Oral and inhaled glucocorticoid use and risk of Achilles or biceps tendon rupture: a population-based case-control study

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Background. Tendinotoxicity of glucocorticoids (GC) has been shown, but evidence on how this translates into clinical practice remains scarce.

Objectives. To explore the association between oral or inhaled GC use and the risk of Achilles or biceps tendon rupture (ATR/BTR).

Methods. We identified patients aged 18 to 89 years with incident ATR or BTR (1995–2013) for a matched (1:4) case-control analysis using the UK-based Clinical Practice Research Datalink. We stratified oral GC use by indication, timing and duration of use, continuous versus intermittent use, cumulative dose, and average daily dose. We stratified inhaled GC use by timing and number of prescriptions.

Results. Among 8,202 cases, we observed increased odds ratios (ORs) around 3.0 for continuous oral GC use, which declined shortly after therapy cessation (similarly across indications). Odds ratios increased with average daily dose (≥10 mg/day, OR 4.05, 95% CI 2.32–7.08) and were elevated after one cycle of high-dose oral GC (≥20 mg/day). There was no effect of inhaled GC at any level of exposure.

Conclusion. Our results provide evidence that oral GC therapy increases the risk of tendon rupture in a dose–response relationship. A single short-term high-dose GC treatment course may be sufficient transiently to increase the risk of tendon rupture.

Key words: Adverse event, Clinical Practice Research Datalink, glucocorticoids, observational, tendon rupture

Introduction

Achilles and biceps tendon ruptures are the two most frequent types of tendon rupture. Achilles tendon ruptures (ATR) often occur in middle-aged men during sports activity, while biceps tendon ruptures (BTR) typically occur spontaneously in elderly patients, mainly as result of chronic shoulder tendinopathy (1–4). Although tendon ruptures are usually preceded by trauma, pre-existing tendon damage may predispose to rupture at little extrinsic stress (5–8). Scarc evidence exists on factors that compromise tendon integrity, though over-use, advanced age, male gender, obesity, genetic factors, diabetes mellitus, dyslipidemia, adrenal disorders, chronic kidney disease, and rheumatic diseases have been considered (9,10).

Use of glucocorticoids (GC) applied systemically, locally injected, or via inhalation has been anecdotally reported to be associated with tendinopathies for more than 45 years (11–15). In vivo and in vitro studies have demonstrated a negative influence of GC on biomechanical properties of tendons, causing pathological changes in tendinocytes shortly after GC application (14,16–20). Two previous observational studies quantified the association between GC use and ATR, although these were only reported as secondary issues within studies of fluoroquinolone-induced ATR (5,13,14). Underlying indication, daily GC dose (the presumed main predictive factor for GC-induced fractures) (21), treatment duration, or differentiation between continuous versus intermittent GC use were not addressed (5,13). Considering the abundant use of GC, in-depth pharmacoepidemiological studies are needed to identify patients at risk of GC-induced tendon ruptures (11,15,19,22,23). In a large observational case-control analysis using data from the UK-based primary-care database Clinical Practice Research Datalink (CPRD), we analysed the risk of ATR/BTR in patients exposed to oral or inhaled GC.
Material and methods

Data source
The CPRD is an anonymous primary-care database comprising approximately 8 million active patients enrolled with selected general practitioners (GPs). In the UK, GPs hold a gatekeeper role within the National Health System. After referrals, consultants are required to send information on diagnoses and treatments to the GP who enters this information into the database. GPs provide information on patient demographics and characteristics (e.g. age, sex, height, weight, smoking status), symptoms or diagnoses, lab test results, and referrals to secondary care. Drug prescriptions are generated via computer, ensuring a complete drug history. Patients are representative of the UK population, and extensive validation has documented high validity of the database (24,25). The study protocol was approved by the Independent Scientific Advisory Committee (ISAC) for Medicines and Healthcare products Regulatory Agency (MHRA) database research.

Study population

Cases
We identified patients aged 18 to 89 years with an incident Read code (24) for ATR or BTR between January 1995 and December 2013, and with ≥ 3 years of recorded active history in the database prior to the ATR/BTR diagnosis (’index date’). We excluded patients with recorded alcoholism, other substance abuse, cancer (except non-melanoma skin cancer), or HIV before the index date (increased risk of bias and confounding), as well as patients with a recorded previous rupture of, or manipulation of, the Achilles or biceps tendons, or with a record of acquired or congenital malformation of the respective tendon. We further excluded patients with a record of a major accident (e.g. vehicle accident, fall from roof or ladder) within 30 days before the index date, to exclude patients with tendon ruptures caused by exceptional extrinsic stress. Cases with recorded trauma, for example during sporting accidents, were kept in. We did not exclude patients with previous Achilles or biceps tendinitis as this may precede tendon rupture and thus lies in the causal pathway (2,5,10,11).

