MD^b, Micki Klearman, MD^b

^a Partnership for Health Analytic Research, LLC, Beverly Hills, CA

^b Real World Data Science/Global Product Development, Genentech, 1 DNA Way, South San Francisco, CA 94080-4990

^c Roche Products Ltd., Welwyn Garden City, UK

ARTICLE INFO

Keywords:

Adverse events
Corticosteroids
Epidemiology
Giant cell arteritis
Health care insurance claims

ABSTRACT

Objective: Corticosteroids (CS) are standard treatment for giant cell arteritis (GCA), but concerns persist over toxicities associated with long-term use. In this retrospective study of medical claims data, we estimated risks for adverse events (AEs) in CS-treated GCA patients.

Methods: Cox regression analyses with CS use as a time-dependent variable were conducted on data from the 2003 to 2012 Truven Health Analytics MarketScan Database. Patients 50 years of age and older who had ≥ 2 claims of newly diagnosed GCA, ≥ 1 filled oral CS prescription, and no AEs before GCA diagnosis were included. The primary outcome was presence of a new CS-related AE.

Results: In total, 2497 patients were included. Their mean age was 71.0 years, and 71% were women. Follow-up was 9680 patient-years (PY). CS treatment continued for a mean (SD) of 1.196 (729.2) days; mean (SD) prescribed cumulative CS dose was 6983.3 mg (6519.9). The overall AE rate was 0.43 events/PY; the most frequent AEs were cataract and bone disease. For each 1000-mg increase in CS exposure, the hazard ratio (HR) increased by 3% (HR = 1.03; 95% CI: 1.02–1.05; $P < 0.001$). Additionally, statistically significant individual associations between increased CS exposure and AE risk were observed for bone-related AEs ($P < 0.001$), cataract ($P < 0.001$), glaucoma ($P = 0.005$), pneumonia ($P = 0.003$), and diabetes mellitus ($P < 0.001$ in a subset of patients with no previous history of diabetes).

Conclusion: CS exposure significantly increased risk for potentially serious AEs, emphasizing a need for new treatment options for GCA patients.

© 2016 Elsevier Inc. All rights reserved.

Introduction

Giant cell arteritis (GCA) is a form of immune-mediated inflammatory systemic vasculitis that affects large and medium-sized arteries, including the extracranial branches of the carotid arteries and the subclavian and axillary branches of the aorta [1].

The annual incidence of GCA in the United States is approximately 10–30 cases per 100,000 persons; the prevalence is estimated to be as high as 278 per 100,000 [2–4]. GCA occurs at

least 2–3 times more often in women and rarely (if ever) in persons younger than 50 years [3,4]. Clinical manifestations of GCA vary, but headache, jaw claudication, polymyalgia rheumatica, and anterior ischemic optic neuropathy are among the most common features [3].

High-dose (1 mg/kg/day), long-term corticosteroids (CS) attenuate systemic inflammation in most patients [4,5]. In a survey of long-term CS users, however, 90% reported ≥ 1 adverse event (AE) attributed to this treatment [6]. Another population-based study that focused specifically on GCA patients reported that 86% experienced AEs, including diabetes mellitus (DM), hypertension, fractures, gastrointestinal bleeding, sleeplessness, mood disturbances, cataracts, and infections [7]. These studies included data on patients treated with CS as early as 1950—shortly after the introduction of cortisone as a therapy for inflammatory disease—but do not provide data beyond 2002. The aim of the current study was to provide clinicians with updated information on AE risk among CS-treated GCA patients.

[☆]We thank Gordon H. Sun, M.D., M.S., for his contributions to the study design and for drafting the initial article, and we thank John H. Stone, M.D., M.P.H., for his thoughtful comments on the article.

^{☆☆}This study was funded by Genentech Inc., a member of the Roche Group. F. Hoffmann-La Roche Ltd. developed the initial concept for the study and provided funding for article preparation.

* Corresponding author.

E-mail address: sarsourk@gene.com (K. Sarsour).

Methods

Study database and selection criteria

In this retrospective cohort analysis, Cox regression models with CS use as a time-dependent variable were used to estimate the risk for AEs in GCA patients. The data source was the 2003–2012 Truven Health Analytics MarketScan Database, which includes health insurance claims from large employers and health plans across the United States. Claims include information on each physician visit, medical procedure, hospitalization, drug dispensed, date of service/prescription, number of days of medication supplied, and test performed.

We included patients who had ≥ 2 medical claims with GCA as a listed diagnosis (*International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM]*, code 446.5) in the identification period (January 1, 2004 to December 31, 2009) and ≥ 1 oral CS prescription fill within 6 months before or after the index date. A CS prescription fill was required to exclude patients who were evaluated for GCA but who might not have had the disease. The index date was the first date of GCA diagnosis in the identification period. We excluded persons younger than 50 because the validity of a GCA diagnosis may be questioned in that age group [2,8]. We also excluded patients who had a GCA claim in the year before the index date (i.e., did not have newly diagnosed GCA). Patients were followed up for ≥ 1 year and until either disenrollment from a plan in the database or study end (December 31, 2012), whichever came first.

Adverse events

The primary outcome was the presence of a new CS-related AE during the post-index period. AEs of interest were those likely, based on published literature [9–11], to be associated with high-dose CS use and identifiable in a claims database. These were categorized as bone-related conditions (nonvertebral/vertebral fractures, osteoporosis, aseptic necrosis of bone, and hip-replacement procedures), opportunistic infections, pneumonia, cataracts, glaucoma, peptic ulcer disease, and DM.

