Association Between Glucocorticoid Exposure and Healthcare Expenditures for Potential Glucocorticoid-related Adverse Events in Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** Oral glucocorticoid (OGC) use for rheumatoid arthritis (RA) is debated because of the adverse event (AE) profile of OGC. We evaluated the associations between cumulative doses of OGC and potential OGC-related AE, and quantified the associated healthcare expenditures.

Methods. Using the MarketScan databases, patients ≥ 18 years old who have RA with continuous enrollment from January 1 to December 31, 2012 (baseline), and from January 1 to December 31, 2013 (evaluation period), were identified. Cumulative OGC dose was measured using prescription claims during the baseline period. Potential OGC-related AE (osteoporosis, fracture, aseptic necrosis of the bone, type 2 diabetes, ulcer/gastrointestinal bleeding, cataract, hospitalization for opportunistic infection, myocardial infarction, or stroke) and AE-related expenditures (2013 US$) were gathered during the evaluation period. Multivariable regression models were fitted to estimate OR of AE and incremental costs for patients with AE.

Results. There were 84,357 patients analyzed, of whom 48% used OGC during the baseline period and 26% had an AE during the evaluation period. A cumulative OGC dose > 1800 mg was associated with an increased risk of any AE compared with no OGC exposure (OR 1.19, 99.65% CI 1.09–1.30). Incremental costs per patient with any AE were significantly greater for cumulative OGC dose > 1800 mg compared with no OGC exposure (incremental cost = $3528, 99.65% CI $2402–$4793).

Conclusion. Chronic exposure to low to medium doses of OGC was associated with significantly increased risk of potential OGC-related AE in patients with RA, and greater cumulative OGC dose was associated with substantially higher AE-related healthcare expenditures among patients with AE. (J Rheumatol First Release January 15 2018; doi:10.3899/jrheum.170418)

Key Indexing Terms:
CORTICOSTEROIDS GLUCOCORTICOIDS ADVERSE EFFECTS
HEALTHCARE COSTS RHEUMATOID ARTHRITIS

Glucocorticoids are commonly used to treat inflammatory conditions such as rheumatoid arthritis (RA)[1,2]. The European League Against Rheumatism guidelines recommend considering short-term glucocorticoids when initiating or changing conventional synthetic disease-modifying antirheumatic drugs (DMARD) for patients with RA; the guidelines recommend tapering glucocorticoids as rapidly as clinically feasible[3]. The 2015 American College of Rheumatology guidelines state that glucocorticoids should be used at the lowest possible dose and for the shortest possible duration based on a benefit-risk analysis for the patient[4].

Adverse events (AE) potentially arising from exposure to glucocorticoids have led to the lack of consensus on the appropriate dose and duration of use in patients with RA. The rate of glucocorticoid-related AE among patients with RA was estimated to be 43 per 100 patient-years[5]. Potential AE include osteoporosis and increased susceptibility to infection. These conditions appear to be more common among patients exposed to higher levels of glucocorticoids[6]. Of particular concern are bone-related AE because daily treatment of > 5 mg of prednisolone or the equivalent has been shown to increase the risk of fracture[7].

Little is known about the economic consequences on the healthcare system of steroid-related AE among patients with RA. One model estimated higher healthcare expenditures among users of glucocorticoids compared with nonusers[8].

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This model, however, used a variety of sources spanning many years, used cost estimates that were not specific to patients with RA, and compared patients taking glucocorticoid monotherapy with patients taking no systemic therapy, which may not be realistic in clinical practice. The objective of our analysis was to evaluate the association between cumulative dose of oral glucocorticoids (OGC) and healthcare expenditures associated with potential OGC-related AE among patients with RA.

MATERIALS AND METHODS

Data source. We used US administrative healthcare claims data from the Truven Health MarketScan Commercial Claims and Medicare Supplemental Databases from January 1, 2012, to December 31, 2013. The Commercial Database contains the healthcare experience of privately insured individuals covered under a variety of fee-for-service, fully capitated, and partially capitated healthcare plans. The Medicare Supplemental Database contains the healthcare experience of retirees whose Medicare supplemental insurance is paid by employers. Medical claims are linked to prescription claims and person-level enrollment data. Data were previously collected, statistically de-identified, and fully compliant with the Health Insurance Portability and Accountability Act of 1996; therefore, approval from an institutional review board was not required in accordance with the policy of Truven Health.

Variables were measured using International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis and procedure codes, Healthcare Common Procedure Coding System codes, and National Drug Codes (NDC), as appropriate. Diagnoses were searched for in all diagnosis positions in the administrative claims. Rule out claims, such as laboratory tests and radiology procedures, were not evaluated.

Sample selection and time periods. We identified patients with ≥ 2 nondiagnostic medical claims with an ICD-9-CM diagnosis code for RA (714.0x) from January 1 through December 31, 2012. At least 2 claims with an RA diagnosis were required to increase the likelihood of selecting true patients with RA. Patients were required to be ≥ 18 years of age, and to be continuously enrolled with pharmacy benefits from January 1, 2012, through December 31, 2013. We excluded patients with ≥ 1 nondiagnostic claim with a diagnosis of any other autoimmune disease (i.e., ankylosing spondylitis, Crohn disease, juvenile idiopathic arthritis, polyarteritis nodosa, psoriatic arthritis, ulcerative colitis, Wegener granulomatosis/granulomatosis with polyangiitis, or systemic lupus erythematosus) from January 1, 2012, through December 31, 2013. The final sample consisted of newly diagnosed and prevalent RA cases, and nonusers, new initiators, and continuing users of OGC. The study period was divided into a 12-month baseline period (January 1 to December 31, 2012) and a 12-month evaluation period (January 1 to December 31, 2013). January 1, 2013, represented the fixed index date for all patients. The index date was not based on any clinical event.

