Incidence of infections associated with oral glucocorticoid dose in people diagnosed with polymyalgia rheumatica or giant cell arteritis: a cohort study in England

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ABSTRACT

BACKGROUND: Most patients with polymyalgia rheumatica or giant cell arteritis are treated with glucocorticoid therapy in primary care. We estimated dose–response risks of infection for this population in England.

METHODS: We conducted a retrospective record-linkage study involving a cohort of people with polymyalgia rheumatica or giant cell arteritis registered in family practices across England (1998–2017). Estimates of first occurring infection per level of time-variant current and cumulative dose were obtained using Kaplan–Meier methods and multilevel proportional-hazards Cox models.

RESULTS: Of 39 938 patients attending 389 family practices, 22 234 (55.7%)

had at least 1 infection over a median follow-up period of 4.8 years, with 5937 (26.7%) requiring hospital admission and 1616 (7.3%) dying within 7 days of diagnosis. Cumulative risks of all-cause infection were 18.3% (95% confidence interval [CI] 17.9%–18.7%) at 1 year, 54.7% (95% CI 54.1%–55.2%) at 5 years and 76.9% (95% CI 76.2%–77.5%) at 10 years. Lower respiratory tract infections, conjunctivitis and herpes zoster were the most commonly diagnosed infections. The increases in adjusted hazard ratios (HRs) for all-cause infection per 5 mg prednisolone-equivalent daily dose increase and per 1000 mg cumulative dose increase in the last year from the patient's end date of follow-up were 1.13 (95% CI 1.12–1.14) and 1.50 (95% CI 1.49–1.52),

respectively. Adjusted HRs associated with periods of current glucocorticoid versus no glucocorticoid use ranged from 1.48 (95% CI 1.39–1.57) for fungal to 1.70 (95% CI 1.60–1.80) for bacterial infection. Stepwise dose-related associations were found for bacterial, viral, parasitic and fungal infections, irrespective of patient age, duration of underlying chronic disease and baseline vaccination status.

INTERPRETATION: We quantified the excess risk of all-cause, bacterial, viral, parasitic and fungal infection conferred by oral glucocorticoids in people with polymyalgia rheumatica or giant cell arteritis and found strong dose responses for all types, even at daily doses of less than 5 mg prednisolone.

Polymyalgia rheumatica and giant cell arteritis are chronic inflammatory diseases requiring immunosuppressive therapy with glucocorticoids to induce remission and treat subsequent episodic flares. Most patients with polymyalgia rheumatica or giant cell arteritis are treated with medium-to-high doses of prednisolone (up to 15 mg for polymyalgia rheumatica and 60 mg for giant cell arteritis) for 6 months to several years.[1,2] Glucocorticoids are effective in reducing symptoms and inflammation associated with both diseases, but their immunosuppressive effects[3–5] are known to increase the risk of infection.

Dose–response estimates of absolute and relative risks of infections in people diagnosed with polymyalgia rheumatica or giant cell arteritis are lacking, despite these conditions being the leading indications for long-term glucocorticoid prescription in primary care.[1,2] It is uncertain whether the magnitude of dose–response risks varies for different types of infections.[6]

Previous studies have provided evidence of the increased risk of serious and opportunistic infection in patients with autoimmune diseases treated with high doses of glucocorticoids.[7–9] Most were observational studies that examined risks of specific infections, such as septicemia and lower respiratory

tract infections, and most were conducted among patients with rheumatoid arthritis, aged 65 years and older, and examined risks of severe infections requiring hospital admission or accident and emergency services.[7,8,10–12] Findings from a recent cohort study suggest that the risk of infection in patients treated with oral glucocorticoids may vary for different types of autoimmune diseases.[13]

For patients with polymyalgia rheumatica or giant cell arteritis, for whom current therapeutic options are limited, adequate characterization of glucocorticoid dose–response relations is required to conduct benefit–harm assessments and cost-effectiveness studies. These results will help guide the introduction of newly licensed glucocorticoid-sparing drugs, such as tocilizumab, into clinical practice.

We aimed to assess the risk of all-cause, bacterial, viral, parasitic and fungal infections associated with current daily and cumulative dose of oral glucocorticoids in a large cohort of people diagnosed with polymyalgia rheumatica or giant cell arteritis in England.

Methods

Study design and follow-up

This was a retrospective cohort study conducted among adults attending Clinical Practice Research Datalink (CPRD) family practices in England that consented to data linkage to hospital databases. All patients continuously registered in their family practice for 1 year or longer between Jan. 1, 1997, and Mar. 15, 2017, aged 18 years and older, and with a diagnosis of polymyalgia rheumatica or giant cell arteritis were eligible for inclusion (Supplemental Figure 1, Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.190178/-/DC1). Patients with prevalent and incident polymyalgia rheumatica or giant cell arteritis were included. For each patient, follow-up started on the earliest date on which all the eligibility criteria were met and ended on the earliest of the following dates: first occurrence of the outcome analyzed, death, date leaving the practice or last date of data collection in the practice.