To ensure that AEs did not pre-date exposure to CS, patients with AEs in the pre-index period were excluded. DM is highly prevalent in older patients [12], and its inclusion would have resulted in the exclusion of close to 20% of otherwise eligible patients. Therefore, we explored the AE of DM in only a subset of patients who did not have DM at baseline. Opportunistic infections were limited to those considered severe (e.g., severe candidiasis and severe herpes simplex) and excluded common conditions such as candidal skin infection. AEs were identified using *ICD-9-CM* diagnosis and/or Current Procedural Terminology codes (Supplementary Table S1) from published studies or from clinician input [13–16]. An AE was considered present in a patient the first time its corresponding code(s) was identified.

CS exposure

The primary measure of CS exposure was cumulative prednisone-equivalent dose [17] from 1 year before the index date and was updated daily throughout the follow-up period such that, on any given day, CS exposure was cumulative from 1 year before the index date to the day of calculation. In sensitivity analyses, we examined 2 other measures of exposure, both of which were also updated daily: cumulative days (from 1 year before the index date to the day of calculation) during which oral CS were available to the patient and contemporaneous oral CS use. Contemporaneous use was a categorical variable designed to describe the most recent CS use. Categories were current use, recent use (within 90 days),

distant use (> 90 days but ≤ 180 days), remote use (> 180 days but ≤ 365 days), and no use within 1 year.

Covariates

Baseline measures included patient demographics (age, sex, region), 2 measures of overall health, and GCA-specific measures. The first measure of overall health was number of chronic conditions, counted using the Healthcare Cost and Utilization Project Chronic Condition Indicator. This defines a chronic condition as one lasting ≥ 12 months and limiting self-care, independent living, and social interactions or resulting in the need for ongoing medical intervention [18,19]. The second measure was the Charlson comorbidity index (CCI) [20,21], a validated measure of overall disease severity, originally developed as a tool for predicting in-hospital mortality.

GCA-specific measures included temporal artery biopsy and specific symptoms (headache, polymyalgia rheumatica, vision deficits, vestibular dysfunction, aortic insufficiency, aneurysm, dissection, stroke, myocardial infarction, left ventricular dysfunction, jaw claudication, arthralgia, fever, and malaise) [22]. Treatment for GCA (oral CS, methotrexate, azathioprine, infliximab, tocilizumab, etanercept, and leflunomide) and the extent to which methotrexate users differed from nonusers in oral CS intake were also reported. Demographics and overall health measures were derived using data from the pre-index period, and other measures were derived using data from the year after the index date (e.g., after the GCA diagnosis was made), with the exception of temporal artery biopsy, which was derived using data from both before and 1 year after the index date.

Statistical analysis

Descriptive statistics, including mean, standard deviation (SD), median, and percentage, were reported for each measure as applicable. Incidence rates were calculated as the number of patients with a given event divided by total patient-years (PY). Total PY were calculated (for each event) as the sum of years from the index date to that event or the end of follow-up. To study the association between AE risk and oral CS use, Cox regression models were used. Separate models were conducted for the initial AE and for selected individual AEs. Oral CS use was updated daily for each day of follow-up as a time-dependent variable in each model. For the initial AE analysis, patients without any AE were censored at the end of follow-up. For individual AE analyses, patients without that AE were censored at the end of follow-up. We reported adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). All data transformations and statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). All tests were 2-sided and had a significance level of 0.05.

Results

From 2004 to 2009, the database contained information on 12,198 persons 50 and older who had ≥ 2 qualifying *ICD-9-CM* codes. Of these, 5645 were not continuously enrolled during the required period of 1 year before and 1 year after the index period. An additional 1196 had no CS fills within 6 months before or after the index date. Overall, 665 persons did not have newly diagnosed GCA, and 2205 had ≥ 1 AE (other than DM) during the pre-index period. Thus, the primary study cohort included 2497 patients with newly diagnosed GCA treated with CS who did not experience an antecedent AE.

Total follow-up time was 9680 PY, and mean follow-up time was 3.9 years/patient. Mean age of the primary study group was

Table 1
Characteristics of 2497 patients with GCA treated between 2004 and 2009

Characteristic	Patients with GCA, N = 2497
Age, years, mean (SD)	71.0 (10.6)
50–59, n (%)	450 (18.0)
60–69, n (%)	606 (24.3)
70–79, n (%)	811 (32.5)
80+, n (%)	630 (25.2)
Female, n (%)	1773 (71.0)
US geographic region, n (%)	
North Central	853 (34.2)
Northeast	269 (10.8)
South	858 (34.4)
West	517 (20.7)
Chronic conditions, mean (SD)	3.4 (1.8)
Charlson comorbidity index, mean (SD)	1.5 (1.7)
Comorbidities, n (%)	
Headache	1321 (52.9)
Arthralgia	777 (31.1)
Polymyalgia rheumatica	617 (24.7)
Stroke	617 (24.7)
Malaise	510 (20.4)
Vision deficits	446 (17.9)
Vestibular dysfunction	297 (11.9)
Aortic insufficiency, aneurysm, and dissection	193 (7.7)
Fever	52 (2.1)
Myocardial infarction	49 (2.0)
Left ventricular dysfunction	22 (0.9)
Jaw claudication	18 (0.7)
Pharmacologic treatment, n (%)	
Methotrexate	291 (11.7)
Azathioprine	49 (2.0)
Infliximab	8 (0.3)
Leflunomide	16 (0.6)
Etanercept	14 (0.6)
Tocilizumab	0 (0.0)

GCA, giant cell arteritis; SD, standard deviation; US, United States.

