Incident Comorbidity Among Patients with Rheumatoid Arthritis Treated or Not with Low-dose Glucocorticoids: A Retrospective Study

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ABSTRACT. ***Objective.*** To assess the prevalence of comorbidity in a cohort of patients with rheumatoid arthritis (RA), treated or not with low-dose glucocorticoids (GC) and who have been followed for at least 10 years.

Methods. This was a retrospective study by review of medical records.

Results. We identified 365 patients: 297 (81.3%) were GC users (4–6 mg methylprednisolone daily) and 68 (18.7%) were nonusers. We found that fragility fractures occurred in 18.2% of GC users and in 6.0% of GC nonusers ($p < 0.02$); arterial hypertension in 32.3% of GC users and in 10.4% of GC nonusers ($p < 0.0005$); acute myocardial infarction in 13.1% of GC users and in 1.5% of the nonusers ($p < 0.01$). Prevalence of diabetes mellitus, cataract, and infections was comparable. We divided GC users into groups of different duration of GC therapy: < 2, 2–5, and > 5 years; the mean duration of GC treatment was 1.3 ± 0.5, 3.6 ± 1.1, and 12.1 ± 5.1 years, respectively. GC treatment for > 5 years was associated with significantly higher prevalence of fragility fractures (26.6%; $p < 0.001$ vs the other groups), arterial hypertension (36.7%; $p < 0.0002$ vs nonusers and GC users < 2 years), myocardial infarction (16.1%; $p < 0.01$ vs nonusers), and infections (9.7%; $p < 0.005$ vs the other groups). GC treatment for 2–5 years was associated with a significantly higher prevalence of arterial hypertension (30.0%; $p < 0.01$) compared to nonusers.

Conclusion. Patients with RA treated with low-dose GC compared to patients never treated with GC show a higher prevalence of fractures, arterial hypertension, myocardial infarction, and serious infections, especially after 5 years of GC treatment. The high prevalence of myocardial infarction and fractures in patients with RA suggests that a more accurate identification of risk factors and prevention measures should be adopted when longterm GC treatment is needed. (J Rheumatol First Release Sept 15 2010; doi:10.3899/jrheum.100461)

Key Indexing Terms:
COMORBIDITY RHEUMATOID ARTHRITIS GLUCOCORTICOIDS DRUG TOXICITY

Glucocorticoids (GC) are often used in addition to disease-modifying antirheumatic drugs (DMARD) in the treatment of rheumatoid arthritis (RA), but even 50 years after their introduction there is still debate about their value. While high doses are associated with well known adverse effects, in low doses (≤ 10 mg prednisone), adverse effects may be outweighed by the significant benefits of rapid symptomatic relief, suppression of disease activity, and even slowing of radiological damage. A systematic review to assess the efficacy of GC in inhibiting radiological progression in adults with RA[1] showed that the patients treated with constant low-dose GC had substantially less joint damage at radiological followup at 1 and 2 years. This has renewed the debate on the risk/benefit ratio of low-dose GC treatment. Safety data from randomized controlled clinical trials of low-dose GC treatment for 2 years in RA[2,3,4,5,6] suggested that GC-induced adverse effects were modest and often not statistically different from those of placebo. However, these trials may be too small and too short to detect adverse outcomes that may occur late in the course of GC use. GC cause several adverse effects including osteoporosis, fractures, hypertension, diabetes mellitus, cataracts, infection, gastrointestinal ulceration, and cardiovascular disease, including myocardial infarction (MI) and stroke[7,8,9,10]. The prevalence of these effects is expected to increase significantly with time of GC exposure.

Since the 1970s at our Rheumatology Unit, 6-methylprednisolone (6-MP) has been the first-choice GC in patients with RA to improve symptoms and reduce disease activity. This drug shows a duration of biological effect (about 24 h) and plasma half-life (< 2 h) that make it appro-

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priate for longterm therapy[11]. To limit the suppression of the hypothalamic-pituitary-adrenocortical (HPA) axis, usually only small doses of 6-MP (i.e., not exceeding 6 mg/day) are given, once daily in the morning. As a consequence, after > 30 years a large number of patients have been treated chronically with 6-MP at daily doses ranging from 4 to 6 mg. Thus it is now possible to assess in this population the association between longterm GC use and some clinical events possibly related to chronic exposure to GC. Our aim was to assess retrospectively the prevalence of comorbidity known to be the possible consequence of GC therapy in a cohort of patients with RA, some treated and some not treated with low-dose GC, who have been followed for at least 10 years at our institution.