Data sources

We analyzed 3 linked data sources (Appendix 2, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.190178/-/DC1). Primary health care records from CPRD contained demographic and health behaviour data, diagnosed diseases (e.g., infections), prescribed medication, and results of laboratory and clinical examinations.[14] Patients are broadly representative of the population in England in terms of age, sex and ethnicity.[14,15] Validation studies have provided evidence of the accuracy of diagnostic and prescribing information recorded.[14] Hospital records from the Hospital Episode Statistics contained diagnoses recorded during hospital admissions for patients receiving care funded by the National Health Service in England.[16] We used data from the mortality registry to identify dates and causes of death. Patients with polymyalgia rheumatica or giant cell arteritis

were identified with codes previously used and validated (Read Version 2: G755100, G755000, G755.00, Nyu4100, G755z00, G755200, N20..00, N20..11, N200.00; *International Classification of Diseases, 10th Revision*: M31.5, M31.6, M35.3).[17,18] The positive predictive value for giant cell arteritis in CPRD is 91%.[18]

Oral glucocorticoid exposure

For each prescription of oral glucocorticoids, the daily dose was derived from recorded information on the product strength (e.g., 1 mg), directions given (e.g., 1 tablet a day) and quantity prescribed (e.g., 28 tablets). We derived the duration of each prescription by dividing the daily dose by the prescribed total dose. The daily dose was converted into milligrams of prednisolone-equivalent dose (Supplemental Table 1, Appendix 3, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.190178/-/DC1) to account for variation in the relative antiinflammatory effects of different types of glucocorticoids.

We predefined several time-variant glucocorticoid exposure variables (Supplemental Figure 2, Appendix 1): 1) binary variable for current use (e.g., whether the patient received glucocorticoids at a given time point or not); 2) current daily dose per 5 mg/d (zero when medication was not prescribed), considered as continuous and categorical (nonuse, > 0.0–4.9 mg, 5.0–14.9 mg, 15.0–24.9 mg, ≥ 25.0 mg/d) variables; 3) cumulative dose since 1 year before follow-up start per 1000 mg, calculated by summing the total dose prescribed up to that point and dividing it by 1000 (this was also considered as continuous and categorical [nonuse, > 0–959 mg, 960–3054 mg, 3055–7299 mg, ≥ 7300 mg, cutoffs as defined by Movahedi and colleagues[19]] variables); and 4) cumulative dose 1 year before the end of follow-up, calculated by summing the total dose from 1 year before the end of follow-up or the whole study period if the duration of follow-up was less than 1 year. To create these variables, we determined the start and end of each medication exposure period and split patient follow-up on the dates on which the dose changed (Appendix 2).

Study outcomes

The primary outcome was the first occurrence of all-cause infection (Supplemental Figure 3, Appendix 1; Supplemental Table 2, Appendix 3). Secondary outcomes were first occurrence of cause-specific types of infection: bacterial, viral, parasitic and fungal. To capture incident cases of infection, we did not consider episodes from patients with the same type of infection code recorded within 14 days (or 1 year for tuberculosis and hepatitis) before the start of follow-up.

Covariates

The covariates considered were as follows: baseline age; sex; smoking status; ethnicity; body mass index; socioeconomic status (index of multiple deprivation,[20] an area-based indicator based on the patient's residence); underlying disease (polymyalgia rheumatica, giant cell arteritis and both); comorbidities

(cardiovascular disease, diabetes, cancer, asthma, chronic obstructive pulmonary disease, renal disease and HIV); vaccination status (within last year for influenza; at any time before start of follow-up for varicella zoster and pneumococcus); the number of hospital admissions, prescribed non-oral glucocorticoids (inhaled, nasal, parenteral, topical and rectal), H_2 antagonists and proton pump inhibitors in the last year; and time-variant prescribed disease-modifying antirheumatic drugs and nonsteroidal antiinflammatory drugs (NSAIDs) during follow-up (Appendix 2).

Statistical analysis

We report standard descriptive statistics for baseline characteristics. Cumulative probabilities of all-cause and type-specific infection were assessed using Kaplan–Meier methods. We estimated incident rates with 95% confidence intervals (CIs) by dividing the number of infections by the total number of person-years of follow-up.

We assessed dose–response associations using Cox proportional hazards models, including the practice identifier as a random intercept to account for clustering effect. We estimated adjusted hazard ratios (HRs) with 95% CIs for each type of infection regressed on each of the time-variant exposures. Every model was adjusted for the covariates listed and using time-variant prescribed disease-modifying antirheumatic drugs and NSAIDs during follow-up. We assessed the proportional hazards assumption using Schoenfeld residuals tests. Missing daily glucocorticoid dose and baseline covariates were replaced through generation of 25 data sets using multiple imputation with chained equations (Appendix 2). All models were conducted for each imputed data set. We generated pooled estimates and accompanying 95% CIs using Rubin's rules.

In secondary analyses, we obtained estimates by sex, duration since diagnosis of polymyalgia rheumatica or giant cell arteritis, age group, baseline vaccination status and use of non-oral glucocorticoids in the last year.

Data management and analyses were performed in Stata version 15 and R version 3.3.1 (http://cran.r-project.org).

Ethics approval

Approval for the study was obtained from the Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency database research.

Results

A total of 39 938 patients attending 389 family practices were included, 32 735 (82.0%) with polymyalgia rheumatica, 4505 (11.3%) with giant cell arteritis and 2698 (6.8%) with both (Table 1). The median time since diagnosis of polymyalgia rheumatica or giant cell arteritis was 4.9 (interquartile range [IQR] 3.0–7.0) years. Of the patients, 12 346 (30.9%) were men, and the median time at risk was 2.4 (IQR 0.9–5.0) years. At the start of follow-up, the mean patient age was 73.0 (standard deviation 10.7) years, 16 966 (42.5%) were nonsmokers, 19 515 (48.9%)

were vaccinated against pneumococcus, 25 640 (64.2%) were vaccinated against influenza, and 7676 (19.2%) received inhaled or nasal glucocorticoids (Supplemental Tables 3 and 4, Appendix 3). At baseline, the most common diagnosed comorbidities were cardiovascular disease (32.7%), asthma (15.9%) and diabetes (12.6%).

