Corticosteroid-Related Adverse Events in Patients with Giant Cell Arteritis: A Claims-Based Analysis

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INTRODUCTION

- Giant cell arteritis (GCA) is an inflammatory vasculitis preferentially affecting large and medium-sized arteries, including branches of the carotid arteries and the aorta.[1]
- The incidence of GCA is approximately 1-30 cases per 100,000 individuals; the prevalence is estimated to be as high as 278 per 100,000.[2-4]
- High-dose oral corticosteroids (CS) are the mainstay of GCA therapy, but adverse events related to CS use are common.
- We examined the risk of oral CS-related adverse events in a US commercially insured population of patients diagnosed with GCA.

METHODS

- This was a retrospective cohort study using the Truven Health Analytics MarketScan® Database during 2003-2012.
- We identified GCA patients who had at least 2 medical claims with a GCA diagnosis (International Classification of Diseases, 9th Revision, Clinical Modification code 446.5), had at least 1 oral CS prescription fill within 6 months before or after the date of first GCA diagnosis (index date), and were at least 50 years old.
- We excluded patients who had a GCA claim in the 1 year before the index date, had evidence of an adverse event of interest before the index diagnosis of GCA was made, or were not continuously enrolled with a health plan for 1 year prior to the index date and for at least 1 year after the index date.
- Patients were followed for at least 1 year until disenrollment or study end (12/31/2012), whichever occurred first.
- We measured oral CS use in 3 ways: cumulative prednisone-equivalent exposure, cumulative number of days, and contemporaneous use (time from the date of interest to last oral CS use, grouped into one of five categories).
  - Categories of "contemporaneous use" included 1) current use (steroid available to the patient on the day the variable was calculated), 2) recent use (any use within 90 days), 3) distant use (any use prior to 90 days but within 180 days), 4) remote (any use prior to 180 days but within 365 days), and 5) no use within 1 year.
  - The primary model of oral CS use in our study was cumulative prednisone-equivalent exposure.
- Our primary outcomes of interest included the following CS-related adverse events: nonvertebral and vertebral fractures; osteoporosis; pneumonia; cataracts; and glaucoma.
- We conducted Cox regression analyses to model oral CS use across time and the resultant risk of developing adverse events. Separate models were conducted for the risk of developing an initial adverse event, as well as selected individual adverse events, with demographics, baseline comorbidities, and oral CS use as independent variables.
- All data transformations and statistical analyses were performed using SAS® version 9.4.

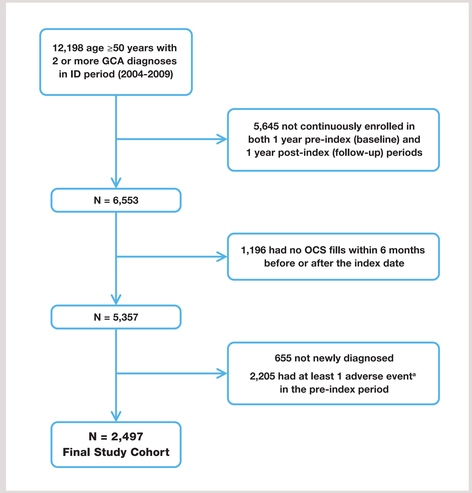
RESULTS

- The patient selection process is outlined in **Figure 1.**
- The cohort contained 2,497 GCA patients with mean age 71 years, 71% women, and mean Charlson comorbidity index 1.5 **(Table 1).**
- Median initial oral CS dose in the cohort was 40 mg/day **(Table 2).** Patients required a median 190 days (6.3 months) to reduce this dose to ≤7.5 mg/day and received a median cumulative oral CS dose of 3,380 mg until this level was reached. They required a median 210 days (7 months) to reach ≤5.0 mg/day and received a median 3,600 mg until this level was reached.
  - The times needed to reduce oral CS dose to 7.5 and 5.0 mg/day were similar to times reported by Proven *et al.*[5]
- Patients with any adverse event were prescribed more days of oral CS (median 195 vs. 102.5 days) and received a higher cumulative prednisone-equivalent dose (median 3,400 vs. 2,145 mg) than those without an adverse event.
- After adjusting for patient characteristics, each additional 1 gram increase in cumulative prednisone-equivalent exposure increased the hazard ratio of developing a first adverse event by 3% (p<.001). In this cohort, the rate of adverse events was 30% with no cumulative prednisone-equivalent exposure, increasing to 56% with 12 g of cumulative prednisone-equivalent dose **(Figure 2).**
- Similar patterns of increase were observed for individual adverse events, as well as for adverse event risk regardless of the method used to measure oral CS use **(Table 3).** Each additional cumulative month of oral CS increased the hazard ratio for first adverse event by 1% (p=.003). For current oral CS users, the hazard ratio for first adverse event was 1.47 (p<.001) compared to non-users.

CONCLUSIONS

- In a large cohort of insured GCA patients, high-dose oral CS use was near-universal.
- Patients were maintained on oral CS for a median of 7 months before tapering to a daily dose of ≤5.0 mg.
- By multiple measures, high-dose oral CS use was associated with a significantly increased risk of adverse events in patients with GCA.