Exposures. Cumulative dose of OGC based on prescriptions during the 12-month baseline period was the exposure of interest. Intravenous glucocorticoid use was not included because the dose could not be accurately determined based on medical claims. Cumulative OGC dose was expressed as prednisone-equivalent mg using standard conversions[9]. A daily dose for a prescription claim was determined using the drug strength associated with the NDC, the daily supply and metric quantity fields from the claim, and the prednisone conversion factor. If a patient filled the prescription for the same OGC prior to the end of the previous prescription, the remaining supply from the first prescription was added to the total supply for the next prescription. If the prescription was for a different OGC, the remaining supply of the prior drug was truncated when the new prescription was filled. Daily doses < 1 mg were set to 1 mg, and daily doses > 60 mg were set to 60 mg, based on review of outliers and clinical input.

We categorized patients' cumulative OGC doses during the baseline period into dosing levels. One level comprised patients with no OGC. The incidence of AE among this group could be considered the background rate of these conditions, unrelated to OGC exposure. Four nonzero levels were determined based on the quantiles observed in cumulative dosing distribution.

Presence of potential OGC-related AE. Binary variables were created to indicate the presence of each potential OGC-related AE based on diagnosis codes in any position (primary or nonprimary) on medical claims during the evaluation period (Supplementary Table 1, available with the online version of this article). Three bone-related AE were examined individually and as an aggregate outcome: osteoporosis, vertebral and nonvertebral fractures, and aseptic necrosis of the bone. Patients with ≥ 1 claims related to osteoporosis, Paget disease, or osteomalacia, or with a prescription claim for any bone disease-related medication (bisphosphonates, raloxifene, denosumab, teriparatide, or calcitonin) in the baseline period were not evaluated for osteoporosis during the evaluation period because osteoporosis preceded the index date. Fractures as a result of motor vehicle accidents (identified by an E code on the same claim) and open fractures (usually caused by trauma) were excluded.

Additional OGC-related AE were hospitalization for pneumonia or opportunistic infections (such as tuberculosis, candidiasis, or herpes zoster), hospitalization for myocardial infarction (MI) or stroke, type 2 diabetes, and gastrointestinal (GI) ulcer disease or GI bleed. Cataracts (excluding traumatic and congenital cataracts) were included in the secondary analysis. Patients with ≥ 1 claims for type 2 diabetes or with a pharmacy claim for any antidiabetes medication in the baseline period were not evaluated for the type 2 diabetes outcome, and patients with a pharmacy claim for medication to treat ulcers in the baseline period were not evaluated for ulcer/GI bleed because both would be considered "preexisting conditions."

Expenditures for potential OGC-related AE. Payments on medical claims with a relevant diagnosis code for a potential AE in any position and pharmacy claims for AE-related medications during the evaluation period were considered potential AE-related expenditures. Payments comprised insurers' payments, as well as patients' cost-sharing. Expenditures were estimated overall and individually for each AE, and were expressed in 2013 constant dollars, adjusted using the medical care component of the Consumer Price Index.

Patient demographics and clinical characteristics. Demographic characteristics were measured at the patient's index date: age, sex, geographic region, payer (commercial vs Medicare), and insurance plan type. We identified the use of biologic and nonbiologic DMARD in the baseline period. Medical claims for potential OGC-related AE and for AE-related medications in the baseline period were identified. Comorbidities assessed during baseline were hypothyroidism, ischemic heart disease, cancer, and asthma/chronic obstructive pulmonary disease (COPD). Additional health indices included the Deyo-Charlson Comorbidity Index (DCCI) score[10], the number of 3-digit ICD-9-CM diagnosis codes in any position on nondiagnostic claims and the number of unique NDC, which measure overall health, and baseline healthcare expenditures.

Statistical analyses. We estimated the OR of experiencing potential OGC-related AE across cumulative dose categories by fitting adjusted logistic regression models. No OGC exposure was the reference. In addition to those reported here, we fit several versions of our models, which is standard practice. Assuming a false-positive rate of 10%, we arrived at an alpha of 0.0035 and compared the p values for our final models to this conservative alpha. Correspondingly, $p < 0.0035$ were considered statistically significant and 99.65% CI were calculated. In secondary analyses, the odds of occurrence of a cataract was estimated separately for age < 45, age 45–65, and age 65+ because ICD-9-CM diagnosis codes do not distinguish between age-related cataracts, such as nuclear and cortical cataract, versus cataracts that are more likely to be caused by OGC exposure, such as posterior subcapsular cataract[11].

Among patients who experienced a potential OGC-related AE, we used generalized linear models with a log link and gamma error distribution to

estimate the adjusted incremental costs and 99.65% CI per patient with AE for each cumulative dose category. Patients with AE and no OGC use served as the reference group. Again, $p < 0.0035$ were considered statistically significant. Covariates used for adjustment in multivariable models were the following: age, sex, geographic region, insurance plan type, population density, payer, biologic and nonbiologic DMARD use during the baseline period, claim for any AE or AE-related medication during the baseline period, diagnosis of hypothyroidism, ischemic heart disease, cancer, asthma/COPD during the baseline period, DCCI, number of 3-digit ICD-9-CM diagnosis codes, number of NDC during the baseline period, and baseline healthcare expenditures.