MATERIALS AND METHODS

We carried out an analysis by review of the medical documentation of all the patients with a diagnosis of RA at the end of 2007. We selected only patients who had been followed continuously for at least 10 years in our institution, and we divided them into 2 groups: GC users, who had been taking GC continuously for at least 6 months; and GC nonusers, who had never taken GC over the entire period of followup. Patients who had been taking GC for < 6 months over 10 years were excluded from the analysis, as were those treated with GC other than 6-MP. For each patient, we calculated the cumulative duration of GC therapy, cumulative dose of GC, and mean daily GC dose. GC users were further divided into subgroups based on the cumulative duration of GC therapy: < 2 years, 2 to 5 years, and > 5 years.

We collected demographic and clinical data, including duration of disease at the time of the study, positive test for rheumatoid factor (RF) and anticitrullinated peptide, presence of erosive disease, use of nonsteroidal antiinflammatory drugs (NSAID) or cyclooxygenase (COX)-2 inhibitors, and use of DMARD. A patient was categorized as an NSAID user if he or she had been using NSAID for at least half the entire followup period. Given the frequent switch from NSAID to COX-2 inhibitors and vice versa, and the varying prevalence of COX-2 inhibitor use over time, we did not make a distinction between the 2 classes of drugs, unless the patient had MI.

Events taken from clinical records.

(1) Incident clinical fragility fractures of vertebrae, femur, pelvis, ribs, distal radius, and humerus, defined as a fracture caused by injury that would be insufficient to fracture a normal bone[12]. If a patient had incurred subsequent fractures, only the first was recorded for this analysis. When there was uncertainty whether the fracture occurred as a result of bone fragility, the fracture was excluded from the analysis. Vertebral fractures identified by radiographs of the spine without a clinical association or a precise indication of the time of occurrence (prevalent fractures) were excluded. Patients with prevalent fragility fracture at the time of disease onset were excluded.

(2) Arterial hypertension, defined by systolic pressure > 140 mm Hg and diastolic pressure > 90 mm Hg that required pharmacological intervention. Cases of arterial hypertension that occurred in strict temporal association with therapy with cyclosporine or leflunomide, which are known to induce elevation of arterial pressure, and that subsided after withdrawal of the drug, were excluded. Arterial blood pressure was routinely measured at least every 6 months.

(3) Acute MI. The diagnosis had to be confirmed by examination of the clinical records of the event. The following were considered diagnostic of MI: rise and fall of cardiac creatine kinase-MB fraction and troponin, accompanied by either ischemic-type chest pain, pathological Q waves, ST elevation, or depression.

(4) Diabetes mellitus (according to the World Health Organization definition) that required pharmacological intervention (oral antidiabetic drugs and/or insulin). Fasting blood glucose levels were routinely evaluated at each visit.

(5) Cataract, partial or complete opacity on or in the lens or capsule of 1 or both eyes.

(6) Serious infections, such as soft tissue, bone and joint infection, pneumonia, central nervous system infections, endocarditis, and any other infection that required hospitalization or was life-threatening. Mild and uncomplicated lower urinary tract and upper airway infections were excluded, since their occurrence may be missed by the patients or may not be accurately assessed and/or recorded by the rheumatologist during the visit.

Gastrointestinal (GI) adverse events were not a subject of this investigation, on the assumption that concomitant NSAID are a far more common cause of GI adverse effect than low-dose GC; that most patients are routinely treated with proton pump inhibitors; and that mild GI complaints are very frequent and not accurately recorded at each visit.

Statistical analysis. Data were compared between the 2 groups (GC users and GC nonusers) through the Student's t-test for unpaired data for continuous variables and the chi-squared test for categorical variables. ANOVA was used when appropriate. Significance was reported at $p \leq 0.05$.