Figure 1. Patient identification flowchart



[a]Nonvertebral and vertebral fractures, osteoporosis, aseptic necrosis of bone, hip replacement, opportunistic infections, pneumonia, cataracts, glaucoma, and ulcer disease.

Figure 2. Relationship between oral corticosteroid exposure within 1 year of diagnosis of giant cell arteritis and rate of adverse events

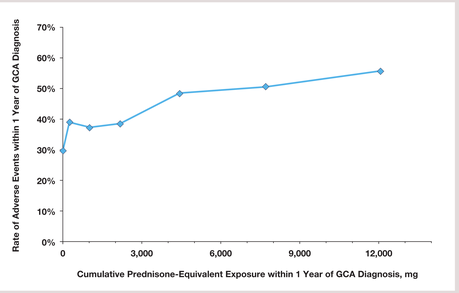


Table 1. Patient characteristics.

Patient Characteristic		Value
Age, year	Mean (SD)	71.0 (10.6)
50-59	no. (%)	450 (18.0)
60-69	no. (%)	606 (24.3)
70-79	no. (%)	811 (32.5)
80+	no. (%)	630 (25.2)
Female	no. (%)	1,773 (71.0)
Region		
North Central	no. (%)	853 (34.2)
Northeast	no. (%)	269 (10.8)
South	no. (%)	858 (34.4)
West	no. (%)	517 (20.7)
Baseline number of chronic conditions	Mean (SD)	3.4 (1.8)
Baseline Charlson comorbidity index	Mean (SD)	1.5 (1.7)
Baseline diabetes mellitus	no. (%)	489 (19.6)

Table 2. Duration of oral corticosteroid treatment in patient cohort.

Category	Number of Patients	Mean	(SD)	[Median]
First dose in study period, mg/d	2,497	38.8	(28.6)	[40]
Observed time on treatment[a], days	2,497	1,196.6	(729.2)	[996]
Cumulative dose during the time on treatment, mg	2,497	6,983.3	(6,519.9)	[5,350]
Days to reduce to ≤7.5 mg/d[b]	1,460	283.8	(329.0)	[190]
Cumulative dose to reduce to ≤7.5 mg/d, mg[c]	1,460	4,442.7	(4,427.6)	[3,380]
Days to reduce to ≤5.0 mg/d[b]	1,381	308.5	(345.8)	[210]
Cumulative dose to reduce to ≤5.0 mg/d, mg[c]	1,381	4,620.9	(4,474.4)	[3,600]

Legend: SD = standard deviation.
Note: Patients who stopped oral corticosteroid treatment before their dose reached the specified level (i.e., 7.5 or 5 mg) were excluded.
[a] Period between the first fill and the end of days of supply of the last oral corticosteroid fill.
[b] Days from first oral corticosteroid fill to the day on which daily dose reached 7.5 (or 5) mg.
[c] Cumulative dose from first oral corticosteroid fill to the day on which listed daily dose was reached.

Table 3. Risk of developing oral corticosteroid-related adverse events based on model of oral corticosteroid use.

Oral Corticosteroid Use Model	Risk of First Adverse Event	Risk of Osteoporosis	Risk of Fracture	Risk of Cataract	Risk of Glaucoma	Risk of Pneumonia
Each Additional Gram of Prednisone-Equivalent Exposure	1.03 (1.02-1.05)*	1.05 (1.03-1.06)*	1.04 (1.03-1.06)*	1.03 (1.02-1.05)*	1.05 (1.01-1.08)*	1.03 (1.01-1.04)*
Each Additional Month of Oral Corticosteroid Use	1.01 (1.00-1.02)*	1.02 (1.01-1.03)*	1.01 (1.01-1.02)*	1.01 (1.00-1.01)	1.02 (1.00-1.03)*	1.01 (1.00-1.02)*
Current Oral Corticosteroid Use vs. No Use in 1 Year of Follow-Up	1.47 (1.25-1.72)*	2.28 (1.80-2.90)*	2.05 (1.60-1.62)*	1.39 (1.15-1.68)*	1.57 (0.99-2.57)	1.63 (1.28-2.07)*

NB: All figures expressed as hazard ratios (95% confidence interval).
* p-value <.05

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DISCLOSURES

Gordon H. Sun, is an employee of Partnership for Health Analytic Research, LLC; Khaled Sarsour, is an employee of Genentech, Inc., a Member of the Roche Group; Eunice Chang, is an employee of Partnership for Health Analytic Research, LLC; Michael S. Broder, is an employee of Partnership for Health Analytic Research, LLC; Neil Collinson, is an employee of Roche Products Ltd; Katie Tuckwell, is an employee of Roche Products Ltd; Pavel Napalkov, is an employee of Genentech, Inc., a Member of the Roche Group; Micki Klearman, is an employee of Genentech, Inc., a Member of the Roche Group.

Presented at the American College of Rheumatology Annual Scientific Meeting; 14-19 November 2014; Boston, MA

Support for third-party writing assistance for this poster was provided by F. Hoffmann-La Roche Ltd.