RESULTS

Cumulative dose of OGC. The final study sample consisted of 84,357 patients. A total of 48% of patients used OGC during the baseline period, with a mean cumulative dose of 1334 mg (median, 770 mg). Patients were categorized into 5 cohorts: (1) 0 mg; (2) > 0 mg and ≤ 300 mg; (3) > 300 mg and ≤ 800 mg; (4) > 800 mg and ≤ 1800 mg; and (5) > 1800 mg. The percentage of patients in each category was 52.4%, 13.6%, 10.5%, 13.1%, and 10.4%, respectively.

Average daily dose of OGC on days where OGC was used displayed a U-shaped trend, with the highest daily dose in the lowest (0–300 mg) category, followed by a generally decreasing trend across dose categories, and an increase in the highest category (> 1800 mg, Table 1). In the > 1800 mg category, the mean daily dose during the baseline period was 10.2 mg during the full baseline period (365 days). Longer-term cumulative dosing tended to be lower per day, suggesting that high cumulative doses of OGC commonly result from the duration of OGC therapy rather than the amount taken daily. The percentage of days on a daily dose of > 10 mg OGC was the highest for the > 1800 mg dose cohort during both the baseline and evaluation periods.

Patient characteristics. Average age ranged from 57.0 years (SD ± 13.2) to 59.7 years (SD ± 13.7, Table 2). Among patients with cumulative dose > 0 mg, there was a trend toward a higher proportion of males taking greater doses of OGC (19.7% male in the 0–300 mg cohort vs 30% in the 1800 mg cohort). During the baseline period, etanercept (14.5%–15.9%) and adalimumab (9.7%–11.4%) were the most frequently used biologic DMARD in all cohorts (Table 2). Methotrexate (47.2%-58.7%) and hydroxychloroquine (22.9%–27.7%) were the most commonly used nonbiologic DMARD. The most common baseline potential OGC-related AE in all dose cohorts was type 2 diabetes (13.1%–19.0%) followed by cataract (12.8%–17.2%). Healthcare expenditures during the baseline period averaged between $21,559 and $35,664, with a dose-dependent increase across cohorts.

Risk of potential OGC-related AE. A total of 26.3% of patients experienced an OGC-related AE, ranging from 25.1% for patients with no OGC exposure, to 33.3% for

Table 1. Duration and dosing information by OGC dosing level during baseline and evaluation periods, stratified by baseline cumulative dose.

Dose Information	Baseline Cumulative Dose									
	0 mg, n = 44,190		> 0 to ≤ 300 mg, n = 11,496		> 300 to ≤ 800 mg, n = 8838		> 800 to ≤ 1800 mg, n = 11,032		> 1800 mg, n = 8801	
No. days with OGC in baseline period										
Mean ± SD			20.3	± 33.2	70.5	± 77.6	192.7	± 111.7	272.5	± 95.4
Median (IQR)			9	(6–28)	40	(20–90)	180	(90–286.5)	300	(208–365)
Average daily dose of OGC in baseline period										
Mean ± SD			17.0	± 11.9	16.9	± 14.1	11.1	± 10.8	15.8	± 14.2
Median (IQR)			17.5	(10.0–17.5)	12.5	(5.6–22.5)	6.9	(5.0–12.2)	10.0	(7.3–17.1)
Average daily dose of OGC in baseline period, including days with no dose[1]										
Mean ± SD			0.5	± 0.2	1.4	± 0.4	3.5	± 0.9	10.2	± 8.4
Median (IQR)			0.4	(0.3–0.6)	1.4	(1.2–1.7)	3.5	(2.7–4.3)	7.5	(6.0–10.4)
No. days with OGC in evaluation period										
Mean ± SD	8.9	± 34.7	26.1	± 62.6	65.5	± 105.1	165.4	± 142.7	218.5	± 134.4
Median (IQR)	0	(0–0)	0	(0–18)	12	(0–90)	150	(12–306)	253	(90–360)
Average daily dose of OGC in evaluation period										
Mean ± SD	4.5	± 10.7	7.6	± 11.7	9.0	± 12.6	7.9	± 9.9	12.4	± 13.9
Median (IQR)	0.0	(0–0)	0.0	(0.0–15.0)	4.7	(0.0–15.0)	5.0	(2.6–10.0)	8.5	(5.0–13.2)
Average daily dose of OGC in evaluation period, including days with no dose[1]										
Mean ± SD	0.3	± 1.4	0.6	± 1.6	1.4	± 2.3	3.0	± 3.1	7.6	± 9.3
Median (IQR)	0.0	(0–0)	0.0	(0.0–0.7)	0.6	(0.0–1.8)	2.6	(0.5–4.9)	5.3	(2.7–9.0)
Days with daily dose > 10 mg in baseline period, %										
Mean ± SD			1.44	± 1.27	3.38	± 3.30	4.66	± 6.86	20.54	± 25.79
Median (IQR)			1.64	(0.00–1.92)	2.74	(0.00–5.48)	0.00	(0.00–8.22)	9.86	(0.00–32.88)
Days with daily dose > 10 mg in evaluation period, %										
Mean ± SD	0.85	± 3.68	1.57	± 4.43	2.68	± 6.84	3.54	± 9.20	13.82	± 25.19
Median (IQR)	0.00	(0–0)	0.00	(0.00–1.64)	0.00	(0.00–2.74)	0.00	(0.00–2.19)	0.00	(0.00–16.44)

[1]After first claim for OGC during the baseline period. Days before first claim were not included in the denominator. IQR: interquartile range; OGC: oral glucocorticoid.

