Quality assurance study of the use of preventative therapies in glucocorticoid-induced osteoporosis in early inflammatory arthritis: results from the CATCH cohort

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Abstract

Objective. To characterize steroid use and compliance with glucocorticoid-induced osteoporosis (GIOP) guidelines within a large early inflammatory arthritis cohort.

Methods. Using the Canadian Early Arthritis Cohort (CATCH) database, patients with inflammatory arthritis on glucocorticoids (oral, IA and i.m.) were identified. Consecutive steroid exposure was defined as using glucocorticoids for two consecutive clinic visits (at least 90 days apart). The primary outcome was the proportion of patients receiving calcium, vitamin D and a bisphosphonate among patients treated with consecutive oral glucocorticoids.

Results. Six hundred and fifty-five patients were in the CATCH database, where 273 patients were identified as glucocorticoid users, of whom 48% were on oral prednisone, 38% received i.m. or IA and 13% both. The median oral daily dose of prednisone was 5 mg (interquartile range 2.5–150 mg). Consecutive users (CUs, n = 78) compared with non-consecutive users (NUs, n = 532) showed that CUs were older (56 vs 50 years, P = 0.001); females were fewer (63% vs 74%, P = 0.04), but a similar proportion were RF positive (51% in CU vs 56% in NU, P = 0.73). For the primary outcome, rates of prophylaxis for users of consecutive oral steroids were as follows: 53% were treated with calcium, 47% with vitamin D and 25% were on a bisphosphonate. For users of oral prednisone at doses ≥ 7.5 mg/day, rates of prophylaxis were as follows: 64% were treated with calcium, 57% with vitamin D and 21% were on a bisphosphonate.

Conclusion. Glucocorticoid therapy is frequently used in early inflammatory arthritis. The use of calcium, vitamin D or a bisphosphonate was low among chronic glucocorticoid users and illustrates the need for more diligence in patients receiving glucocorticoids to prevent GIOP.

Key words: early rheumatoid arthritis, early inflammatory arthritis.
Introduction

Glucocorticoids are commonly used in inflammatory conditions such as RA and inflammatory arthritis that has not yet been diagnosed. In chronic use of glucocorticoids, physicians warn patients of the broad array of side effects, the most serious being osteoporosis (OP), fractures and avascular necrosis of bone. Glucocorticoids have effects on bone resorption through hormonal, signalling and bone matrix regulations that ultimately lead to decreases in bone turnover [1]. Steroids are known to cause decreases in osteoblast number and alterations in osteoblast function through inhibition of collagen synthesis, leading to an extracellular matrix devoid of the necessary ingredients for mineralization of bone, less calcium absorption and more renal calcium excretion [1–3]. Evidence shows that glucocorticoids reduce the expression of growth factors, including insulin-like growth factors (IGFs) and TGF-β [4]. Glucocorticoid use preferentially affects trabecular bone (thus the spine is affected more than the hip) and fractures occur at generally better BMDs than in those with senile or post-menopausal OP as the architecture is more affected [5–8].

Bone loss from glucocorticoids is known to occur early on and can occur with relatively small doses. In a retrospective cohort study, the relative risks of vertebral fracture were 1.55 (1.20–2.01) at daily doses <2.5 mg of prednisolone, 2.59 (2.16–3.10) for doses 2.5–7.5 mg and 5.18 (4.25–6.31) for doses ≥7.5 mg [9]. Systemic therapy poses the highest risk for decline in bone mass; however, even inhaled glucocorticoids have been shown to be associated with bone loss at the hip [10].

The ACR has published guidelines for the prevention and treatment of glucocorticoid-induced osteoporosis (GIOP). The pharmacological recommendations are to initiate calcium and vitamin D supplementation (plain form at 800–1000IU/day or to achieve therapeutic levels of 25-hydroxyvitamin D) in all patients and to initiate a bisphosphonate in all men and post-menopausal women when long-term (duration of ≥3 months) glucocorticoid treatment at ≥7.5 mg is being started in low- and medium-risk patients, and at lower doses (<5 mg/day for ≤1 month) in high-risk patients [11]. The effectiveness of calcium and vitamin D supplementation has been shown in randomized clinical trials (RCTs) to not only maintain bone mass but also prevent further bone loss [12, 13].