71.0 years; 71.0% of the patients were women (Table 1). Patients had a mean of 3.4 (SD = 1.8) chronic conditions and a CCI of 1.5 (SD = 1.7). The most common GCA-related comorbidities reported during the 1-year post-index period included headache (52.9%), arthralgia (31.1%), polymyalgia rheumatica (24.7%), and stroke (24.7%). The most common treatment other than oral CS (a requirement for inclusion) was methotrexate (11.7%).

The median initial oral CS dose was 40 mg/day (mean = 38.8, SD = 28.6) (Table 2). CS treatment continued for a median of 996 days or 33.2 months (mean = 1196.6, SD = 729.2), and the median cumulative dose was 5350 mg (mean = 6983.3, SD = 6519.9). CS dose was reduced from the initial 40 mg/day over the course of

Table 2
Oral CS treatment in GCA patients from start of study period to end of follow-up^a

Category	Patients, n	Mean	SD	Median
First dose in study period, mg/day	2497	38.8	28.6	40
Observed time on treatment, days ^b	2497	1196.6	729.2	996
Cumulative dose during the time on treatment, mg	2497	6983.3	6,519.9	5350
Days to reduce to ≤ 7.5 mg/day ^c	1460	283.8	329.0	190
Cumulative dose to reduce to ≤ 7.5 mg/day, mg ^d	1460	4442.7	4427.6	3380
Days to reduce to ≤ 5.0 mg/day ^c	1381	308.5	345.8	210
Cumulative dose to reduce to ≤ 5.0 mg/day, mg ^d	1381	4620.9	4474.4	3600

CS, corticosteroids; GCA, giant cell arteritis; SD, standard deviation.

Patients who stopped oral corticosteroid treatment before their dose reached the specified level (7.5 or 5.0 mg) were excluded.

^a Patients were followed up for ≥ 1 year and until either disenrollment or study end (December 31, 2012), whichever came first.

^b Period between the first fill and the end of days of supply of the last oral corticosteroid fill.

^c Days from first oral corticosteroid fill to the day on which daily dose was reached 7.5 (or 5) mg.

^d Cumulative dose from first oral corticosteroid fill to the day on which listed daily dose was reached.

Table 3
Rate of oral CS-related AEs over 9680 PY

Oral CS-related AE	Events/PY
Any	0.426
Cataract	0.158
Bone disease	0.156
Osteoporosis	0.099
Fractures	0.066
Hip replacement	0.008
Aseptic necrosis of bone	0.004
Pneumonia	0.068
Glaucoma	0.022
Opportunistic infections	0.010
Ulcer disease	0.006

AE, adverse event; CS, corticosteroids; PY, patient-year.

treatment. The median time to a daily dose of ≤ 7.5 mg/day was 190 days (6.3 months) [mean = 283.8 days (9.4 months), SD = 329.0], and the median time to ≤ 5.0 mg/day was 210 days (7.0 months) [mean = 308.5 days (10.3 months), SD = 345.8].

The overall rate of AEs was 0.43 events/PY (Table 3). The most frequent AE was cataract (0.16 events/PY), followed by bone disease (osteoporosis, fracture, hip replacement, and aseptic necrosis). Patients who experienced any AE, compared with those who did not experience any AE, had been prescribed more days of oral CS (median = 195 vs 102.5 days) and received a higher cumulative prednisone-equivalent dose (median = 3400 vs 2145 mg). The population was divided into 7 groups by CS exposure, and the AE rate in the 1-year post-index period was plotted for each group (Fig.).

To estimate risk for a first AE, we conducted Cox regression analysis with daily updated CS exposure as the independent variable. The model included age, sex, geographic region, number of chronic conditions, CCI, and DM (at baseline) as covariates. The model demonstrated that for each 1000-mg increase in CS exposure, the hazard ratio for first AE increased by 3% (HR = 1.03; 95% CI: 1.02–1.05; *P* < 0.001) (Table 4). In this model, age 60 or older, female sex, and number of chronic conditions were statistically significantly associated with elevated risk for initial AE.

Additional Cox models addressed individual AEs. A statistically significant association between increased oral CS exposure and increased AE risk was observed for bone-related AEs (HR = 1.05; 95% CI: 1.03–1.06; *P* < 0.001), cataract (HR = 1.03; 95% CI: 1.02–1.05; *P* < 0.001), glaucoma (HR = 1.05; 95% CI: 1.01–1.08; *P* = 0.005), and pneumonia (HR = 1.03; 95% CI: 1.01–1.04; *P* = 0.003) (Tables 4 and 5). There was no such relationship between CS exposure and risk for ulcer disease, hip replacement, or opportunistic infection. A subset of 2008 patients who did not have DM in the pre-index period was used to estimate the association between