Table 2. Patient demographics and baseline clinical characteristics stratified by baseline cumulative dose of OGC. Values are n (%) or mean ± SD.

Variables	Baseline Cumulative Dose									
	0 mg, n = 44,190		> 0 to ≤ 300 mg, n = 11,496		> 300 to ≤ 800 mg, n = 8838		> 800 to ≤ 1800 mg, n = 11,032		> 1800 mg, n = 8801	
Age, yrs	58.9	± 13.4	57.0	± 13.2	57.5	± 13.3	59.7	± 13.7	59.6	± 13.2
Female	33,809	(76.5)	9236	(80.3)	6881	(77.9)	8231	(74.6)	6162	(70.0)
Geographic region										
Northeast	9828	(22.2)	2178	(19.0)	1926	(21.8)	2423	(22.0)	2091	(23.8)
North central	11,072	(25.1)	2730	(23.8)	2156	(24.4)	2955	(26.8)	2325	(26.4)
South	13,358	(30.2)	4379	(38.1)	3082	(34.9)	3613	(32.8)	2575	(29.3)
West	9478	(21.4)	2057	(17.9)	1539	(17.4)	1910	(17.3)	1717	(19.5)
Unknown	454	(1.0)	152	(1.3)	135	(1.5)	131	(1.2)	93	(1.1)
Payer										
Commercial	28,940	(65.5)	8145	(70.9)	6137	(69.4)	6917	(62.7)	5511	(62.6)
Medicare	15,250	(34.5)	3351	(29.2)	2701	(30.6)	4115	(37.3)	3290	(37.4)
Biologic DMARD therapy										
Adalimumab	4293	(9.7)	1275	(11.1)	954	(10.8)	1228	(11.1)	999	(11.4)
Etanercept	6539	(14.8)	1826	(15.9)	1284	(14.5)	1666	(15.1)	1278	(14.5)
Infliximab	2572	(5.8)	650	(5.7)	548	(6.2)	692	(6.3)	569	(6.5)
Other biologic DMARD	3753	(8.5)	1351	(11.8)	1225	(13.9)	1782	(16.2)	1909	(21.7)
Nonbiologic DMARD										
Hydroxychloroquine	10,140	(22.9)	2988	(26.0)	2419	(27.4)	3052	(27.7)	2376	(27.0)
Leflunomide	3020	(6.8)	1178	(10.2)	980	(11.1)	1441	(13.1)	1278	(14.5)
Methotrexate	20,873	(47.2)	5979	(52.0)	4967	(56.2)	6471	(58.7)	4874	(55.4)
Sulfasalazine	2579	(5.8)	787	(6.8)	632	(7.2)	852	(7.7)	820	(9.3)
Other nonbiologic DMARD	2277	(5.2)	715	(6.2)	546	(6.2)	736	(6.7)	826	(9.4)
Claim with a diagnosis for an AE[1]	16,006	(36.2)	4093	(35.6)	3090	(35.0)	4484	(40.7)	4171	(47.4)
Osteoporosis	4079	(9.2)	1028	(8.9)	801	(9.1)	1389	(12.6)	1228	(14.0)
Fracture	1660	(3.8)	502	(4.4)	367	(4.2)	587	(5.3)	636	(7.2)
Aseptic necrosis of bone	89	(0.2)	27	(0.2)	13	(0.1)	43	(0.4)	40	(0.5)
Cataract	6430	(14.6)	1505	(13.1)	1135	(12.8)	1666	(15.1)	1516	(17.2)
Opportunistic infection[2]	378	(0.9)	175	(1.5)	165	(1.9)	267	(2.4)	380	(4.3)
MI or stroke	604	(1.4)	168	(1.5)	145	(1.6)	230	(2.1)	227	(2.6)
Type 2 diabetes	6453	(14.6)	1582	(13.8)	1160	(13.1)	1604	(14.5)	1668	(19.0)
Ulcer/GI bleed	1138	(2.6)	344	(0.0)	245	(0.0)	385	(0.0)	380	(0.0)
Claim for AE-related medication	35,175	(79.6)	10,317	(89.7)	7966	(90.1)	9954	(90.2)	8130	(92.4)
Baseline comorbid conditions										
Hypothyroidism	5834	(13.2)	1675	(14.6)	1193	(13.5)	1502	(13.6)	1304	(14.8)
Ischemic heart disease	4465	(10.1)	1212	(10.5)	1005	(11.4)	1483	(13.4)	1379	(15.7)
Cancer	2929	(6.6)	779	(6.8)	671	(7.6)	987	(8.9)	851	(9.7)
Asthma/COPD	4218	(9.5)	1772	(15.4)	1555	(17.6)	1888	(17.1)	1815	(20.6)
Paget disease/osteomalacia	51	(0.1)	11	(0.1)	12	(0.1)	12	(0.1)	15	(0.2)
Deyo-Charlson Comorbidity Index[3]	1.72	± 1.35	1.79	± 1.39	1.83	± 1.42	1.94	± 1.54	2.15	± 1.71
Count of unique 3-digit ICD-9-CM[3] codes	13.46	± 9.00	15.76	± 9.87	16.01	± 9.91	16.05	± 10.27	18.33	± 11.77
Count of unique National Drug Codes[3]	12.20	± 7.71	16.04	± 8.63	17.08	± 9.12	17.63	± 9.24	20.44	± 10.37
Baseline healthcare costs	$21,559	± $29,446	$24,813	± $33,687	$25,652	± $32,421	$28,262	± $39,729	$35,664	± $60,597