The median glucocorticoid cumulative dose received during follow-up was 3451.5 (IQR 1606.5–6465.0) mg and in the last year of follow-up was 1598.4 (IQR 780.0–2552.7) mg. During follow-up, 3809 (9.5%) patients received a disease-modifying antirheumatic drug.

Incidence, type and severity of infection

A total of 22 234 (55.7%) people had an infection during 138 412 person-years of follow-up; the median duration of follow-up per patient was 4.8 (IQR 2.2–8.5) years. The incidence of all-cause infection was 160.7 (95% CI 159.3–162.2) per 1000 person-years (Supplemental Table 5, Appendix 3). Types of infection most frequently diagnosed were lower respiratory tract infections (6064 [27.3%]), conjunctivitis (1905 [8.6%]) and herpes zoster (1642 [7.4%]) (Supplemental Table 6, Appendix 3). Of the 22 234 patients who had an infection, 5937 (26.7%) were admitted to hospital on the date of or within 7 days after infection diagnosis, 1930 (8.7%) died within 30 days of diagnosis and 1616 (7.3%) died within 7 days of diagnosis. The most common causes of death from infection were pneumonia (1015 [52.6%]), urinary tract infection (58 [3.0%]) and peritonitis (43 [2.2%]).

The cumulative probabilities of all types of infection increased with higher daily dose (Table 2). At 1 year, probabilities of all-cause infection increased from 12.9% (95% CI 12.4%–13.4%) for periods of nonuse, through 18.0% (95% CI 17.1%–18.8%) for a dose between greater than 0.0 and 4.9 mg/d, to 35.8% (95% CI 32.9%–38.6%) for 25.0 mg/d or greater.

Dose–response associations

Compared with periods of nonuse of oral glucocorticoids, adjusted HRs of all types of infection were higher in periods of current use (adjusted HR 1.49, 95% CI 1.44–1.53 for all-cause infection; Table 3). The highest estimates were seen for bacterial infections (adjusted HR 1.70, 95% CI 1.60–1.80) and the lowest for fungal infections (adjusted HR 1.48, 95% CI 1.39–1.57). Compared with nonuse of oral glucocorticoids, the increase in adjusted HR per 5 mg daily dose was 1.13 (95% CI 1.12–1.14) for all-cause infection, with adjusted HRs increasing from 1.39 (95% CI 1.34–1.45) for a dose between greater than 0.0 and 4.9 mg/d to 2.30 (95% CI 2.13–2.49) for 25 mg/d or greater. The increase in adjusted HR per 1000 mg cumulative dose during the last year was 1.50 (95% CI 1.49–1.52).

Secondary analyses showed similar dose–response estimates regardless of sex and time since diagnosis of the underlying disease (Table 4; Supplemental Tables 7 and 8, Appendix 3; Appendix 4, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.190178/-/DC1). Higher cumulative probabilities

of all-cause and bacterial infection were found in older patients (Supplemental Table 9, Appendix 3). Patients who were vaccinated had higher risks of all types of infections than those not vaccinated. Patients prescribed non-oral glucocorticoids had higher risks of all types of infections than those not treated with non-oral glucocorticoids (Supplemental Tables 10–12, Appendix 3).

Interpretation

In this population-based study including 39 938 patients diagnosed with polymyalgia rheumatica or giant cell arteritis, we found high absolute risks of all types of infection and a marked stepwise increase in risk with higher oral glucocorticoid doses. In periods with prescribed medication, patients'

	Table 1: Baseline characteristics of adult patients attending 389 family practices in England, by disease type			
	No. (%) of patients or mean ± SD*			
Characteristic	**Total** n = 39 938	**GCA only** n = 4505	**PMR only** n = 32 735	**PMR and GCA** n = 2698
Sociodemographic information				
Sex, male	12 346 (30.9)	1391 (30.9)	10 373 (31.7)	582 (21.6)
Age, yr	73.0 ± 10.7	71.1 ± 12.6	73.2 ± 10.5	73.9 ± 8.7
Ethnicity†				
White	35 692 (89.4)	4001 (88.8)	29 205 (89.2)	2486 (92.1)
Other	959 (2.4)	220 (4.9)	671 (2.0)	68 (2.5)
Index of Multiple Deprivation (fifths)				
First (least deprived)	7583 (19.0)	709 (15.7)	6358 (19.4)	516 (19.1)
Fifth (most deprived)	5311 (13.3)	829 (18.4)	4104 (12.5)	378 (14.0)
Biomarkers				
Body mass index†	27.5 ± 5.6	27.3 ± 6.0	27.5 ± 5.5	26.9 ± 5.7
C-reactive protein, mg/L	33.1 ± 43.4	36.7 ± 57.2	32.2 ± 40.8	40.0 ± 53.6
Erythrocyte sedimentation rate, mm/h	40.4 ± 29.0	41.4 ± 32.5	39.9 ± 28.2	45.2 ± 32.1
Total white blood cells, x10^9/L	8.7 ± 2.7	8.5 ± 3.0	8.7 ± 2.7	9.0 ± 2.9
Neutrophils, x10^9/L	5.8 ± 2.4	5.7 ± 2.7	5.8 ± 2.3	6.2 ± 2.6
Lymphocytes, x10^9/L	2.0 ± 0.9	2.0 ± 1.0	2.0 ± 0.9	1.9 ± 0.9
Eosinophils, x10^9/L	0.2 ± 0.2	0.2 ± 0.2	0.2 ± 0.2	0.2 ± 0.2
Hemoglobin, g/L	128 ± 14	129 ±15	128 ± 14	126 ± 14
Creatinine, μmol/L	88.8 ± 33.6	92.2 ± 49.7	88.5 ± 31.2	87.0 ± 29.8
Smoking status†				
Nonsmoker	16 966 (42.5)	1710 (38.0)	14 084 (43.0)	1172 (43.4)
Former smoker	8302 (20.8)	824 (18.3)	6982 (21.3)	496 (18.4)
Current smoker	8197 (20.5)	1221 (27.1)	6440 (19.7)	536 (19.9)
Duration since first recorded diagnosed disease, yr, median (IQR)	4.9 (3.0–7.0)	4.0 (2.0–6.0)	4.9 (3.0–7.0)	6.1 (2.0–9.0)
No. of hospital admissions in last year	0.6 ± 2.6	0.9 ± 4.0	0.5 ± 2.4	0.6 ± 1.3
Comorbidities‡				
Cardiovascular disease	13 044 (32.7)	1649 (36.6)	10 464 (32.0)	931 (34.5)
Diabetes	5020 (12.6)	647 (14.4)	4055 (12.4)	318 (11.8)
Asthma	6336 (15.9)	817 (18.1)	5057 (15.4)	462 (17.1)
COPD	2987 (7.5)	466 (10.3)	2328 (7.1)	193 (7.2)
Cancer	4050 (10.1)	466 (10.3)	3348 (10.2)	236 (8.7)
Chronic renal disease	1347 (3.4)	163 (3.6)	1095 (3.3)	89 (3.3)