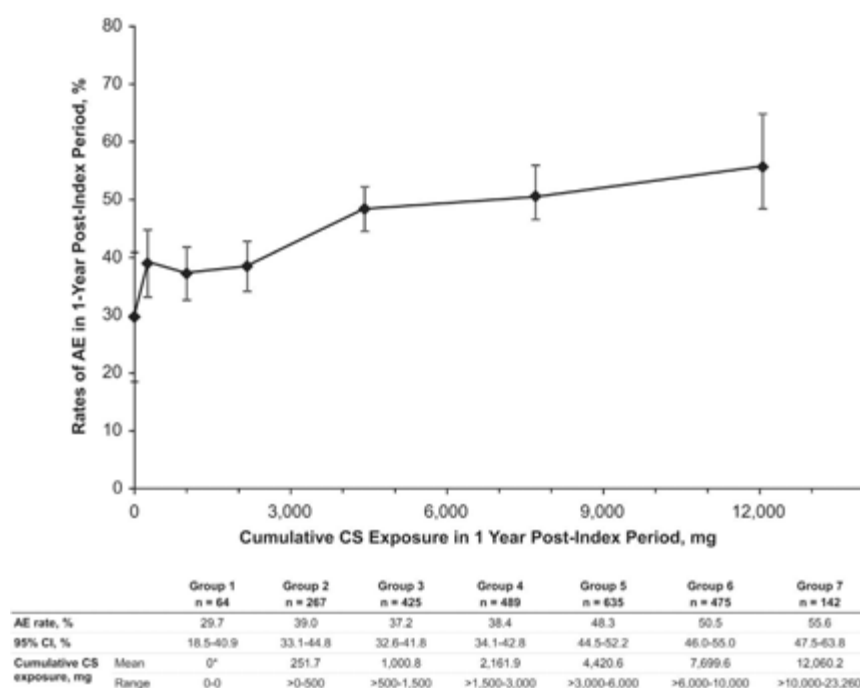


Fig. Relationship between oral CS exposure during the year after GCA diagnosis and the rate of CS-related AEs. Cumulative oral CS use in the post-index period. To be included in the study, each patient had to have ≥ 1 prescription for CS filled in the 6 months before or after the index date. AE, adverse event; CI, confidence interval; CS, corticosteroids; GCA, giant cell arteritis.

CS use and DM. The HR for DM increased by 5% with each 1000-mg CS exposure (HR = 1.05; 95% CI: 1.03–1.07; $P < 0.001$) in patients with no history of DM (not shown).

We compared oral CS use between 291 users and 2206 non-users of methotrexate. Users filled a mean of 225 days' supply of CS over 1 year, or 5645 mg, compared with 161 days and 3664 mg for nonusers. Sensitivity analyses were conducted to investigate the impact of different methods of specifying CS exposure on the Cox model results. The first sensitivity analysis used cumulative months of treatment with oral CS as a predictor of AE risk, and the second used contemporaneous use of CS (classified as current, recent, distant, or remote). Both models were consistent with the

primary analysis, demonstrating a statistically significant increase in first AE risk as CS exposure became greater or more recent. The models also confirmed a statistically significant relationship between CS use and risk for all the individual outcomes identified in the primary model (Supplementary Table S2).

Discussion

Oral CS at relatively high doses and for prolonged periods are the mainstay of treatment for GCA, but they are not without risk. In this study of 2497 GCA patients, the median initial CS dose was

Table 4
Cox regression model of risk for first AE and bone-related AEs based on daily updated cumulative oral CS exposure

	HR (95% CI)					
	First AE	Bone-related AE	Osteoporosis	Fracture	Hip replacement	Aseptic necrosis of bone
Age, years						
60–69 vs 50–59	1.41 (1.19–1.66)*	1.29 (1.03–1.62)**	1.36 (1.04–1.78)**	1.41 (0.99–2.01)	1.12 (0.47–2.67)	0.85 (0.32–2.27)
70–79 vs 50–59	2.16 (1.86–2.51)*	1.98 (1.62–2.42)**	2.12 (1.67–2.70)**	2.30 (1.69–3.14)*	1.76 (0.83–3.74)	0.97 (0.41–2.31)
80+ vs 50–59	2.14 (1.83–2.51)*	2.18 (1.77–2.69)**	2.09 (1.62–2.69)**	3.20 (2.34–4.38)*	1.88 (0.86–4.09)	0.90 (0.35–2.29)
Female vs male	1.33 (1.20–1.48)*	2.07 (1.77–2.41)*	2.29 (1.89–2.77)*	1.91 (1.54–2.37)*	1.63 (0.92–2.88)	1.18 (0.59–2.37)
US geographic region						
North Central vs South	0.98 (0.88–1.10)	0.89 (0.77–1.04)	0.90 (0.75–1.08)	0.94 (0.77–1.16)	1.12 (0.65–1.91)	0.68 (0.33–1.41)
Northeast vs South	0.97 (0.83–1.15)	1.17 (0.95–1.44)	1.14 (0.89–1.46)	1.03 (0.77–1.39)	1.12 (0.52–2.41)	0.51 (0.15–1.73)
West vs South	1.03 (0.91–1.18)	1.03 (0.87–1.22)	1.16 (0.95–1.41)	0.98 (0.77–1.24)	0.69 (0.34–1.41)	0.58 (0.24–1.40)
No. chronic conditions	1.04 (1.01–1.07)**	1.08 (1.04–1.12)**	1.05 (1.01–1.10)**	1.10 (1.04–1.16)*	1.09 (0.95–1.26)	0.98 (0.81–1.19)
Charlson comorbidity index	1.03 (1.00–1.07)	0.98 (0.94–1.03)	0.98 (0.93–1.03)	0.96 (0.90–1.03)	0.87 (0.72–1.05)	1.19 (1.00–1.43)
Diabetes mellitus	0.93 (0.82–1.06)	0.78 (0.65–0.93)**	0.65 (0.52–0.81)*	1.09 (0.86–1.38)	1.00 (0.52–1.95)	0.59 (0.23–1.47)
Cumulative exposure, per 1 g prednisone equivalent ^a	1.03 (1.02–1.05)*	1.05 (1.03–1.06)*	1.05 (1.03–1.07)*	1.04 (1.03–1.06)*	1.04 (0.99–1.08)	1.06 (1.01–1.12)**

AE, adverse event; CI, confidence interval; CS, corticosteroid; HR, hazard ratio; US, United States. Values in bold are significant.

* $P < 0.001$.