[1]Evaluated in inpatient or outpatient claims. [2]Includes opportunistic infections such as tuberculosis, candidiasis, and herpes zoster (complete list in Supplementary Table 1, available with the online version of this article). [3]Measures of overall health, with a higher score indicating worse health (scores can range from 0 to 33; each of 17 conditions is weighted as 1, 2, 3, or 6).[10] AE: adverse event; ICD-9-CM: International Classification of Diseases, 9th revision, Clinical Modification; COPD: chronic obstructive pulmonary disease; DMARD: disease-modifying antirheumatic drugs; GI: gastrointestinal; MI: myocardial infarction; OGC: oral glucocorticoid.

patients with cumulative dose > 1800 mg (Table 3). The most common AE were osteoporosis, fracture, and cataract. A cumulative OGC dose > 1800 mg was associated with an increased risk of any OGC-related AE compared with no OGC exposure (adjusted OR 1.19, 99.65% CI 1.09–1.30; Table 4). For individual AE, significantly greater adjusted odds for the highest cumulative OGC dose (> 1800 mg) versus no dose were observed for osteoporosis, fracture, aseptic necrosis of bone, opportunistic infection, MI or stroke, type 2 diabetes (all statistically significant), and

Table 3. Percentages of RA patients with a potential OGC-related AE by baseline cumulative dose of OGC. Values are n or n (%).

Variables	Baseline Cumulative Dose									
	0 mg		> 0 to ≤ 300 mg		> 300 to ≤ 800 mg		> 800 to ≤ 1800 mg		> 1800 mg	
Any AE										
Eligible patients	44,190		11,496		8838		11,032		8801	
Patients with AE	11,088	(25.1)	2892	(25.2)	2179	(24.7)	3119	(28.3)	2929	(33.3)
Bone-related AE										
Eligible patients	44,190		11,496		8838		11,032		8801	
Patients with AE	2950	(6.7)	822	(7.2)	613	(6.9)	1034	(9.4)	1052	(12.0)
Osteoporosis										
Eligible patients	37,613		9854		7464		8688		6596	
Patients with AE	1292	(3.4)	323	(3.3)	247	(3.3)	423	(4.9)	396	(6.0)
Fracture										
Eligible patients	44,190		11496		8838		11,032		8801	
Patients with AE	1769	(4.0)	518	(4.5)	394	(4.5)	663	(6.0)	715	(8.1)
Aseptic necrosis of bone										
Eligible patients	44,190		11,496		8838		11,032		8801	
Patients with AE	80	(0.2)	22	(0.2)	18	(0.2)	31	(0.3)	48	(.5)
Cataract										
Eligible patients	44,190		11,496		8838		11,032		8801	
Patients with AE	7015	(15.9)	1731	(15.1)	1271	(14.4)	1775	(16.1)	1504	(17.1)
Opportunistic infection										
Eligible patients	44,190		11,496		8838		11,032		8801	
Patients with AE	585	(1.3)	186	(1.6)	163	(1.8)	275	(2.5)	387	(4.4)
MI or stroke										
Eligible patients	44,190		11,496		8838		11,032		8801	
Patients with AE	611	(1.4)	176	(1.5)	122	(1.4)	217	(2.0)	238	(2.7)
Type 2 diabetes										
Eligible patients	37,195		9766		7557		9279		7011	
Patients with AE	892	(2.4)	237	(2.4)	196	(2.6)	244	(2.6)	275	(3.9)
Ulcer or GI bleed										
Eligible patients	32,930		7847		5776		7138		5145	
Patients with AE	681	(2.1)	207	(2.6)	129	(2.2)	188	(2.6)	170	(3.3)

AE: adverse event; GI: gastrointestinal; OGC: oral glucocorticoids; MI: myocardial infarction; RA: rheumatoid arthritis.

Table 4. Adjusted[1] OR for potential OGC-related AE by baseline cumulative dose of OGC among all patients.

All Patients		Baseline Cumulative Dose					
	With AE, n	0 mg	> 0–300 mg, OR (99.65% CI)	> 300–800 mg, OR (99.65% CI)	> 800–1800 mg, OR (99.65% CI)	> 1800 mg, OR (99.65% CI)	p[2]
Any AE	22,207	Ref	1.01 (0.93–1.09)	0.94 (0.86–1.03)	1.00 (0.92–1.08)	1.19 (1.09–1.30)	< 0.001
Bone-related AE	6471	Ref	1.03 (0.91–1.17)	0.97 (0.85–1.12)	1.24 (1.11–1.40)	1.53 (1.35–1.73)	< 0.001
Osteoporosis	2681	Ref	1.00 (0.83–1.21)	1.01 (0.81–1.25)	1.43 (1.20–1.71)	1.81 (1.50–2.18)	< 0.001
Fracture	4059	Ref	1.03 (0.88–1.21)	0.99 (0.84–1.18)	1.22 (1.06–1.42)	1.49 (1.29–1.73)	< 0.001
Aseptic necrosis of bone	199	Ref	0.92 (0.45–1.89)	0.99 (0.45–2.15)	1.29 (0.68–2.44)	2.13 (1.19–3.81)	< 0.001
Cataract	13,296	Ref	0.99 (0.90–1.08)	0.90 (0.81–1.00)	0.88 (0.80–0.97)	0.90 (0.81–0.99)	0.002
Opportunistic infection[3]	1596	Ref	1.03 (0.80–1.34)	1.08 (0.82–1.42)	1.28 (1.02–1.60)	1.89 (1.52–2.34)	< 0.001
MI or stroke	1364	Ref	1.09 (0.84–1.42)	0.93 (0.69–1.26)	1.14 (0.89–1.46)	1.38 (1.08–1.76)	< 0.001
Type 2 diabetes	1844	Ref	0.92 (0.74–1.15)	0.92 (0.73–1.18)	0.89 (0.71–1.11)	1.20 (0.96–1.50)	0.016
Ulcer or GI bleed	1375	Ref	1.15 (0.90–1.47)	0.96 (0.72–1.29)	1.06 (0.82–1.37)	1.16 (0.88–1.53)	0.106