Controls
We randomly matched four ATR/BTR-free controls to each case on age (year of birth), sex, GP, calendar time (index date), and number of years of recorded history in the database prior to the index date. We applied the same exclusion criteria to controls as to cases.

Exposure
We defined exposure as ≥ 1 recorded prescription for any oral (see WHO-ATC H02AB) or inhaled (see WHO-ATC R03BA) GC prior to the index date, classified as new use (i.e. ≥ 365 days of GC-free history before the first GC prescription) or prevalent use (existing GC use at the start of the record). We compared new oral GC use to never use, stratified by timing of use (current, recent, or past, i.e. last prescription < 180, 180–364, or ≥ 365 days before the index date, respectively). New current oral GC use was further stratified by time since GC treatment start (< 1 month, 1–3 months, 3–6 months, 6 months–1.5 years, 1.5–5 years, ≥ 5 years) prior to the index date, and sub-stratified by number of recorded prescriptions prior to the index date as proxy for continuity of GC use. In a sub-analysis we assessed time since last prescription within patients with < 6 months treatment duration with ≥ 2 prescriptions recorded. We further sub-stratified the analysis on oral GC use by time since treatment start by gender and age (≥/≤ 65 years).

We classified new current oral GC use according to the presumed underlying indication by capturing previous Read codes of diseases associated with GC use, i.e. asthma or chronic obstructive pulmonary disease (COPD) only, connective tissue disease (CTD) only (rheumatoid arthritis, polymyalgia rheumatica, systemic lupus erythematosus, other CTD), vasculitis only, inflammatory bowel disease (IBD) only, ≥ 2 of these diseases, or none of them). We stratified the two largest subgroups (asthma/ COPD and CTD) by timing and by time since oral GC treatment start, as well as by number of prescriptions. We also stratified new current oral GC use by cumulative GC dose (total mg prednisone equivalents) prior to the index date. We reviewed records of current users of prednisone/prednisolone-only over 2 years prior to the index date and decided for each patient whether prednisone was used continuously or not, taking into account frequency of prescriptions, number of tablets, underlying indication, disease duration, and dosage instructions, where available. Within the selected subset of continuous prednisone-only users we calculated the average daily prednisone dose by dividing the total mg prescribed by the number of oral prednisone-exposed days during this 2-year period.

We compared new users of inhaled GC to never users, stratified by timing (current, recent, past use) and duration of drug use (number of prescriptions) prior to the index date. In a sensitivity analysis we excluded users of inhaled GC with concomitant (< 180 days) oral GC use.

Small sample size precluded analysis of intravenously administered GC which occurs mostly in inpatients. Locally injected GC is contraindicated for Achilles tendinopathies but is used for pain relief in patients with shoulder tendinopathies (26,27). As manual profile review revealed that 70% of patients with a local GC injection within 180 days before BTR diagnosis had a record for pre-existing shoulder disorders, we did not assess this association due to likely protopathic bias.

Statistical analysis
We conducted multivariable conditional logistic regression analyses to evaluate the association between GC exposure and ATR/BTR using SAS 9.4 (SAS Institute, Cary, NC, US). We calculated relative risk estimates as odds ratios (ORs) with 95% confidence intervals (CIs). Based on clinical knowledge (28), we defined a priori the potential confounders for the multivariable model and adjusted all ORs for smoking (non, current, ex, unknown), alcohol consumption (<15 units per week, or unknown), obesity, and for the co-morbidities diabetes mellitus, chronic kidney disease (including hemodialysis), osteoporosis, osteoarthritis, infectious arthritis, and gout. We adjusted for concomitant use (last prescription < 180 days before the index date) of fluoroquinolones, hormone replacement therapy, statins, fibrates, and locally injected no more query fields (29–31). We adjusted all models, except the analysis on GC indications, for systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, and polymyalgia rheumatic. We further adjusted analyses of inhaled GC for concomitant oral GC use.