In a meta-analysis, a total of 274 patients taking systemic glucocorticoids being supplemented with calcium and vitamin D had significantly less bone loss than the controls at the lumbar spine [weighted mean difference (WMD) = 2.6, 95% CI 0.7, 4.5] and the radius (WMD = 2.5, 95% CI 0.6, 4.4), but results were not significant for the cortical site, the femur (WMD = 0.4, 95% CI −1.1, 1.8) [14]. Bisphosphonates inhibit bone resorption and RCTs have shown they increase BMD [13, 15, 16] and should be used to prevent and treat GIOP [16].

Despite the recommendations, the actual practice patterns are worrisome [17–22]. In a Canadian survey of rheumatologists on the management of GIOP, 53% stated their initial strategy included calcium and vitamin D in pre-menopausal women, whereas in post-menopausal women calcium and HRT were prescribed (29%) [23]. We wanted to further understand adherence to practice guidelines and evaluate the use of preventive therapies in patients taking oral, i.m. or IA glucocorticoids, as guidelines currently exist only for the patients taking oral glucocorticoids. This study characterizes glucocorticoid use and evaluates use of preventative therapies for GIOP within a large early inflammatory arthritis cohort.

Methods

Study design

The Canadian Early Arthritis Cohort (CATCH) database was used to identify the study population from November 2006 until April 2009. CATCH is a prospective, multicentre, cohort of adults with new onset inflammatory arthritis symptoms within Canada. Inclusion criteria were age >16 years, between 6 weeks and 12 months of persistent synovitis, and ≥2 swollen joints or 1 swollen MCP orPIP joint with ≥1 of the following: positive RF, positive anti-CCP, morning stiffness for >45 min, response to NSAIDs or painful MTP squeeze test. Patients were evaluated according to a standard protocol that included a baseline assessment and follow-up in every 3 months. Patients with a history of OP were excluded because they may have had prescribed preventative therapies but were not necessarily using them to prevent GIOP.

Patients with inflammatory arthritis receiving glucocorticoids (oral, i.m. or IA) were identified by analysing the physician and patient medication records within the database. If there was an inconsistency, the physician medication record was used for the purposes of identifying consecutive steroid users. We then subdivided patients as to whether they were users of oral or i.m. and IA glucocorticoid. A consecutive user (CU) was defined as using glucocorticoids (oral, i.m. and IA) for two consecutive clinic visits (at least 3 months apart) at any time from their baseline visit up to their month 12 visit. Hence CUs were on steroids for a minimum of 3 months and a maximum of 12 months. Non-consecutive users (NUs) were defined as never exposed to glucocorticoid or occasional exposure (history of one time treatment with steroids). Fig. 1 outlines how patients were identified and subdivided from the database.

For the purposes of describing the population and primary outcome, we subdivided the consecutive glucocorticoid users into oral, i.m. or IA users of steroid. We wanted to identify consecutive oral users of steroids and compare them with users of IA/i.m. steroid, as the ACR guidelines for prophylaxis of GIOP have been made for oral glucocorticoids only. There were three patients who were CUs of both oral and IA/i.m. forms of steroid; because these patients did not fall into either category (oral or IA/i.m.) they were not included in the analysis of demographic information of the subdivided categories. They were, however, included in all other analyses for CUs of glucocorticoids. The average prednisone dose was calculated from the dosage of prednisone at the
second consecutive visit among consecutive steroid users. OP medications, including the use of calcium, vitamin D and a bisphosphonate, were identified anytime during the follow-up period for patients who were on glucocorticoid. We collected demographic information, including age, gender, BMI and, if a diagnosis of RA was confirmed, autoimmune laboratory markers and symptom duration. Positivity rates for RF and anti-CCP antibodies were determined using cut-off values specific to each site. We also collected DASs, including component scores for CRP, global health, total and subjective joint counts.