Note: COPD = chronic obstructive pulmonary disease, GCA = giant cell arteritis, IQR = interquartile range, PMR = polymyalgia rheumatica, SD = standard deviation.
*Unless stated otherwise.
†Data on ethnicity, body mass index and smoking status were missing for 8.1%, 29.8% and 16.2% of patients, respectively.
‡Two patients had HIV infection at baseline.

risk was 50% higher than when it was not prescribed. Increases in risk ranged from 48% for fungal to 70% for bacterial infections. For every increase of 5 mg daily dose and of 1000 mg cumulative dose in the last year, the increased risks of all-cause infection were 13% and 50%, respectively.

When assessing dose response with total cumulative dose, we found evidence of increased risk only for a dose of 7300 mg or greater. This weaker association is expected given that the risk conferred by glucocorticoids would decrease with time since exposure discontinuation. Dose–response estimates

Table 2 (part 1 of 2): Kaplan–Meier estimates of infection per level of time-variant current daily and cumulative oral glucocorticoid prednisolone-equivalent dose

Variable	Cumulative probability, % (95% CI)*; infection type				
	All-cause	Bacterial	Viral	Parasitic	Fungal
Incident infections, no. (%)	22 234 (100)	5234 (23.5)	5344 (24.0)	1120 (5.0)	5416 (24.4)
At 1 year	18.3 (17.9–18.7)	3.2 (3.0–3.3)	3.8 (3.6–3.9)	0.9 (0.8–1.0)	3.9 (3.7–4.1)
Current daily dose, mg					
Nonuse	12.9 (12.4–13.4)	2.1 (1.8–2.3)	2.5 (2.2–2.7)	0.6 (0.5–0.7)	2.4 (2.2–2.7)
> 0.0–4.9	18.0 (17.1–18.8)	3.4 (3.0–3.8)	3.6 (3.2–4.0)	0.8 (0.6–1.0)	4.0 (3.6–4.5)
5.0–14.9	21.1 (20.4–21.8)	3.5 (3.1–3.8)	4.6 (4.2–5.0)	1.1 (0.9–1.3)	4.7 (4.3–5.1)
15.0–24.9	30.4 (28.5–32.2)	6.3 (5.3–7.4)	7.2 (6.1–8.3)	2.0 (1.4–2.5)	7.3 (6.3–8.4)
≥ 25.0	35.8 (32.9–38.6)	7.9 (6.2–9.7)	8.0 (6.2–9.7)	2.1 (1.1–3.0)	8.5 (6.7–10.3)
Cumulative dose in last year, mg					
Nonuse	5.1 (4.8–5.3)	0.7 (0.6–0.8)	0.8 (0.7–0.9)	0.2 (0.1–0.2)	0.9 (0.7–1.0)
> 0.0–959.9	39.0 (37.4–40.5)	11.4 (10.0–12.7)	13.9 (12.5–15.3)	3.6 (2.8–4.4)	12.9 (11.6–14.3)
960.0–3054.9	49.2 (47.9–50.4)	17.1 (15.7–18.5)	18.5 (17.1–19.9)	5.6 (4.7–6.5)	20.3 (18.9–21.7)
≥ 3055.0	60.2 (57.9–62.4)	23.3 (20.2–26.3)	25.8 (22.7–28.7)	7.9 (5.9–9.9)	24.4 (21.3–27.3)
Total cumulative dose, mg					
Nonuse	20.6 (19.6–21.6)	3.5 (3.0–4.0)	4.0 (3.5–4.5)	1.0 (0.8–1.3)	4.3 (3.8–4.9)
> 0.0–959.9	29.0 (27.8–30.3)	5.4 (4.7–6.0)	6.9 (6.2–7.6)	1.6 (1.2–1.9)	6.6 (5.9–7.3)
960.0–3054.9	21.9 (21.2–22.6)	4.0 (3.7–4.4)	4.5 (4.2–4.9)	1.1 (1.0–1.3)	5.2 (4.8–5.6)
3055.0–7299.9	10.2 (9.7–10.7)	1.8 (1.5–2.0)	2.1 (1.9–2.4)	0.5 (0.4–0.6)	1.8 (1.6–2.1)
≥ 7300.0	7.4 (6.0–8.9)	0.6 (0.2–1.0)	1.2 (0.7–1.8)	0.4 (0.1–0.8)	1.4 (0.8–2.0)
At 5 years	54.7 (54.1–55.2)	11.6 (11.2–12.0)	13.1 (12.7–13.5)	2.8 (2.6–3.0)	13.7 (13.3–14.1)
Current daily dose, mg					
Nonuse	42.1 (41.3–42.9)	7.6 (7.2–7.9)	8.8 (8.4–9.2)	1.9 (1.7–2.1)	9.4 (8.9–9.8)
> 0.0–4.9	65.0 (63.6–66.4)	17.0 (15.8–18.1)	17.7 (16.4–18.8)	3.3 (2.7–3.8)	18.5 (17.3–19.7)