Diagnostic validity
While ATR is a relatively straightforward diagnosis (7), BTR is more complicated to diagnose as it frequently coexists with other shoulder pathologies. In a sensitivity analysis we identified ATR/BTR patients whose diagnosis was preceded within 180 days by an established diagnostic imaging procedure (ultrasound, magnetic resonance imaging, arthrogram, or X-ray) (2,12,32) or by a consultation with a specialist (5,7). Within this sample we repeated
the analyses stratified by timing and time since treatment start, and stratified by timing of use and by number of prescriptions. We also stratified the study population into ATR versus BTR cases (and their controls), and reassessed use of oral or inhaled GCs in short-term high-dose patients, ORs closely correlated with the time since last prescription, with the highest OR in patients with a prescription within 30 days prior to the index date (< 30 days: OR 3.58 [1.87–6.86]; 30–59 days: OR 2.07 [1.04–4.13]; 60–89 days: OR 1.22 [0.45–3.28]; 90–180 days: OR 1.37 [0.83–2.26].

Odds ratios increased with increasing average daily dose in the subset of current continuous prednisone-only users (311 patients); the OR was 4.05 (95% CI 2.32–7.08) in patients with ≥ 10 mg/day (Table III, Figure 1). On the other hand, ORs plateaued at around 2.0 with cumulative oral GC dose ≥ 1,000 mg prednisone equivalent (2,500–5,000 mg prednisone equivalent, highest OR of 3.37, 95% CI 2.45–4.62) (Table III, Figure 2). Most new current oral GC users had an underlying respiratory disorder only (137 cases, 34.3%, OR 1.87, 95% CI 1.51–2.31), followed by CTD only (103 cases, 25.4%, OR 3.26, 95% CI 2.49–4.26) (Table IV). Most CTD patients had continuous treatment, whereas about half of all respiratory patients had intermittent GC treatment. Risks were similar in the two subgroups. Stratified analyses revealed slightly higher ORs in women than in men. Current long-term GC use was more frequent in patients aged ≥ 65 years, and relative risks were slightly higher (Supplementary Table I, to be found online at http://informahealthcare.com/doi/abs/10.3109/07853890.2015.1074272). We observed similar results for ATR and BTR separately (Supplementary Tables 2 and 3, available online).

Use of inhaled GCs was not associated with an altered risk of ATR or BTR at any level of duration or timing (Table V), nor after excluding patients with concomitant oral GC use (data not displayed). The sensitivity analysis of patients with an ATR/BTR diagnosis preceded by referrals or diagnostic

Table I. Demographics, life-style factors and co-morbidities of ATR and BTR cases and controls separately.

| Controls | Cases ATR | Controls | Cases BTR | Controls BTR |
|----------|-----------|----------|-----------|--------------|
| (n=5027) | (n=20108) | (n=3175) | (n=12700) |
| Male | 3457 | 68.8 | 13828 | 68.8 | NA | NA | 2323 | 73.2 | 9292 | 73.2 | NA | NA |
| Female | 1570 | 31.2 | 6280 | 31.2 | NA | NA | 852 | 26.8 | 3408 | 26.8 | NA | NA |
| Mean age (SD) | 65.1 years (14.7 y) | 65.1 years (14.7 y) | 65.1 years (14.7 y) | 65.1 years (14.7 y) |

Table percentages are rounded to the nearest decimal. Smoke status.

*Female only.

ATR = Achilles tendon rupture; BTR = biceps tendon rupture; CI = confidence interval; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; HRT = hormone replacement therapy; OR = odds ratio; SD = standard deviation.
Table II. Oral GC use stratified by timing of use, time since treatment start, and continuous versus intermittent use.

| Cases (n = 8202) (%) | Controls (n = 32808) (%) | OR crude | 95% CI | OR adjusted a | 95% CI |
|---------------------|-------------------------|----------|--------|---------------|--------|

Continuous oral GC use stratified by timing and duration of GC treatment

No oral GC

Prevalent GC use

New GC use

Current (by time since treatment start)

< 1 month

1–3 months

> 1 prescription

3–6 months

> 2 prescriptions

6 months–1.5 years

1–4 prescriptions

> 4 prescriptions

1.5–5 years

1–12 prescriptions

> 12 prescriptions

≥ 5 years

1–19 prescriptions

> 19 prescriptions

Recent (last prescription 180–364 days)

Past (last prescription ≥ 365 days)

a Adjusted for smoking, obesity, alcohol consumption, diabetes, gout, chronic kidney disease, osteoarthritis, infectious arthritis, osteoporosis, rheumatoid arthritis, lupus, polymyalgia rheumatica, inflammatory bowel disease, vasculitis, concomitant use of fluoroquinolones, hormone replacement therapy, statins, fibrates, and locally injected GC.