** $P < 0.05$.

^a Cumulative oral CS use since the beginning of the pre-index period; time-dependent variable, updated daily.

Table 5
Cox regression model of non–bone-related AE risk based on daily updated cumulative oral CS exposure

	HR (95% CI)				
	Cataract	Pneumonia	Glaucoma	Opportunistic infection	Ulcer disease
Age, years					
60–69 vs 50–59	1.87 (1.49–2.34)*	0.99 (0.72–1.38)	1.43 (0.84–2.44)	0.86 (0.47–1.60)	1.71 (0.58–5.03)
70–79 vs 50–59	2.88 (2.34–3.54)*	1.60 (1.21–2.11)*	1.80 (1.10–2.93)**	0.56 (0.31–1.02)	3.03 (1.16–7.94)**
80+ vs 50–59	1.46 (1.16–1.83)*	2.43 (1.84–3.20)*	2.49 (1.52–4.06)*	0.92 (0.51–1.64)	2.65 (0.98–7.19)
Female vs male	1.18 (1.03–1.36)**	0.97 (0.81–1.16)	1.22 (0.89–1.68)	0.93 (0.60–1.45)	0.72 (0.42–1.22)
US geographic region					
North Central vs South	0.94 (0.81–1.09)	1.11 (0.91–1.35)	1.27 (0.90–1.79)	1.15 (0.70–1.88)	0.82 (0.45–1.49)
Northeast vs South	0.94 (0.76–1.17)	0.96 (0.72–1.29)	0.91 (0.53–1.56)	1.09 (0.53–2.23)	0.51 (0.17–1.47)
West vs South	1.03 (0.87–1.22)	0.89 (0.70–1.14)	1.43 (0.98–2.09)	1.01 (0.56–1.82)	0.91 (0.45–1.83)
No. chronic conditions	0.98 (0.95–1.02)	1.05 (0.99–1.10)	1.06 (0.97–1.16)	1.05 (0.93–1.19)	0.93 (0.79–1.09)
Charlson comorbidity index	1.04 (0.99–1.09)	1.13 (1.08–1.19)*	0.87 (0.78–0.98)**	1.15 (1.02–1.29)**	1.13 (0.97–1.33)
Baseline diabetes	0.93 (0.78–1.10)	0.99 (0.80–1.23)	1.68 (1.18–2.39)**	0.95 (0.56–1.61)	1.21 (0.63–2.30)
Cumulative exposure, per 1 g prednisone equivalent ^a	1.03 (1.02–1.05)*	1.03 (1.01–1.04)**	1.05 (1.01–1.08)**	1.04 (1.00–1.08)	1.00 (0.94–1.06)

AE, adverse event; CI, confidence interval; CS, corticosteroid; HR, hazard ratio; US, United States. Values in bold are significant.

* $P \leq 0.001$.

** $P < 0.05$.

^a Cumulative oral CS use since the beginning of the pre-index period; time-dependent variable, updated daily.

equivalent to 40 mg/day prednisone. The next most common treatment, methotrexate, was used by only 11% of patients. Moreover, methotrexate users filled more days and had higher total doses of CS than nonusers, suggesting that this medication is still used by clinicians as a “steroid-sparing” treatment despite good evidence that its efficacy, if any, in GCA is limited [23] and indicating methotrexate may not be steroid sparing.

Oral CS treatment continued an average of >3 years, and >6 months elapsed before the daily dose fell below 7.5 mg. In a Cox regression model, controlling for a variety of covariates, increasing exposure to CS was significantly associated with increased risk for various AEs. Each gram of CS prescribed increased the risk for AEs by 3%. For individual AEs such as fracture, osteoporosis, cataract, and glaucoma, the increase in risk was 3–5%. We observed no increased risk for ulcer, opportunistic infection, or hip replacement. In patients who did not previously have DM, the risk for DM rose 5% with each 1000-mg CS exposure. Even a successful 1-year glucocorticoid taper—assuming a starting dose of 60 mg/day, continued for 1 month and then tapered to 7.5 mg/day by 6 months, followed by discontinuation by 1 year—would lead to a cumulative prednisone dose of approximately 6000 mg. Unfortunately, GCA patients may require treatment with CS for many years, with cumulative doses >10,000 mg, thereby greatly increasing their risk for DM. The results were consistent whether CS exposure was measured in milligrams of prednisone-equivalent steroids, months of exposure, or time since last use.

Oral CS use in this recent national sample of GCA patients appears consistent with recommendations from published guidelines. Although there is some variation in the initial starting dose, most guidelines consider oral CS use for this indication “high dose,” ranging from 40 to 60 mg/day [24–26]. Little appears to have changed in the past several decades in the use of CS to treat GCA patients. In a study of patients in Olmsted County, Minnesota, with diagnoses of GCA from 1950 to 1991 and monitored for a median of 10 years, Proven et al. [7] reported an initial CS dose of 60 mg/day, 6.5 months to reduce the dose to 7.5 mg/day, and 7.5 months to reduce the dose to 5 mg/day, virtually identical to our findings.

The major risks associated with CS use have been long established. Prolonged use of high CS doses places patients at substantial risk for as many as 21 different types of complications, including bone fractures, hyperglycemia and DM, infections,

hypertension, cataracts, and weight gain [27]. Increasing dose and duration have been associated with increased toxicity [28]. The present study supplements an older body of knowledge pertaining to the use of CS in patients with autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis (RA) and adds disease-specific risk estimates for complications of therapy in GCA patients [29,30]. Disease-specific risk estimates are useful because the typical CS regimens vary considerably across diseases. RA patients have benefited substantially, in terms of decreased morbidity and decreased AE burden, from the development of novel therapies that reduce the reliance on CS [31]. The development of CS-sparing treatments for GCA might provide similar benefit [4,32]. In particular, the anti-IL-6 receptor- α monoclonal antibody tocilizumab may result in improvement in patients with refractory GCA and/or unacceptable side effects related to corticosteroids [33]. In the present study, the use of methotrexate did not result in lower CS use. We did not adjust for differences between methotrexate users and nonusers, suggesting additional analyses are necessary to confirm it.