Outcome measures

The primary outcome, the proportion of patients being treated with calcium, vitamin D and/or a bisphosphonate, was determined for consecutive oral steroid users (all users and users of prednisone at doses ≥ 7.5 mg/day). We also determined the use of preventative therapy for CUs of i.m./IA steroids. Alendronate, etidronate, risedronate and pamidronate were included as bisphosphonate medications. Zoledronate was excluded because it would only need to be given once over a year and may not have been included on the medication profiles. Secondary analysis was done to determine which factors were associated with the use of preventative therapies.

Statistical analysis

Standard descriptive statistics were used to characterize the population using SPSS software (version 19.0). Frequency distributions [means, s.d.s, medians and interquartile (IQR) ranges] were used to describe the demographic characteristics of the CU and NU within the population for normally and non-normally distributed variables. The t-tests were used to compare the means for differences between the CUs and NUs when the data were normally distributed, and Mann–Whitney U-test when the data were not normally distributed.

Odds ratios (ORs), with 95% CIs, were calculated to compare which factors were associated with being more likely to be treated with preventative therapies for all consecutive steroid users and users of oral steroids. All statistical tests were two-tailed and considered statistically significant at $P < 0.05$. 

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**FIG. 1** Flow diagram of how patients within the CATCH were subdivided.

![Flow diagram](https://academic.oup.com/rheumatology/article-abstract/51/9/1662/1791223)
This project received ethics approval by the University of Western Ontario Ethics Review Board. All enrolled patient sites had ethics approval for the CATCH database and all patients had consented.

Results

The CATCH database (from November 2006 to April 2009) had 655 patients, where 273 patients with inflammatory arthritis were identified as glucocorticoid users. Forty-eight per cent were on oral prednisone, 38% received i.m. or IA steroids and 13% received both. Forty-five patients with a history of OP were excluded. Seventy-eight patients were identified as CUs, where 57 were CUs of oral steroid and 18 of IA/i.m. steroid, three patients were users of both forms of steroid at different times. Fourteen patients of the 57 CUs were on doses 7.5 mg at both of their consecutive visits, whereas 43 patients had low dose (<7.5 mg) on at least one of their visits. The median oral daily dose of prednisone was 5.0 mg (IQR 2.5–8.9) and 80 mg (IQR 40–80), respectively. Among the CUs, the mean age was 56 years (s.d. = 16 years) and the majority was women (63% female). Mean age was significantly higher among the CUs compared with the NUs (56 years, s.d. = 16 vs 50 years, s.d. = 15, P = 0.001). BMI was slightly lower among CUs, although not statistically significant (BMI in CUs = 26.5, s.d. = 5.0 vs BMI in NUs = 27.4, s.d. = 6.8, P = 0.37). There were significantly more females in the NUs vs CUs (74 vs 63%, P = 0.04). Sixty-three per cent of CUs had a confirmed diagnosis of RA, which was similar to NUs (63 vs 57%, P = 0.3). The DAS CRP was similar among CUs [4.7 (s.d. = 1.4)] and NUs [4.9 (s.d. = 1.6), P = 0.38]. Table 1 displays the demographic characteristics of CUs and NUs.

Among the consecutive oral glucocorticoid users, 53% were treated with calcium, 47% with vitamin D and 25% were taking a bisphosphonate. Treatment rates were slightly higher for the use of calcium and vitamin D, but similar for the use of a bisphosphonate among patients on doses of prednisone > 7.5 mg, which is shown in Fig. 2. The rates of prophylaxis were slightly lower for IA/i.m. users of glucocorticoid; 28% were taking calcium, 28% were on vitamin D and none was on a bisphosphonate (Fig. 3). Compared with CUs of the IA/i.m. form of steroid, users of oral glucocorticoids have 2.96 times the odds of being given preventative therapy with calcium, vitamin D or a bisphosphonate (34/57 vs 6/18, OR 2.96, P = 0.056).