CI = confidence interval; GC = glucocorticoids; OR = odds ratio; y = years.

Discussion

This case-control study provides evidence that oral GC therapy increases the risk of tendon rupture in a dose–response relationship, with increasing ORs in patients with high average daily doses. Odds ratios increased shortly after therapy initiation and declined quickly after treatment cessation. One short-term course of high-dose oral GC may be sufficient to transiently increase the risk of tendon rupture. Inhaled GC use was not associated with an altered risk of ATR/BTR.

A previous CPRD study reported a crude OR of 2.6 (95% CI 2.2–3.1) for ever use of oral GCs and ATR (13). Another study using US health plan data reported an adjusted OR of 1.4 (95% CI 1.0–1.8) in patients with current oral GC use (within 6 months) and ATR (5). We observed increased ORs of around 4.0 for cur-

a Adjusted for smoking, obesity, alcohol consumption, diabetes, gout, chronic kidney disease, osteoarthritis, infectious arthritis, osteoporosis, rheumatoid arthritis, lupus, polymyalgia rheumatica, inflammatory bowel disease, vasculitis, concomitant use of fluoroquinolones, hormone replacement therapy, statins, fibrates, and locally injected GC.

CI = confidence interval; GC = glucocorticoids; OR = odds ratio; y = years.

Table III. Current oral GC use stratified by average daily dose (continuous prednisone-only users) and by total cumulative dose (in prednisone equivalents).

| Cases (n = 8202) (%) | Controls (n = 32808) (%) | OR crude | 95% CI | OR adjusted a | 95% CI |
|---------------------|-------------------------|----------|--------|---------------|--------|

Average daily prednisone dose before the index date in current continuous prednisone-only users (Figure 1)

No oral GC

Ocular prednisone-only use

Current continuous use

< 5 mg/d

5–10 mg/d

≥ 10 mg/d

Recent/past use

Not classified as continuous prednisone-only use

Cumulative prednisone dose ever before the index date in incident current GC users (Figure 2)

No oral GC

Prevalent GC use

New GC use

Current use (by total mg)

< 200

200–1,000

1,000–2,500

2,500–5,000

5,000–10,000

≥ 10,000

NA

Recent/past GC use

a Adjusted for smoking, obesity, alcohol consumption, diabetes, gout, chronic kidney disease, osteoarthritis, infectious arthritis, osteoporosis, rheumatoid arthritis, lupus, polymyalgia rheumatica, inflammatory bowel disease, vasculitis, concomitant use of fluoroquinolones, hormone replacement therapy, statins, fibrates, and locally injected GC.

CI = confidence interval; GC = glucocorticoids; OR = odds ratio; y = years.
the risk for tendon rupture, which then declines rapidly after.

Glasheen et al. previously reported an association between cumulative oral GC dose and the risk of ATR among people exposed within 6 months before diagnosis (maximum category ≥ 301 mg prednisone equivalents) (9). In our data set, ORs plateaued at cumulative GC dose ≥ 1,000 mg prednisone equivalents, while ORs linearly increased with increasing average daily dose in the subset of continuous prednisone-only users. While the effect of continuous use was evaluated only in a subset of current prednisone-only users, prednisone is the primary chronic GC therapy and is thus likely representative of all continuous GC use, an evaluation of which was otherwise not practical. Most short-term intermittent oral GC users (< 6-month treatment duration, ≤ 2 prescriptions) likely received daily GC doses of ≥ 20 mg (mostly for acute respiratory conditions), and time since last prescription was strongly associated with the risk of ATR/BTR (highest OR of 3.7 in patients with a prescription < 30 days). Thus, a single cycle of high-dose GC therapy (≥ 20 mg/d) may be sufficient may be sufficient the risk for tendon rupture, which then declines rapidly after treatment cessation. This may explain the lower ORs in current intermittent oral GC users; although current users had a recorded prescription within 180 days before the index date, intermittent users likely have a time-lag between the last ingested dose and the index date. Our results are consistent with a previously suggested risk for Achilles tendinopathies in association with high-dose oral GC use (median daily dose ≥ 80 mg prednisone) in analyses of pharmacovigilance data and case reports (14).

Vasculitis, CTD, and IBD have been independently associated with tendon rupture (13,19,33). We observed increased ORs across all strata of indication including approximately 3-fold increased ORs in continuous oral GC users with asthma/COPD only, which to our knowledge has not been independently associated with tendon rupture (we found a null result in users of inhaled GC). The somewhat higher ORs in the CTD subgroup may be due to inflammatory activity, but differences in average daily GC doses may also play a role.