An important strength of our study is the expansion of prior literature—most of which describe small samples—and the identification of nearly 2500 GCA patients (Supplementary Table S3). Previous studies of CS use in GCA include 5 randomized controlled trials with sample sizes of 21–98 patients [23,34–37]. These studies, and a meta-analysis of 3 of them [38], were too small to confirm the statistical significance of even large differences in CS AE rates. Other previously published cohort analyses were based on national or county-level epidemiological data from southern Australia [39], northern Germany [40], Olmsted County, Minnesota [7,41], the U.K. [42], Spain [43,44], Brazil [45], Israel [46], France [47], and Sweden [1]. In a Spanish retrospective study of 103 GCA patients, Les and colleagues found that a statistically significantly higher proportion of patients receiving >30 mg/day prednisone had CS-related AEs compared to those receiving \leq 30 mg/day (66% vs 43%; $P = 0.02$) [43]. In a 2014 retrospective study of 106 patients, Alba compared GCA patients who experienced relapses with those who did not and found the first group had received higher cumulative CS doses (by almost 1 g over a year) and had higher rates of osteoporosis (66% vs 32%; $P = 0.001$) but not other CS-related AEs [44]. Most other studies identified relatively high rates of CS-related AEs but either were not designed to detect or were underpowered to detect statistically significant differences in

risk between high and low CS users. Our study provides a unique perspective on U.S. patients who have commercial insurance. Additional strengths included the use of CS exposure variables updated daily. This allowed us to estimate CS exposure at the time of an AE instead of simply measuring annual exposure, which in some cases might have occurred after the outcome of interest. We used 3 distinct measures of exposure and found consistent results. The use of Cox regression allowed us to observe patients for variable time periods and to control for measurable variation between patients.

This study also has potential limitations. We have no direct evidence that observed CS prescription fills resulted in the observed increase in AEs. In addition, distinguishing between an underlying (pre-existing) comorbidity and a true AE resulting from CS is particularly difficult using administrative claims. Claims are submitted for payment, not collected for research purposes, and they lack detailed clinical information that would permit confirmation of patient diagnoses and allow nuanced patient characterization. We had to rely on proxies, albeit validated ones such as CCI, to estimate disease severity and on individual *ICD-9-CM* codes, with no clinical or pathological validation, to identify outcomes. For example, the prevalence of stroke in our cohort was 24.7% higher than previously reported [48,49]. We used a single *ICD-9-CM* code for identifying comorbidities, which might have resulted in the inclusion of “rule-out” cases, although our strategy was similar to what has been used in other studies [50]. We have no reason to believe that miscoding occurred differentially, depending on CS exposure. Such miscoding would have the effect of reducing the observed difference—bias toward the null hypothesis. Exclusion of patients with pre-index claims for *ICD-9-CM* codes for AEs might have led to an underestimation of risk. Although we used multiple methods for measuring exposure, other techniques have been described. A “recency-weighted” method that combines variables such as drug dose and duration into a “composite” weight has been used to model the impact of CS on infection in RA [51,52]. We considered this approach; however, the composite variable was designed using a different health insurance database and for a different disease. Finally, we could not measure actual CS use, only prescription fills, a limitation common to all studies using insurance claims.

Conclusions

High-dose oral CS use has been the primary treatment for GCA patients for many years. Current practice involves initial doses of approximately 40 mg/day, with typical CS exposure of >5 g over the course of several years. At these dosing levels, AEs are common. Each additional 1000 mg prednisone raises the HR for new AEs by 3% and the HR for new-onset DM by 5%. New treatments that improve outcomes for GCA patients while reducing CS exposure are needed.

Author contributions

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. MSB had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Study conception and design: Broder, Sarsour, Chang, Collinson, Tuckwell, Napalkov, and Klearman.

Acquisition of data: Broder, Sarsour, and Chang.

Analysis and interpretation of data: Broder, Sarsour, Chang, Collinson, Tuckwell, Napalkov, and Klearman.

Competing interests

Sarsour, Napalkov, and Klearman are employees of Genentech, a member of the Roche Group. Collinson and Tuckwell are employees of Roche Products Ltd. Broder and Chang are employees of Partnership for Health Analytic Research, LLC, a health services research company that received funding for this research from Genentech.