5.0–14.9	69.8 (68.7–71.0)	17.6 (16.6–18.6)	20.3 (19.2–21.4)	4.5 (4.0–5.1)	20.5 (19.4–21.6)
15.0–24.9	77.9 (75.4–80.1)	23.7 (20.8–26.5)	24.6 (21.8–27.4)	6.4 (4.8–8.0)	27.7 (24.6–30.7)
≥ 25.0	81.5 (78.2–84.3)	28.4 (24.0–32.5)	27.5 (23.1–31.6)	7.2 (4.6–9.7)	26.7 (22.6–30.5)
Cumulative dose in last year, mg					
Nonuse	32.6 (31.8–33.3)	4.9 (4.6–5.2)	5.9 (5.6–6.2)	1.1 (1.0–1.3)	6.3 (5.9–6.6)
> 0.0–959.9	74.9 (73.3–76.3)	24.0 (22.1–25.8)	26.1 (24.2–27.9)	5.4 (4.5–6.4)	26.7 (24.9–28.5)
960.0–3054.9	84.5 (83.4–85.4)	33.1 (31.2–35.0)	35.0 (33.1–36.9)	9.2 (7.9–10.4)	36.9 (35.0–38.8)
≥ 3055.0	92.7 (91.0–94.0)	50.3 (45.5–54.8)	47.7 (43.0–52.1)	13.4 (9.9–16.7)	45.2 (40.6–49.5)
Total cumulative dose, mg					
Nonuse	58.7 (57.1–60.2)	12.3 (11.2–13.4)	14.3 (13.2–15.5)	3.4 (2.8–4.0)	15.6 (14.3–16.8)
> 0.0–959.9	62.4 (60.8–64.0)	14.2 (13.0–15.4)	17.2 (15.9–18.5)	3.9 (3.2–4.5)	17.3 (16.0–18.6)
960.0–3054.9	61.7 (60.5–62.8)	14.5 (13.7–15.4)	16.1 (15.1–17.0)	3.6 (3.1–4.1)	18.0 (17.1–19.0)
3055.0–7299.9	55.2 (54.1–56.2)	11.9 (11.2–12.6)	13.7 (13.0–14.4)	2.8 (2.4–3.1)	13.8 (13.0–14.5)
≥ 7300.0	36.1 (34.8–37.3)	7.2 (6.6–7.8)	7.4 (6.8–8.0)	1.4 (1.2–1.7)	7.5 (6.9–8.1)

Table 2 (part 2 of 2): Kaplan–Meier estimates of infection per level of time-variant current daily and cumulative oral glucocorticoid prednisolone-equivalent dose

Variable	Cumulative probability, % (95% CI)*; infection type				
	All-cause	Bacterial	Viral	Parasitic	Fungal
At 10 years	76.9 (76.2–77.5)	21.0 (20.4–21.7)	21.2 (20.6–21.8)	4.2 (4.0–4.5)	21.2 (20.6–21.8)
Current daily dose, mg					
Nonuse	68.0 (67.1–68.9)	15.6 (15.0–16.3)	15.9 (15.2–16.6)	3.0 (2.7–3.3)	16.2 (15.6–16.9)
> 0.0–4.9	84.4 (82.9–85.8)	29.2 (27.2–31.1)	27.9 (26.0–29.8)	5.3 (4.4–6.2)	28.6 (26.6–30.4)
5.0–14.9	88.7 (87.6–89.7)	30.6 (28.8–32.4)	30.9 (29.2–32.6)	6.8 (5.8–7.8)	29.4 (27.8–31.1)
15.0–24.9	92.3 (89.9–94.2)	35.9 (31.2–40.2)	38.2 (33.2–42.8)	9.6 (6.7–12.5)	36.1 (31.8–40.1)
≥ 25.0	93.1 (90.1–95.2)	45.5 (37.9–52.2)	39.4 (32.5–45.5)	11.6 (7.0–15.9)	36.9 (30.6–42.6)
Cumulative dose in last year, mg					
Nonuse	62.5 (61.5–63.5)	12.8 (12.1–13.4)	13.1 (12.5–13.7)	2.3 (2.0–2.5)	13.3 (12.7–13.9)
> 0.0–959.9	88.7 (87.1–90.1)	33.1 (30.4–35.7)	33.1 (30.4–35.7)	6.7 (5.4–7.9)	32.9 (30.4–35.4)
960.0–3054.9	93.1 (92.0–94.0)	41.8 (39.0–44.4)	40.5 (37.8–43.1)	10.4 (8.6–2.2)	37.8 (35.5–40.1)
≥ 3055.0	97.2 (95.7–98.2)	54.4 (48.4–59.7)	50.7 (43.9–56.7)	10.7 (6.5–14.6)	47.0 (40.6–52.7)
Total cumulative dose, mg					
Nonuse	79.3 (77.5–80.9)	22.3 (20.3–24.2)	23.4 (21.5–25.2)	5.2 (4.2–6.2)	23.2 (21.4–25.0)
> 0.0–959.9	82.2 (80.4–83.8)	22.6 (20.7–24.5)	25.8 (23.8–27.8)	5.8 (4.7–6.8)	26.2 (24.2–28.1)
960.0–3054.9	81.3 (80.0–82.5)	24.2 (22.7–25.6)	23.7 (22.3–25.1)	5.2 (4.5–5.9)	26.0 (24.6–27.4)
3055.0–7299.9	76.0 (74.8–77.2)	21.0 (19.8–22.1)	21.6 (20.4–22.7)	4.0 (3.5–4.6)	21.5 (20.4–22.7)
≥ 7300.0	67.4 (65.9–68.8)	17.4 (16.3–18.4)	16.1 (15.1–17.1)	2.9 (2.5–3.3)	14.8 (13.8–15.8)