Our results may be explained by mechanisms recently described by Muto et al. who reported apoptotic tendinocytes, increased MMP-3 activity, and impaired biomechanical properties of rats’ Achilles tendons within 1 week after local GC injection, an effect that resolved within 3 weeks (20). A similar risk pattern has been shown for GC-induced fractures, which increased rapidly after oral GC treatment initiation and declined shortly after treatment cessation (21,34,35). Similar to our results, high daily dose was presumed to be a strong risk factor for GC-induced fractures, an effect which is likely due to an interaction with increasing therapy duration/cumulative dose, and a higher risk in continuous GC users (35–37).

Previous studies have shown a preponderance of males among ATR patients, although women were more likely to have pre-existing predisposing factors when an acute ATR occurred (3,4,8). In concordance, within our predominantly male study population, 8.2% of female cases and only 3.8% of male cases were currently exposed to oral GC (slightly higher ORs in women than in men). We found a decreased OR for ATR/BTR in smokers, which has been reported in a previous observational study and which may be explained by the presumption that smokers engage less in sports activity (10). Sports and leisure activities are not captured in the CPRD, but we adjusted our analyses for smoking, alcohol consumption, and obesity, all proxies for a patient’s lifestyle.

We did not observe an increased risk for ATR/BTR across all strata of timing and duration of inhaled GC use in our data set, which is consistent with the only previous multivariable analysis on ATR in association with inhaled GC (5).

The sensitivity analysis restricted to ATR/BTR cases with a previously recorded diagnostic imaging work-up or a referral/discharge to/from a specialist, i.e. cases with little risk for misclassification, yielded virtually the same results for patients with exposure to oral or inhaled GC. Furthermore, the fact that results were similar within separate analyses on ATR and BTR patients suggests a GC effect irrespective of the tendon rupture site.

This observational case-control study is based on a large and extensively validated primary-care database, but several limitations nevertheless have to be considered. First, our study population may include some ATR/BTR events caused by extreme extrinsic stress. However, such outcome misclassification would dilute our result toward the null rather than producing spuriously high associations. Second, we cannot rule out the possibility that some patients had ATR/BTR before database entry, which in theory may have affected the likelihood of getting GC therapy later on. Third, the CPRD neither routinely captures sports activities nor does it completely capture conditions such as misalignment.
of extremities, discrepancies in limb length, muscular insufficiency, or inappropriate footwear, unless they were clearly diagnosed and recorded; thus, we could not control for such factors in the analyses on ATR (10). Finally, we cannot rule out residual confounding and chance, since we could not control for ethnic background, socio-economic status, profession, or nutrition, as these parameters are not routinely recorded in the CPRD. Despite these limitations, this is, to our knowledge, the first in-depth analysis of the association between GC use and tendon rupture in a large observational study.

In summary, our findings suggest that oral, but not inhaled, GC therapy increases the risk of tendon rupture, an effect that starts shortly after treatment initiation and declines shortly after treatment cessation. One single course of high-dose GC therapy (daily doses >20 mg/day) may be sufficient to increase the risk of tendon rupture. This association is closely similar to one reported for GC-induced fractures. A transient effect of GC use on tendons through apoptosis and increasing MMP-3 activity may support the etiologic plausibility of our findings (20).

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Table IV. Current oral GC use stratified by indication, timing, duration, and continuity of GC treatment.