Appendix A. Supplementary material

Supplementary data are available in the online version of this article at <http://dx.doi.org/10.1016/j.semarthrit.2016.05.009>

References

- [1] Zoller B, Li X, Sundquist J, Sundquist K. Occupational and socio-economic risk factors for giant cell arteritis: a nationwide study based on hospitalizations in Sweden. *Scand J Rheumatol* 2013;42:487–97.
- [2] Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States, Part II. *Arthritis Rheum* 2008;58:26–35.
- [3] Borchers AT, Gershwin ME. Giant cell arteritis: a review of classification, pathophysiology, geoeconomics, and treatment. *Autoimmun Rev* 2012;11:A544–54.
- [4] Salvarani C, Cantini F, Hunder GG. Polymyalgia rheumatica and giant-cell arteritis. *Lancet* 2008;372:234–45.
- [5] Weyand CM, Goronzy JJ. Clinical practice: giant-cell arteritis and polymyalgia rheumatica. *N Engl J Med* 2014;371:50–7.
- [6] Curtis JR, Westfall AO, Allison J, Bijlsma JW, Freeman A, George V, et al. Population-based assessment of adverse events associated with long-term glucocorticoid use. *Arthritis Rheum* 2006;55:420–6.
- [7] Proven A, Gabriel SE, Orces C, O’Fallon WM, Hunder GG. Glucocorticoid therapy in giant cell arteritis: duration and adverse outcomes. *Arthritis Rheum* 2003;49:703–8.
- [8] Gonzalez-Gay MA, Martinez-Dubois C, Agudo M, Pompei O, Blanco R, Llorca J. Giant cell arteritis: epidemiology, diagnosis, and management. *Curr Rheumatol Rep* 2010;12:436–42.
- [9] van Staa TP, Leufkens HG, Cooper C. The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. *Osteoporos Int* 2002;13:777–87.
- [10] Da Silva JA, Jacobs JW, Kirwan JR, Boers M, Saag KG, Inês LB, et al. Safety of low dose glucocorticoid treatment in rheumatoid arthritis: published evidence and prospective trial data. *Ann Rheum Dis* 2006;65:285–93.
- [11] de Jong DJ, Corstens FH, Mannaerts L, Van Rossum LG, Naber AH. Corticosteroid-induced osteoporosis: does it occur in patients with Crohn’s disease? *Am J Gastroenterol* 2002;97:2011–5.
- [12] Geiss LS, Wang J, Cheng YJ, Thompson TJ, Barker L, Li Y, et al. Prevalence and incidence trends for diagnosed diabetes among adults aged 20 to 79 years, United States, 1980–2012. *J Am Med Assoc* 2014;312:1218–26.
- [13] Li J, Morlet N, Ng JQ, Semmens JB, Knuijan MW. Significant nonsurgical risk factors for endophthalmitis after cataract surgery: EPSWA fourth report. *Invest Ophthalmol Vis Sci* 2004;45:1321–8.
- [14] Ozminkowski RJ, Wang S, Walsh JK. The direct and indirect costs of untreated insomnia in adults in the United States. *Sleep* 2007;30:263–73.
- [15] Taylor JK, Schoenbaum M, Katon WJ, Pincus HA, Hogan DM, Unutzer J. Strategies for identifying and channeling patients for depression care management. *Am J Manag Care* 2008;14:497–504.
- [16] Brooks RA, Kleinman NL, Melkonian AK. Health care cost comparisons by point of service for employees with or without insomnia. Presented at Academy of Managed Care Pharmacy 19th Annual Meeting Showcase, San Diego, CA; April 10–13, 2007.
- [17] Garber EK, Targoff C, Paulus HE. Glucocorticoid preparations. In: Paulus HE, Furst DE, Droomgoole SH, (eds). *Drugs for Rheumatic Diseases*. New York, NY: Churchill Livingstone; 1987. p. 446.
- [18] Chronic Condition Indicator (CCI) for ICD-9-CM. Rockville, MD: Agency for Healthcare Policy and Research. (<http://www.hcup-us.ahrq.gov/toolssoftware/chronic/chronic.jsp>); Accessed April 28, 2016.
- [19] Hwang W, Weller W, Ireys H, Anderson G. Out-of-pocket medical spending for care of chronic conditions. *Health Aff (Millwood)* 2001;20:267–78.
- [20] 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.