Note: CI = confidence interval.
*Unless stated otherwise.

were similar regardless of sex, disease subtype (i.e., polymyalgia rheumatica, giant cell arteritis or both), and disease duration. However, higher dose–response risks of all infections were observed for patients prescribed than for those not prescribed non-oral glucocorticoids, and higher risks of bacterial infections were found in older patients than in younger patients. Higher dose–response risks were also found for patients vaccinated against pneumococcus, influenza and varicella zoster than for patients not vaccinated. This is consistent with patients with high morbidity burden (e.g., older patients) being more often vaccinated and having high risk for infections for which they are unprotected.

A previous study conducted among 1664 patients with giant cell arteritis reported adjusted rate ratios of lower respiratory tract infections, upper urinary tract infections and sepsis for oral glucocorticoid users, compared with matched controls.[9] Studies among patients with rheumatoid arthritis have reported increased risk of common serious infections (e.g., bacterial pneumonia and herpes zoster)[8,10–12,21] but not of nonserious infections.[21] In contrast, in a large case–control study involving patients with rheumatoid arthritis, the risk of nonserious infections was higher in patients receiving oral glucocorticoids, with adjusted HRs increasing from 1.10 for patients receiving 5–10 mg/d, to 1.85 for those receiving 20 mg/d or more, compared with controls.[9]

In our study, 26.7% of patients with infection required hospital admission, and 7.3% died within 7 days of diagnosis. Furthermore, by considering periods of drug use and changes in dosage over time (i.e., through time-variant exposure variables), we found marked dose–response effects for current and recent cumulative glucocorticoid use. This is consistent with results of a nested case–control study, conducted in Canada among 1947 cases and 16 207 controls who had rheumatoid arthritis and were aged 60 years and older,[7] in which the risk of infections requiring hospital admission varied with dosage and treatment duration. In agreement with our findings, a study in the United Kingdom identified older age but not sex as a risk factor for septicemia, lower respiratory tract infections and herpes zoster in patients treated with oral glucocorticoids, compared with nonusers.[13]

The large sample allowed the investigation of dose responses for different infection types and relevant subgroups (e.g., by disease duration). The contemporary study period and data linkage across primary and secondary care databases allowed for a large unselected cohort of patients with uncommon diseases and assessment of risk for both serious and nonserious infections. To minimize length and time-dependent bias,[22,23] the start and end of follow-up were unrelated to dates of prescribed glucocorticoids, and medication variables identified periods with and without treatment (i.e., time variant).

Table 3: Association between time-variant prescribed oral glucocorticoids and incident infections

Variable	Adjusted hazard ratio* (95% CI); infection type				
	All-cause	Bacterial	Viral	Parasitic	Fungal
Current use	1.49 (1.44–1.53)	1.70 (1.60–1.80)	1.53 (1.44–1.62)	1.50 (1.32–1.71)	1.48 (1.39–1.57)
Current daily dose per 5 mg daily	1.13 (1.12–1.14)	1.16 (1.14–1.19)	1.13 (1.11–1.15)	1.14 (1.09–1.18)	1.11 (1.09–1.14)
Current daily dose category, mg					
Nonuse (Ref.)	1.00	1.00	1.00	1.00	1.00
> 0.0–4.9	1.39 (1.34–1.45)	1.58 (1.43–1.75)	1.47 (1.34–1.62)	1.41 (1.14–1.74)	1.46 (1.34–1.59)
5.0–14.9	1.46 (1.41–1.52)	1.64 (1.51–1.78)	1.46 (1.34–1.59)	1.42 (1.21–1.68)	1.41 (1.31–1.53)
15.0–24.9	1.66 (1.55–1.77)	1.95 (1.71–2.23)	1.78 (1.54–2.06)	1.87 (1.43–2.43)	1.62 (1.42–1.85)
≥ 25	2.30 (2.13–2.49)	3.02 (2.51–3.63)	2.28 (1.89–2.74)	2.40 (1.70–3.40)	2.10 (1.74–2.52)
Cumulative dose in last year (per 1000 mg)	1.50 (1.49–1.52)	1.53 (1.51–1.55)	1.51 (1.50–1.53)	1.52 (1.49–1.55)	1.59 (1.57–1.61)
Cumulative dose in last year category, mg					
Nonuse (Ref.)	1.00	1.00	1.00	1.00	1.00
> 0.0–959.9	1.88 (1.84–1.92)	2.17 (2.09–2.25)	2.30 (2.22–2.37)	2.43 (2.25–2.60)	2.31 (2.23–2.39)
960–3054.9	2.50 (2.47–2.54)	2.85 (2.78–2.92)	2.95 (2.88–3.02)	3.12 (2.97–3.26)	2.98 (2.91–3.04)
≥ 3055	3.23 (3.19–3.28)	3.69 (3.60–3.79)	3.72 (3.63–3.81)	3.90 (3.70–4.10)	3.66 (3.56–3.75)
Total cumulative dose (per 1000 mg)	1.01 (1.00–1.01)	1.02 (1.01–1.02)	1.01 (1.00–1.01)	1.01 (1.00–1.02)	1.00 (1.00–1.01)
Total cumulative dose category, mg					
Nonuse (Ref.)	1.00	1.00	1.00	1.00	1.00
> 0.0–959.9	1.08 (1.03–1.14)	1.10 (0.98–1.23)	1.08 (0.97–1.21)	1.08 (0.86–1.36)	1.07 (0.96–1.18)
960–3054.9	1.01 (0.97–1.06)	1.08 (0.98–1.20)	0.96 (0.87–1.05)	1.00 (0.81–1.23)	1.07 (0.97–1.17)
3055–7299.9	1.05 (1.00–1.09)	1.10 (1.00–1.21)	1.06 (0.97–1.16)	1.08 (0.88–1.32)	1.02 (0.93–1.13)
≥ 7300	1.11 (1.06–1.17)	1.36 (1.23–1.51)	1.13 (1.02–1.25)	1.17 (0.94–1.47)	1.07 (0.96–1.19)