[1]Models adjusted for patient age, sex, geographic region, insurance plan type, population density, payer, and baseline measures of: biologic DMARD, nonbiologic DMARD, any AE or AE-related medication, hypothyroidism, ischemic heart disease, cancer, asthma/COPD, Deyo-Charlson Comorbidity Index, no. 3-digit ICD-9-CM diagnosis codes, no. NDC (measures of overall health), healthcare costs. [2]p value for comparison of 1800 mg cohort with 0 mg (reference) cohort; $p < 0.0035$ were considered statistically significant. [3]Includes opportunistic infections such as tuberculosis, candidiasis, and herpes zoster (Supplementary Table 1 shows the complete list, available with the online version of this article). AE: adverse event; COPD: chronic obstructive pulmonary disease; DMARD: disease-modifying antirheumatic drug; GI: gastrointestinal; ICD-9-CM: International Classification of Diseases, 9th revision, Clinical Modification; MI: myocardial infarction; NDC: National Drug Codes; OGC: oral glucocorticoids.

ulcer/GI bleed (not significant). Cataract was inversely associated with dose; however, a subanalysis revealed effect modification by age. Patients aged < 45 years displayed similar increasing trends by dose as the other AE (data not shown). Overall bone-related AE, osteoporosis, and fracture individually, and opportunistic infections were additionally associated with increased risk at the > 800–1800 mg cumulative dose.

Potential AE-related healthcare costs. Among patients who experienced AE, average unadjusted AE-related costs ranged from $6079 for patients with no OGC exposure to $12,311 for patients with > 1800 mg cumulative exposure (Table 5). The highest observed costs were for hospitalization for pneumonia or an opportunistic infection ($28,250–$43,245) and hospitalization for MI or stroke ($28,313–$43,533). In multivariable analyses, among patients who experienced an AE, a greater cumulative OGC dose was associated with higher AE-related healthcare expenditures, with statistically significant results for the highest dose compared with no OGC exposure (adjusted cost ratio, 1.53, 99.65% CI 1.36–1.72; p < 0.0001; Table 5). Correspondingly, adjusted costs per patient with any AE were substantially greater for the highest dose compared with no OGC exposure (adjusted incremental cost $3528, 99.65% CI $2402–$4793; p < 0.0001).

For individual AE, general trends of greater adjusted cost ratios and incremental costs for higher categories of cumulative OGC dose exposure were observed for osteoporosis, fracture, cataract, type 2 diabetes, ulcer/GI bleed (all statistically significant at the highest dose compared with no exposure), as well as aseptic necrosis of bone, hospitalization for infection, and hospitalization for MI or stroke (although not statistically significant at the highest dose). At dose > 1800 mg versus 0 mg, the highest statistically significant adjusted incremental costs were observed for ulcer/GI bleed ($9646, 99.65% CI $3564–$18,814; p < 0.0001).

DISCUSSION

In our large claim-based, real-world study, we observed that greater cumulative OGC dose was associated with increased risk of experiencing a potential OGC-related AE. This elevated risk was primarily observed at cumulative doses > 1800 mg over a 12-month period. Among patients who experienced a potential OGC-related AE, greater cumulative OGC dose was associated with substantially increased AE-related healthcare costs. For patients exposed to a cumulative dose of OGC > 1800 mg over 12 months, the adjusted incremental costs for any AE among those who experienced an AE was $3528 higher than for patients with no OGC exposure.

OGC use has been associated with various AE, including osteoporosis[9], fracture[12,13], infection[14,15], and MI[16]. Among patients with RA, current or past use of OGC has been associated with a higher rate of a variety of AE, although results from randomized controlled trials indicate that AE are modest and not substantially different from placebo for a low-dose OGC use[6,17]. However, randomized trials assessing safety of OGC use have been limited by small size and/or short duration[17]. Our study, conducted in a large sample of patients with RA evaluated over a relatively long period in a community setting, provides support for increased risk of potential OGC-related AE, and confirms that that risk is linked to higher levels of cumulative dose.

Compared to no OGC use, the greatest risk of potential AE observed here was for opportunistic infections and bone-related AE among patients with cumulative dose > 1800 mg. Elevated risk of infection and fractures has been reported in previous research among patients with RA, as well as patients with other conditions[6,12,13,15,18]. One retrospective review of medical records of patients with RA reported that fragility fractures occurred in 18.2% of OGC users[19]. High rates of severe complications such as fractures may thus be of particular concern to this patient population.

To our knowledge, ours is the first observational study to evaluate costs of potential OGC-related AE among patients with RA using real-world data. Pisu, *et al* conducted a literature review of studies that reported risks of AE in patients with RA and developed a Markov model to estimate costs[8]. They estimated that glucocorticoid users spent an average of $445 more than nonusers over a 2-year period[8]. However, their cost inputs were based on other analyses that were not limited to patients with RA[8]. Similarly, the economic effect of OGC-related AE among all patients (not confined to RA) in the United Kingdom has also been assessed by Manson, *et al*[20]. In their review of 61 studies, the annual cost per patient associated with OGC-related AE was estimated to be £165[20]. These expenditures were lower than our estimates; however, their results were based on an analysis using 2007 costs for AE estimated in the general UK population, and not specifically from OGC users with RA who experienced AE.