| Oral GC stratified by indication (asthma/COPD and connective tissue diseases sub-stratified by continuity and duration of use) | Cases (n = 8202) (%) | Controls (n = 32808) (%) | OR crude | 95% CI | OR adjusted | 95% CI |
|---|---|---|---|---|---|---|
| No oral GC use | 6857 | 83.6 | 28976 | 88.3 | 1.00 | (ref.) | 1.00 | (ref.) |
| Prevental GC use | 217 | 2.7 | 572 | 1.7 | 1.64 | (1.40–1.92) | 1.49 | (1.27–1.76) |
| New current GC use | | | | | | | |
| Connective tissue disease | | | | | | | |
| 0–3 months | 103 | 1.3 | 133 | 0.4 | 3.51 | (2.69–4.57) | 3.26 | (2.49–4.26) |
| 3 months–1.5 years | 10 | 0.1 | 8 | 0.0 | 5.38 | (2.12–13.67) | 5.31 | (2.05–13.74) |
| ≥4 prescriptions | b | b | b | b | 1.42 | (0.15–16.65) | 1.78 | (0.19–17.13) |
| >4 prescriptions | 39 | 0.5 | 27 | 0.1 | 6.33 | (3.87–10.36) | 6.27 | (3.81–10.32) |
| ≥1.5 years | 53 | 0.7 | 95 | 0.3 | 2.56 | (1.82–3.61) | 2.27 | (1.60–3.23) |
| ≥6 prescriptions | 0 | 0.0 | 0 | 0.0 | NA | (NA) | NA | (NA) |
| Asthma/COPD | 137 | 1.7 | 303 | 0.9 | 1.99 | (1.62–2.45) | 1.87 | (1.51–2.31) |
| 0–3 months | 16 | 0.2 | 22 | 0.1 | 3.17 | (1.66–6.05) | 2.92 | (1.51–5.65) |
| 3 months–1.5 years | 23 | 0.3 | 52 | 0.2 | 1.97 | (1.20–3.23) | 1.77 | (1.40–2.30) |
| ≥4 prescriptions | 17 | 0.2 | 44 | 0.1 | 1.71 | (0.97–3.01) | 1.54 | (0.86–2.73) |
| >4 prescriptions | 6 | 0.1 | 8 | 0.0 | 3.42 | (1.18–9.90) | 3.17 | (1.04–9.72) |
| ≥1.5 years | 98 | 1.2 | 229 | 0.7 | 1.89 | (1.49–2.40) | 1.80 | (1.40–2.30) |
| ≥6 prescriptions | 33 | 0.4 | 93 | 0.3 | 1.56 | (1.04–2.32) | 1.40 | (0.93–2.10) |
| Vasculitis | 20 | 0.2 | 13 | 0.0 | 6.88 | (3.41–13.85) | 7.05 | (3.41–14.59) |
| IBD | 11 | 0.1 | 16 | 0.1 | 3.01 | (1.39–6.51) | 2.93 | (1.34–6.38) |
| >1 of the above | 63 | 0.8 | 93 | 0.3 | 3.09 | (2.23–4.28) | 2.85 | (2.05–3.98) |
| Other | 71 | 0.9 | 176 | 0.5 | 1.77 | (1.34–2.34) | 1.60 | (1.20–2.12) |
| Recent or past GC use | 723 | 8.8 | 2526 | 7.7 | 1.25 | (1.14–1.37) | 1.18 | (1.08–1.29) |

Table V. Use of inhaled GC stratified by timing of use and by number of prescriptions.

| Cases (n = 8202) (%) | Controls (n = 32808) (%) | OR crude | 95% CI | OR adjusted | 95% CI |
|---|---|---|---|---|---|
| No inhaled GC use | 6989 | 85.2 | 28945 | 88.2 | 1.00 | (ref.) | 1.00 | (ref.) |
| Prevental GC use | 428 | 5.2 | 1183 | 3.6 | 1.51 | (1.35–1.70) | 1.30 | (1.15–1.47) |
| New GC use | | | | | | | |
| Timing and duration | | | | | | | |
| Current use ≤9 prescriptions | 101 | 1.2 | 324 | 1.0 | 1.30 | (1.04–1.63) | 1.14 | (0.90–1.44) |
| Current use 10–39 prescriptions | 129 | 1.6 | 409 | 1.3 | 1.31 | (1.08–1.61) | 1.17 | (0.95–1.44) |
| Current use ≥40 prescriptions | 55 | 0.7 | 190 | 0.6 | 1.22 | (0.90–1.65) | 1.03 | (0.75–1.41) |
| Past use | 500 | 6.1 | 1757 | 5.4 | 1.19 | (1.07–1.32) | 1.07 | (0.96–1.19) |

aAdjusted for smoking, obesity, alcohol consumption, diabetes, gout, chronic kidney disease, osteoarthritis, infectious arthritis, osteoporosis, concomitant use of fluoroquinolones, hormone replacement therapy, statins, fibrates, and locally injected GC.

bDue to ethics regulations to preserve confidentiality, we are not allowed to display cells with a count of <5 patients.

CI = confidence interval; COPD = chronic obstructive pulmonary disease; GC = glucocorticoids; IBD = inflammatory bowel disease; OR = odds ratio.
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Supplementary material available online
Supplementary Table I–IV, to be found online at http://informahealthcare.com/doi/abs/10.3109/07853890.2015.1074272.