Note: CI = confidence interval, Ref. = reference category.
*Hazard ratios from Cox proportional models adjusted for baseline age, sex, index of multiple deprivation, smoking status, ethnicity, body mass index, chronic inflammatory disease type, comorbidities (cardiovascular disease, diabetes, HIV, cancer, asthma, chronic obstructive pulmonary disease and renal disease), vaccination status (varicella zoster, pneumococcus and influenza), number of hospital admissions in last year, prescribed non-oral glucocorticoids, proton pump inhibitors and H$_2$ antagonists, and time-variant use of disease-modifying antirheumatic drugs and nonsteroidal antiinflammatory drugs; the practice identifier was included as a random intercept to account for clustering effect.

The observed high excess infection risk and infection-related mortality in patients with polymyalgia rheumatica or giant cell arteritis, even for daily doses of less than 5 mg, and the high dose–response estimates in users of non-oral glucocorticoids and vaccinated patients highlight the need for regular review of glucocorticoid requirements, even at low doses. Patients and clinicians should be educated about the risk of infection, need for symptom identification, prompt treatment, timely vaccination and documentation of history of chronic infection (e.g., herpes zoster).

Limitations

To define incident episodes of infection and its types, we used an algorithm combining diagnostic codes for infection and antibiotic and antiviral drug use. Reporting bias related to a higher suspicion of infections during periods of glucocorticoid use cannot be excluded. However, in our cohort, 93.7% of infections were diagnosed on dates on which oral glucocorticoids were not prescribed, suggesting the primary reason for consultation was new infection-related symptoms. It remains likely that self-treated minor infections were missed.

No information on adherence or on hospital-prescribed medication was available, and missing glucocorticoid dose during tapering periods was imputed. This might underestimate medication use when patients are treated by specialists (e.g., around diagnosis or serious disease flares). Nevertheless, the median time since diagnosis was 5 years, a low proportion of patients had newly diagnosed polymyalgia rheumatica or giant cell arteritis, and the bulk of prescribing in the UK happens in primary care.

Conclusion

In this large, contemporary population-based study, we estimated absolute and relative risks of all-cause, bacterial, viral, parasitic and fungal infections and found strong glucocorticoid dose responses for all types among people diagnosed with polymyalgia rheumatica or giant cell arteritis. The estimates of dose response can be used to conduct benefit–harm evaluations and cost-effectiveness studies of new glucocorticoid-sparing drugs required to guide policy and improve patient care outcomes in patients with polymyalgia rheumatica or giant cell arteritis.

Table 4: Kaplan–Meier estimates of infections per level of time-variant current daily and cumulative oral glucocorticoid prednisolone-equivalent dose by time since diagnosis of polymyalgia rheumatica or giant cell arteritis