Table 2 describes factors associated with the prescription of preventative therapies. Males were somewhat less likely to be treated with preventative therapies compared with females, and this did reach significance among CUs of all forms of steroid, but not in the oral group. Post-menopausal females were somewhat more likely to be treated compared with pre-menopausal women; however, this was not statistically significant (OR 3.00, 95% CI 0.78, 11.54). Patients aged 50 or older were also somewhat more likely to be treated than younger patients among the group as a whole (OR 1.27, 95% CI 0.50, 3.22), but not in the oral group (OR 1.04, 95% CI 0.35, 3.08). The proportion treated with preventative therapies was highest among patients between the ages of 50 and 70 (59%), and similar among patients younger than 50 (50%) and those 70 or older (50%).

Patients with a history of fracture were less likely to be treated; however, history of fracture was not specific for...
an osteoporotic fracture and included a history of lifetime fracture among patients. Smokers and former smokers were also less likely to be treated, but the result was not significant (Table 2). The results showed only small differences when the analysis was repeated for CUs of oral glucocorticoids (Table 3). Age was less of a factor, as the OR was 1.04 (95% CI 0.35, 3.08) in consecutive oral users compared with all CUs of steroids, and use of hormonal treatment is slightly different between all CUs and consecutive oral users (OR 1.15 vs 0.97); however, because the CIs include 1, these results are not considered significant.

Disease activity was the same between patients who received prophylaxis and those who did not [DAS (CRP) = 4.7, s.d. = 1.2 vs 4.7, s.d. = 1.5, P = 0.26]. There was a significant difference in the median starting dose of oral prednisone between patients who received prophylaxis and those who did not [10 mg (IQR 10.0–15.0 mg) vs 10 mg (IQR 5.0–10.0 mg), P = 0.03], as measured by the Mann-Whitney U-test. However, at the second consecutive visit, the median doses of oral prednisone were not significantly different between those who received prophylaxis and those who did not [5.0 mg (IQR 2.5–10.0) vs 5.0 mg (IQR 2.5–7.5 mg), P = 0.43].

Discussion

Our results indicate that the use of calcium, vitamin D and bisphosphonates was suboptimal among users of consecutive steroids in patients with early inflammatory arthritis, which is highlighted in other populations [17, 18, 20, 24] and clinical settings [19, 21, 22, 25]. Results from a Latin American study involving patients receiving both oral and i.m. steroids found that 55% received calcium and vitamin D and only 6.3% received a bisphosphonate [19]. This study is similar to ours in that it included patients treated with both oral and i.m. steroids. We wanted to capture all potential patients that required repeat glucocorticoid treatment for their inflammatory arthritis. There is some evidence that different forms of steroids, including i.m., have effects on bone turnover and metabolism [10, 26, 27], although the data are conflicting [28]. In a study of 13 patients suffering from multiple sclerosis receiving i.v. methylprednisolone at 15 mg/kg daily for 10 days, bone turnover markers (alkaline phosphatase) had normalized by day 10 and others (carboxy-terminal telopeptide of type I collagen and urinary calcium/creatinine ratio) showed a decrement in their initial fall by day 10. Bone density also showed no change after 6 months of therapy [28]. The conflicting data on the different forms of glucocorticoid and the effects on BMD may be one of the reasons the ACR does not address the use of multiple injections of CS, despite the use of IA injections by rheumatologists. In an academic rheumatology practice, Solomon et al. [17] studied the rates of prescription medication use >2 years among 236 glucocorticoid users and found that 29% received treatment, excluding HRT. Rates for bisphosphonate therapy were 19% for alendronate and 2% for etidronate. Our study showed comparable results and found a treatment rate of 25% for bisphosphonates, including alendronate, etidronate, risedronate and pamidronate. We did find a slightly higher rate of prophylaxis for calcium and vitamin D among patients on doses of steroid >7.5 mg/day compared with all oral steroid users, but a similar percentage of patients were given a bisphosphonate in both groups. This may suggest that clinicians are to some degree better at following the ACR guidelines for therapies known to prevent further bone loss, but a care gap still exists for the use of a prescribed medication, such as a bisphosphonate.