Among those patients with AE, we observed substantial incremental costs for any AE associated with the highest level of OGC exposure compared with no exposure, with adjusted incremental costs for individual AE ranging from $304 for cataract to $15,502 for aseptic necrosis of the bone. Though not statistically significant at 0.0035 level, we noted extremely high average adjusted annual costs at the > 1800 mg level, which were highest for hospitalization for pneumonia and other opportunistic infections ($38,897). The highest statistically significant adjusted incremental costs were observed for ulcer/GI bleed ($9646). High expenses associated with complicated ulcers have been noted in previous studies, with bleeding and perforation resulting in very high healthcare costs[21]. Among patients with AE, the mechanism by which higher OGC dose results in higher AE-related healthcare costs was not examined and is an area of future research. We hypothesize that patients with the highest levels of OGC dose may have more severe AE that

Table 5. Adjusted[1] cost ratios and incremental costs for potential OGC-related AE by baseline cumulative dose of OGC among patients with a potential OGC-related AE.

Baseline Cumulative Dose	Observed Costs	Adjusted Costs	Cost Per Patient with AE Cost Ratio (99.65% CI)	Incremental Costs (99.65% CI)	p[2]
Any AE					
> 1800 mg	$12,311	$10,180	1.53 (1.36–1.72)	$3528 ($2402–$4793)	< 0.0001
> 800–1800 mg	$7,370	$7,293	1.10 (0.98–1.23)	$641 ($–125 to $1503)	0.0149
> 300–800 mg	$6418	$6,208	0.93 (0.82–1.06)	$–445 ($–1182 to $394)	0.1108
> 0–300 mg	$6365	$6130	0.92 (0.82–1.02)	$–522 ($–1177 to $204)	0.0322
0 mg	$6079	$6653	Reference	Reference	
Bone–related AE					
> 1800 mg	$9900	$9327	1.50 (1.23–1.83)	$3096 ($1419–$5196)	< 0.0001
> 800–1800 mg	$6065	$6210	1.00 (0.82–1.21)	$–20 ($–1121 to $1322)	0.9658
> 300–800 mg	$5366	$5712	0.91 (0.72–1.16)	$–519 ($–1733 to $994)	0.2720
> 0–300 mg	$4419	$4656	0.75 (0.61–0.92)	$–1575 ($–2453 to $–505)	< 0.0001
0 mg	$6164	$6231	Reference	Reference	
Osteoporosis					
> 1800 mg	$2359	$2333	1.62 (1.19–2.19)	$888 ($279–$1715)	< 0.0001
> 800–1800 mg	$2237	$2125	1.46 (1.11–1.93)	$681 ($154–$1344)	< 0.0001
> 300–800 mg	$1602	$2340	1.61 (1.14–2.28)	$896 ($208–$1848)	< 0.0001
> 0–300 mg	$1635	$1374	0.95 (0.71–1.27)	$–71 ($–422–$391)	0.5944
0 mg	$1409	$1445	Reference	Reference	
Fracture					
> 1800 mg	$10,842	$11,768	1.38 (1.08–1.75)	$3201 ($682–$6455)	0.0001
> 800–1800 mg	$8013	$8419	0.98 (0.78–1.25)	$–148 ($–1922–$2138)	0.8483
> 300–800 mg	$7334	$7755	0.90 (0.68–1.21)	$–812 ($–2783–$1787)	0.3063
> 0–300 mg	$5828	$6360	0.74 (0.57–1.27)	$–2207 ($–3665–$–330)	0.0007
> 0 mg	$8971	$8567	Reference	Reference	
Aseptic necrosis of bone					
> 1800 mg	$42,650	$28,980	2.17 (0.59–8.05)	$15,502 ($–5561 to $95,057)	0.0821
> 800–1800 mg	$11,099	$13,476	1.00 (0.25–3.99)	$–2 ($–10,135 to $40,362)	0.9923
> 300–800 mg	$10,980	$48,081	3.47 (0.46–26.26)	$34,603 ($–7308 to $340,396)	0.0721
> 0–300 mg	$9046	$7240	0.54 (0.11–2.64)	$–6238 ($–11,976 to $22,111)	0.2576
0 mg	$10,915	$13,478	Reference	Reference	
Cataract					
> 1800 mg	$1419	$1329	1.30 (1.14–1.47)	$304 ($148–$482)	< 0.0001
> 800–1800 mg	$1072	$1045	1.02 (0.91–1.15)	$21 ($–93 to $149)	0.6019
> 300–800 mg	$926	$908	0.89 (0.78–1.01)	$–116 ($–228 to $10)	0.0069
> 0–300 mg	$1035	$1066	1.04 (0.93–1.17)	$42 ($–74 to $172)	0.3067
0 mg	$993	$1025	Reference	Reference	
Opportunistic infection[3]					
> 1800 mg	$43,245	$38,897	1.17 (0.95–1.44)	$5616 ($–1592 to $14,585)	0.0255
> 800–1800 mg	$28,250	$29,286	0.88 (0.71–1.09)	$–3995 ($–9689 to $3071)	0.0833
> 300–800 mg	$30,759	$34,089	1.02 (0.79–1.33)	$807 ($–6971 to $10,827)	0.7914
> 0–300 mg	$31,517	$30,129	0.90 (0.70–1.16)	$–3152 ($–9821 to $5342)	0.2382
0 mg	$33,150	$33,282	Reference	Reference	
MI or stroke					
> 1800 mg	$43,533	$37,510	1.13 (0.90–1.43)	$4104 ($–3476 to $14,278)	0.1218
> 800–1800 mg	$28,313	$29,944	0.90 (0.71–1.13)	$–3461 ($–9721 to $4460)	0.1723
> 300–800 mg	$35,190	$37,796	1.13 (0.85–1.51)	$4390 ($–5011 to $17,128)	0.2014
> 0–300 mg	$34,713	$38,177	1.14 (0.88–1.46)	$4772 ($–3939 to $15,447)	0.1401
0 mg	$33,666	$33,406	Reference	Reference	
Type 2 diabetes					
> 1800 mg	$11,350	$11,480	1.59 (1.02–2.46)	$4248 ($151–$10,566)	0.0022
> 800–1800 mg	$5237	$5606	0.77 (0.49–1.22)	$–1627 ($–3667 to $1557)	0.0962
> 300–800 mg	$6270	$8577	1.19 (0.74–1.92)	$1345 ($–1900 to $6630)	0.2890
> 0–300 mg	$6180	$6885	0.95 (0.61–1.50)	$–348 ($–2843 to $3606)	0.7585
0 mg	$7429	$7232	Reference	Reference	
Ulcer or GI bleed					
> 1800 mg	$22,933	$16,482	2.39 (1.52–3.75)	$9646 ($3564–$18,814)	< 0.0001
> 800–1800 mg	$6077	$5623	0.82 (0.53–1.25)	$–1214 ($–3193–$1728)	0.1664
> 300–800 mg	$5036	$5093	0.75 (0.46–1.20)	$–1744 ($–3685–$1401)	0.0729
> 0–300 mg	$6117	$6656	0.97 (0.63–1.49)	$–180 ($–2504–$3325)	0.8371
0 mg	$6449	$6837	Reference	Reference	