Variable	Cumulative probability, % (95% CI)*; time since diagnosis				
	Within 1 year	First year	Second year	Third year	After third year
All-cause infections					
Incident infections, no. (%)	15 187 (54.2)	1703 (62.7)	1015 (62.3)	807 (61.6)	3522 (56.3)
At 1 year	18.2 (17.8–18.7)	18.0 (16.6–19.5)	18.8 (16.8–20.7)	18.0 (15.8–20.1)	18.7 (17.7–19.7)
Current daily dose, mg					
Nonuse	11.0 (10.4–11.7)	13.0 (11.0–15.0)	13.5 (11.0–15.9)	14.1 (11.4–16.7)	16.8 (15.6–18.0)
> 0.0–4.9	17.3 (16.4–18.3)	19.2 (15.8–22.5)	20.2 (15.2–25.0)	22.2 (16.6–27.5)	19.8 (17.0–22.4)
5.0–14.9	20.8 (20.0–21.6)	22.2 (19.2–25.1)	24.6 (20.5–28.5)	20.2 (15.4–24.7)	21.6 (19.1–24.0)
15.0–24.9	31.2 (29.1–33.2)	27.5 (19.6–34.6)	28.2 (16.8–38.0)	26.5 (9.9–40.0)	24.4 (17.3–30.9)
≥ 25.0	35.7 (32.5–38.8)	26.1 (12.7–37.4)	28.6 (9.5–43.6)	47.9 (24.1–64.2)	42.0 (29.3–52.4)
Bacterial infections					
Incident infections, no. (%)	3421 (12.2)	422 (15.5)	254 (15.6)	227 (17.3)	910 (14.5)
At 1 year	2.9 (2.7–3.1)	3.1 (2.5–3.8)	3.0 (2.1–3.8)	3.6 (2.5–4.6)	4.3 (3.8–4.9)
Current daily dose, mg					
Nonuse	1.4 (1.2–1.7)	2.0 (1.2–2.8)	1.8 (0.9–2.7)	3.0 (1.7–4.3)	3.6 (3.0–4.2)
> 0.0–4.9	3.0 (2.6–3.5)	3.6 (1.9–5.2)	3.8 (1.5–6.1)	5.7 (2.5–8.7)	5.7 (4.1–7.2)
5.0–14.9	3.3 (2.9–3.6)	4.0 (2.6–5.4)	3.1 (1.4–4.8)	3.0 (1.1–5.0)	4.9 (3.6–6.2)
15.0–24.9	6.3 (5.1–7.4)	6.3 (2.0–10.5)	9.7 (2.6–16.4)	2.7 (0.0–7.8)	6.2 (2.4–9.9)
≥ 25.0	7.5 (5.7–9.4)	4.2 (0.0–9.8)	8.4 (0.0–18.8)	10.0 (0.0–22.2)	15.0 (5.4–23.6)
Viral infections					
Incident infections, no. (%)	3731 (13.3)	361 (13.3)	240 (14.7)	193 (14.7)	819 (13.1)
At 1 year	3.9 (3.6–4.1)	3.3 (2.6–4.0)	4.1 (3.1–5.1)	3.8 (2.7–4.9)	3.3 (2.8–3.8)
Current daily dose, mg					
Nonuse	2.2 (1.9–2.5)	2.1 (1.2–2.9)	3.2 (2.0–4.4)	3.2 (1.9–4.5)	2.8 (2.3–3.4)
> 0.0–4.9	3.6 (3.1–4.1)	4.0 (2.3–5.8)	5.7 (2.9–8.5)	3.9 (1.2–6.6)	2.4 (1.3–3.4)
5.0–14.9	4.6 (4.2–5.1)	4.5 (3.0–6.0)	4.3 (2.3–6.3)	4.1 (1.8–6.4)	4.7 (3.5–6.0)
15.0–24.9	7.3 (6.1–8.5)	5.6 (1.5–9.6)	5.9 (0.1–11.4)	2.7 (0.0–7.8)	9.1 (4.4–13.5)
≥ 25.0	8.4 (6.4–10.3)	2.2 (0.0–6.3)	4.2 (0.0–11.8)	20.0 (0.4–35.7)	3.5 (0.0–8.3)
Parasitic infections					
Incident infections, no. (%)	771 (2.8)	73 (2.7)	40 (2.5)	54 (4.1)	182 (2.9)
At 1 year	1.0 (0.8–1.1)	0.7 (0.4–1.0)	1.0 (0.5–1.4)	1.1 (0.5–1.7)	0.8 (0.6–1.0)
Current daily dose, mg					
Nonuse	0.6 (0.4–0.8)	0.3 (0.0–0.5)	0.6 (0.1–1.2)	1.0 (0.3–1.8)	0.7 (0.4–0.9)
> 0.0–4.9	0.8 (0.6–1.0)	0.4 (0.0–1.0)	1.5 (0.0–3.0)	1.0 (0.0–2.3)	0.9 (0.2–1.5)
5.0–14.9	1.1 (0.9–1.4)	1.2 (0.4–1.9)	1.0 (0.0–1.9)	1.1 (0.0–2.3)	1.2 (0.5–1.8)
15.0–24.9	1.9 (1.3–2.6)	3.0 (0.1–5.9)	2.6 (0.0–6.0)	5.3 (0.0–12.1)	0.6 (0.0–1.7)
≥ 25.0	2.3 (1.2–3.4)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	1.7 (0.0–5.0)
Fungal infections					
Incident infections, no. (%)	3890 (13.9)	351 (12.9)	226 (13.9)	177 (13.5)	772 (12.3)
At 1 year	4.2 (4.0–4.4)	3.0 (2.3–3.6)	4.0 (3.0–5.0)	2.6 (1.7–3.5)	3.2 (2.8–3.7)
Current daily dose, mg					
Nonuse	2.3 (2.0–2.6)	1.7 (1.0–2.5)	3.2 (2.0–4.5)	2.2 (1.1–3.3)	3.0 (2.4–3.5)
> 0.0–4.9	4.1 (3.6–4.7)	4.0 (2.3–5.7)	4.2 (1.7–6.6)	4.2 (1.5–6.9)	3.1 (1.9–4.3)
5.0–14.9	5.0 (4.6–5.5)	3.8 (2.4–5.2)	4.8 (2.7–6.8)	2.1 (0.4–3.7)	3.7 (2.6–4.8)
15.0–24.9	7.8 (6.5–9.0)	5.4 (1.4–9.3)	7.1 (0.9–12.9)	2.7 (0.0–7.8)	5.0 (1.5–8.3)
≥ 25.0	9.4 (7.3–11.4)	2.0 (0.0–5.9)	4.3 (0.0–12.3)	5.3 (0.0–14.8)	5.1 (0.0–10.6)

Note: CI = confidence interval.
*Unless stated otherwise.

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