In our secondary analysis, males and pre-menopausal women were less likely to be treated, although our results were not statistically significant for pre-menopausal women. These groups seem to be under-recognized to be
at risk for OP, as previous reports have found similar results. In a large, retrospective cohort study by Feldstein et al. [18], which identified patients taking >5 mg/day of prednisone for at least 90 days, antiresorptive treatment was prescribed more frequently for women (18.3%) compared with men (8.9%). It has been shown that patient’s sex is a significant predictor variable for receiving treatment [22, 25]. Cruse et al. [20] evaluated a cohort of men \( n = 370 \) taking oral prednisone for a variety of conditions, the most common diagnoses being chronic obstructive pulmonary disease and RA, and reported that 24% were treated with a bisphosphonate, 51% were given calcium and 44% were given vitamin D. Among the patients who did not have a bone BMD test, only 8% were taking a bisphosphonate, indicating that empiric, preventative treatment is lower. One hypothesis for the lower rate of treatment for males is the higher peak bone mass in men, which provides them with later onset of fragility fractures compared with women. However, one would argue that because glucocorticoids are known to affect bone quality (e.g. trabecular connectivity in bone) as well as BMD [6], clinicians should be treating and preventing GIOP with the same emphasis in men and women. Pre-menopausal women on glucocorticoids have an increased relative risk of fracture compared with non-glucocorticoids users, but they do represent a unique population because of the risk that bisphosphonates pose in childbearing years. The ACR recommends caution when prescribing bisphosphonates because they may cross the placenta and affect the developing fetus [11]; however, this does not preclude the use of calcium and vitamin D, as pre-menopausal women are still at risk for GIOP [29], even with adequate estrogen stores. In our study, the rate of prophylaxis among pre-menopausal women was 31%, compared with 69% among post-menopausal women. The use of bisphosphonates in pre-menopausal women should be individualized; an investigation for BMD as well as a discussion of plans for pregnancy is recommended for the management of GIOP in this patient population.

In our study, the median daily dose of prednisone was lower compared with previous studies [17, 18, 24, 25, 30]. Differences in the method of how mean glucocorticoid was computed may account for these differences. In the study by Yood et al. [25], the mean prednisone dose was based on the cumulative dose and the time period over which the glucocorticoid was prescribed, whereas this study recorded the daily dose of prednisone from their second consecutive visit and patients may have been tapering down the steroid from their initial clinic visit. We also found that the baseline prednisone dose was significantly different in those patients who got prophylaxis compared with those who did not. There was a higher proportion of patients on prophylaxis with calcium and vitamin D among patients on steroid doses \( \geq 7.5 \text{ mg/day} \), but a similar proportion of patients were given a bisphosphonate among all consecutive oral users and those just on doses \( \geq 7.5 \text{ mg/day} \). However, we did not investigate higher dosage categories for the use of preventative therapies. Previous studies have investigated glucocorticoid dosage and rates of treatment and found that dosage is not a significant predictor variable [25], and higher doses of steroid do not mean more likelihood of receiving prophylaxis [17].