[1]Models adjusted for patient age, sex, geographic region, insurance plan type, population density, payer, and baseline measures of: biologic DMARD, nonbiologic DMARD, any AE or AE-related medication, hypothyroidism, ischemic heart disease, cancer, asthma/COPD, Deyo-Charlson Comorbidity Index, no. 3-digit ICD-9-CM diagnosis codes, no. NDC (measures of overall health), healthcare costs. [2]$p < 0.0035$ were considered statistically significant. [3]Includes opportunistic infections such as tuberculosis, candidiasis, and herpes zoster (Supplementary Table 1 shows complete list, available with the online version of this article). AE: adverse event; COPD: chronic obstructive pulmonary disease; DMARD: disease-modifying antirheumatic drug; GI: gastrointestinal; ICD-9-CM: International Classification of Diseases, 9th revision, Clinical Modification; MI: myocardial infarction; NDC: National Drug Codes; OGC: oral glucocorticoids.

require more care, or they may experience more episodes of acute AE, resulting in higher costs. It is possible that patients with more OGC use may require more healthcare encounters and that AE are recorded as the secondary diagnoses on these claims, resulting in an overestimate of AE-related costs. It is also possible that patients with more OGC use are sicker and have conditions associated with the AE measured in these analyses. We adjusted for baseline healthcare costs and measures of general health in our models to counter these potential biases.

Our study included both new and prevalent OGC users, which may have led to biases such as underascertainment of early events or "healthy user bias" as a result of prevalent users being adherent to medication, and including users with fewer risk factors for AE outside of OGC use. However, because our focus was costs, a prevalence-based study with fixed 1-year time frame provided generalizable information most relevant from a payer perspective. OGC use and AE occurring outside of the study period were not evaluated as exposures, outcomes, or exclusion criteria. Another limitation was that it was not feasible to control for severity of RA; this may have confounded the effect of cumulative OGC exposure on AE outcomes. Chronic inflammatory conditions such as RA may increase the risk of some potential OGC-related AE evaluated in our study, including increased fracture risk as a result of bone density loss, which affects the ability to distinguish RA complications from OGC effects, particularly for those on low doses[19]. Additionally, the reasons for prescribing an OGC are not recorded in the databases, so patients may be taking OGC for conditions other than RA. Steroid dosing in this study was categorized by quantiles, but there may be a nonlinear dose response; this could be explored in future research using other sophisticated statistical modeling methodologies. We measured OGC use and DMARD use in the 12-month baseline period, not lifetime use or use in the evaluation period. Because some AE may be associated with current use rather than prior use, our comparisons may be biased if patients' use differed between the baseline and evaluation periods, or if they reached a hypothetical threshold of cumulative dose associated with AE during the evaluation period.

Other limitations include those common to claims-based analyses. Our study was limited to patients with commercial or private Medicare supplemental insurance. The results cannot be generalized to patients with other insurance or without health insurance. Data are subject to data coding limitations and data entry error, which might have led to misclassification. We used a 12-month followup period, and patients who might have had more serious health conditions that caused them to have shorter followup period were excluded. Lastly, by looking at cumulative dose over a 12-month time period, we might have obscured different patterns of OGC use, including different durations of use, which may affect risk for potential AE.

Among patients with RA, higher cumulative OGC dose over a 1-year period resulted in a greater risk of experiencing a potential OGC-related AE during the following year, and the incremental costs associated with this increased risk were substantial for patients at the highest cumulative level of exposure. Given that uncertainty remains about the appropriate use of OGC among patients with RA, these results suggest that all efforts (such as earlier implementation of steroid-sparing treatment) should be made to avoid high dose and chronic OGC therapy.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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