- [21] Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 1992;45:613–9.
- [22] Kawasaki A, Purvin V. Giant cell arteritis: an updated review. *Acta Ophthalmol* 2009;87:13–32.
- [23] Hoffman GS, Cid MC, Hellmann DB, Guillevin L, Stone JH, Schousboe J, et al. A multicenter, randomized, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis. *Arthritis Rheum* 2002;46:1309–18.
- [24] Dasgupta B, Borg FA, Hassan N, Alexander L, Barraclough K, Bourke B, et al. BSR and BHRP guidelines for the management of giant cell arteritis. *Rheumatology (Oxford)* 2010;49:1594–7.
- [25] Ozaki S, Ando M, Isobe M, Kobayashi S, Matsunaga N, Miyata T, et al. Guideline for management of vasculitis syndrome (JCS 2008): Japanese Circulation Society. *Circ J* 2011;75:474–503.
- [26] Warrington KJ, Matteson EL. Management guidelines and outcome measures in giant cell arteritis (GCA). *Clin Exp Rheumatol* 2007;25(Suppl. 47):S137–41.
- [27] Manson SC, Brown RE, Cerulli A, Vidaurre CF. The cumulative burden of oral corticosteroid side effects and the economic implications of steroid use. *Respir Med* 2009;103:975–94.
- [28] Liu D, Ahmet A, Ward L, Krishnamoorthy P, Mandelcorn ED, Leigh R, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. *Allergy Asthma Clin Immunol* 2013;9:30.
- [29] Wolfe F, Caplan L, Michaud K. Treatment for rheumatoid arthritis and the risk of hospitalization for pneumonia: associations with prednisone, disease-modifying antirheumatic drugs, and anti-tumor necrosis factor therapy. *Arthritis Rheum* 2006;54:628–34.
- [30] Zonana-Nacach A, Barr SG, Magder LS, Petri M. Damage in systemic lupus erythematosus and its association with corticosteroids. *Arthritis Rheum* 2000;43:1801–8.
- [31] O'Dell JR. Therapeutic strategies for rheumatoid arthritis. *N Engl J Med* 2004;350:2591–602.
- [32] Silva-Fernandez L, Loza E, Martinez-Taboada VM, Blanco R, Rúa-Figueroa I, Pego-Reigosa JM, et al. Biological therapy for systemic vasculitis: a systematic review. *Semin Arthritis Rheum* 2014;43:542–57.
- [33] Loricera J, Blanco R, Hernández JL, Castañeda S, Mera A, Pérez-Pampín E, et al. Tocilizumab in giant cell arteritis: multicenter open-label study of 22 patients. *Semin Arthritis Rheum* 2015;44:717–23.
- [34] Jover JA, Hernandez-Garcia C, Morado IC, Vargas E, Banares A, Fernandez-Gutierrez B. Combined treatment of giant-cell arteritis with methotrexate and prednisone: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2001;134:106–14.
- [35] Spiera RF, Mitnick HJ, Kupersmith M, Richmond M, Spiera H, Peterson MG, et al. A prospective, double-blind, randomized, placebo controlled trial of methotrexate in the treatment of giant cell arteritis (GCA). *Clin Exp Rheumatol* 2001;19:495–501.
- [36] Kyle V, Hazleman BL. Treatment of polymyalgia rheumatica and giant cell arteritis; II: relation between steroid dose and steroid associated side effects. *Ann Rheum Dis* 1989;48:662–6.
- [37] Mazlumzadeh M, Hunder GG, Easley KA, Calamia KT, Matteson EL, Griffing WL, et al. Treatment of giant cell arteritis using induction therapy with high-dose glucocorticoids: a double-blind, placebo-controlled, randomized prospective clinical trial. *Arthritis Rheum* 2006;54:3310–8.
- [38] Mahr AD, Jover JA, Spiera RF, Hernández-García C, Fernández-Gutiérrez B, Lavalley MP, et al. Adjuvant methotrexate for treatment of giant cell arteritis: an individual patient data meta-analysis. *Arthritis Rheum* 2007;56:2789–97.
- [39] Dunstan E, Lester SL, Rischmueller M, Dodd T, Black R, Ahern M, et al. Epidemiology of biopsy-proven giant cell arteritis in South Australia. *Intern Med J* 2014;44:32–9.
- [40] Herlyn K, Buckert F, Gross WL, Reinhold-Keller E. Doubled prevalence rates of ANCA-associated vasculitides and giant cell arteritis between 1994 and 2006 in northern Germany. *Rheumatology (Oxford)* 2014;53:882–9.
- [41] Labarca C, Koster MJ, Crowson CS, Makol A, Ytterberg SR, Matteson EL, et al. Predictors of relapse and treatment outcomes in biopsy-proven giant cell arteritis: a retrospective cohort study. *Rheumatology (Oxford)* 2016;55:347–56.
- [42] Smeeth L, Cook C, Hall AJ. Incidence of diagnosed polymyalgia rheumatica and temporal arteritis in the United Kingdom, 1990–2001. *Ann Rheum Dis* 2006;65:1093–8.
- [43] Les I, Pijoán JI, Rodríguez-Álvarez R, Ruiz-Irastorza G, Martínez-Berriotxo A. Effectiveness and safety of medium-dose prednisone in giant cell arteritis: a retrospective cohort study of 103 patients. *Clin Exp Rheumatol* 2015;33(Suppl. 89):S-90–7.
- [44] Alba MA, García-Martínez A, Prieto-González S, Tavera-Bahillo I, Corbera-Bellalta M, Planas-Rigol E, et al. Relapses in patients with giant cell arteritis: prevalence, characteristics, and associated clinical findings in a longitudinally followed cohort of 106 patients. *Medicine (Baltimore)* 2014;93:194–201.
- [45] Souza AW, Okamoto KY, Abrantes F, Schau B, Bacchiega AB, Shinjo SK. Giant cell arteritis: a multicenter observational study in Brazil. *Clinics (Sao Paulo)* 2013;68:317–22.
- [46] Neshet G, Sonnenblick M, Friedlander Y. Analysis of steroid related complications and mortality in temporal arteritis: a 15-year survey of 43 patients. *J Rheumatol* 1994;21:1283–6.
- [47] Delecoeuillerie G, Joly P, Cohen de Lara A, Paolaggi JB. Polymyalgia rheumatica and temporal arteritis: a retrospective analysis of prognostic features and different corticosteroid regimens (11 year survey of 210 patients). *Ann Rheum Dis* 1988;47:733–9.
- [48] Samson M, Jacquin A, Audia S, Daubail B, Devilliers H, Petrella T, et al. Stroke associated with giant cell arteritis: a population-based study. *J Neurol Neurosurg Psychiatry* 2015;86:216–21.
- [49] Zenone T, Puget M. Characteristics of cerebrovascular accidents at time of diagnosis in a series of 98 patients with giant cell arteritis. *Rheumatol Int* 2013;33:3017–23.
- [50] Liou TH, Huang SW, Lin JW, Chang YS, Wu CW, Lin HW. Risk of stroke in patients with rheumatism: a nationwide longitudinal population-based study. *Sci Rep* 2014;4:5110.
- [51] Dixon WG, Abrahamowicz M, Beauchamp ME, Ray DW, Bernatsky S, Suissa S, et al. Immediate and delayed impact of oral glucocorticoid therapy on risk of serious infection in older patients with rheumatoid arthritis: a nested case-control analysis. *Ann Rheum Dis* 2012;71:1128–33.
- [52] Sylvestre MP, Abrahamowicz M. Flexible modeling of the cumulative effects of time-dependent exposures on the hazard. *Stat Med* 2009;28:3437–53.