Our study must include a review of its limitations. First, this was a retrospective review of a database and thus was dependent on recorded lists of medications according to the patient and physician. Physicians and patients may not consider calcium and vitamin D as medications,

![Fig. 3](https://www.rheumatology.oxfordjournals.org)

**Fig. 3** The use of calcium, vitamin D and bisphosphonates among CUs of IA/i.m. forms of steroid.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Receipt of calcium, vitamin D or a bisphosphonate</th>
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<tbody>
<tr>
<td></td>
<td>OR</td>
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<tr>
<td>Female gender (reference: male)</td>
<td>2.82</td>
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<tr>
<td>Post-menopausal (reference: pre-menopausal)</td>
<td>3.00</td>
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<tr>
<td>Hormonal treatment (reference: no use of hormones)</td>
<td>0.97</td>
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<tr>
<td>History of fracture (reference: no fracture)</td>
<td>0.39</td>
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<tr>
<td>Age ( &gt; 50 \text{ years} ) (reference: age ( &lt; 50 \text{ years} ))</td>
<td>1.27</td>
</tr>
<tr>
<td>Smoker or ex-smoker (reference: never)</td>
<td>0.51</td>
</tr>
</tbody>
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**Table 2** ORs for factors associated with the use of preventative therapies among all consecutive steroid users
thus their medication records may not be reliable. Medication reconciliation performed by a pharmacist may be a more accurate method to document patients' medications in future studies. Furthermore, we did not account for patients' co-morbidities, and this may explain the lower rate of preventative therapy, as patients with polypharmacy may be less likely to take preventative therapy. Secondly, we calculated the median daily dose of prednisone from the second consecutive visit, and this may not be the most accurate method to do so. Other studies have used different methods than ours to calculate mean daily dose of prednisone [18, 24, 25]. In addition, we included patients on all doses on oral or IA/i.m. glucocorticoid and this may not accurately reflect the patients needing prophylaxis. Regardless of the prednisone dose, the Osteoporosis Society of Canada recommends that even patients on low-dose prednisone should be assessed for risk of OP and have BMD measured [31]. Also, we excluded zoledronic acid from our study and we were not able to determine how often it was used; thus we may have miscategorized patients as not receiving prophylaxis when they actually were. It is important to recognize the small sample sizes when interpreting our results. Some of the subgroups, for example, pre- and post-menopausal women, are based on sample sizes of <50 patients, and it is important to take into consideration that most of the CIs include 1, thus those results are not statistically significant. Lastly, this study did not address the use of BMD testing, as this was not available on all patients. This is an important component of the management of GIOP and future studies should also include this in their methodology.

This study’s strengths are a large population of patients with early inflammatory arthritis and real-world clinical outcomes. We addressed the use of both oral and parenteral steroids and found a lower proportion of patients were using consecutive IA/i.m. forms of steroid. It remains to be determined if prophylaxis is warranted in patients receiving repeated i.m. or IA injections of steroid. Future research involving the effect of steroid injection on bone mass and/or fracture risk is needed to make recommendations for adequate prophylaxis therapy. In conclusion, data from this study illustrate a care gap in the management of GIOP.

**Rheumatology key messages**

- In chronic glucocorticoid users, calcium, vitamin D and bisphosphonate use was low.
- Calcium, vitamin D and bisphosphonates must be used diligently in patients to prevent GIOP.

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### References


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| Table 3 | ORs for factors associated with the use of preventative therapies among consecutive oral glucocorticoid users |
|---|---|---|---|
| Characteristic | Receipt of calcium, vitamin D or a bisphosphonate | OR | 95% CI | P-value |
| Female gender (reference: male) | 2.62 | 0.87, 7.88 | 0.09 |
| Post-menopausal (reference: pre-menopausal) | 2.50 | 0.46, 13.52 | 0.29 |
| Hormonal treatment (reference: no use of hormones) | 1.15 | 0.26, 5.22 | 0.85 |
| History of fracture (reference: no fracture) | 0.42 | 0.06, 2.72 | 0.36 |
| Age >50 years (reference: age <50 years) | 1.04 | 0.35, 3.08 | 0.95 |
| Smoker or ex-smoker (reference: never) | 0.44 | 0.14, 1.33 | 0.15 |
et al 16 Yamada S, Takagi H, Tsuchiya H