RESULTS

In December 2007, 2724 patients with RA were recorded in our outpatient rheumatology unit: 1697 (62.3%) had been treated with GC for at least 6 months and 1027 (37.7%) had not. Ninety-four patients were excluded because they were treated with GC other than 6-MP (32 deflazacort, 62 prednisolone). Three hundred sixty-five patients had a followup for at least 10 years. Among them, 297 (81.3%) were GC users and 68 (18.7%) were nonusers, according to the definition. The mean duration of followup was 14.2 ± 4.0 years (range 10–22) in the GC users group and 14.1 ± 4.0 years (range 10–23) in the GC nonusers group (p = NS).

Table 1 shows the main demographic and clinical features of the 2 groups. They were comparable in mean age, ratio of men to women, mean disease duration, and evidence of erosive disease; the percentages of GC users and GC nonusers who had been treated with NSAID/COX-2 inhibitors were similar. However, GC users had more frequently tested positive for RF and for anticitrullinated peptide, these differences being statistically significant ($p < 0.01$). Further, GC users had used more DMARD than GC nonusers. This likely reflects the presence of a more active disease in the patients treated with GC.

With regard to the prevalence of adverse events, we found that fragility fractures, arterial hypertension, and acute MI occurred more frequently among GC users than among nonusers (Table 2), the difference being statistically significant. Prevalence of diabetes mellitus, cataract, and infections was not statistically significantly different between GC users and nonusers. The occurrence of any adverse event was 53.9% among GC users and 32.4% among nonusers ($p < 0.002$).

Among GC users, incident fragility fractures (n = 54) were vertebral (n = 34), hip (n = 6), and other nonvertebral (n = 14). At the time of fracture, the mean age was 66.0 ± 9 years, the duration

Table 1. Characteristics of the patients using/not using glucocorticoids (GC). Data expressed as percentage or mean ± SD.

Characteristic	GC Nonusers, n = 68	GC Users, n = 297	p
Men, no.	26.4	35.5	NS
Age, yrs (range)	66.1 ± 12.3 (28–90)	66.7 ± 11.7 (26–89)	NS
BMI	26.2 ± 4.6	26.3 ± 5.1	NS
Disease duration, yrs	16.3 ± 6.1	16.8 ± 6.3	NS
Daily GC dose, mg (range)	—	4.1 ± 1.2 (4–6)	—
Cumulative GC dose, g (range)	—	12 ± 10 (1–38)	—
Duration of GC use, yrs (range)	—	8 ± 6 (1–20)	—
Erosive disease, no.	71.2	74.3	NS
NSAID/COX-2 inhibitor users, no.	65.5	71.2	NS
No. DMARD used (range)	1.8 ± 1.3 (1–4)	3.2 ± 1.5 (1–6)	< 0.01
RF-positive, no.	52	64	< 0.05
Anti-CCP-positive, no.	34	58	< 0.01

BMI: body mass index; NSAID: nonsteroidal antiinflammatory drug; COX: cyclooxygenase; DMARD: disease modifying antirheumatic drug; RF: rheumatoid factor; anti-CCP: anticyclic citrullinated peptide. NS: nonsignificant.

Table 2. Cumulative prevalence of adverse events.

Events	GC Nonusers, %	GC Users, %	p
Any adverse event	32.4	53.9	< 0.002
Fractures	6	18.2	< 0.02
Arterial hypertension	10.4	32.3	< 0.0005
Myocardial infarction	1.5	13.1	< 0.01
Diabetes mellitus	13.4	12.1	NS
Cataract	10.4	13.9	NS
Infections	3	6.1	NS

GC: glucocorticoid: NS: not significant.

of GC use was 7.7 ± 6.2 years, and the cumulative GC dose was 11.9 ± 8.0 g. Women had significantly more fractures than men: 22.4% vs 10.5% ($p < 0.02$). The majority of the patients were under bisphosphonate treatment at the time of the fracture (51.8%); 74.1% were taking calcium and vitamin D supplementation. Forty-five patients with fractures (83.3%) had been screened for osteoporosis by dual-energy x-ray absorptiometry and 28 of them had vertebral or hip T-scores < –2.5, according to the WHO definition of osteoporosis.

Arterial hypertension was detected in 96 GC users. The mean age at time of detection of hypertension was 66.9 ± 10.1 years, disease duration 10.2 ± 6.0 years, duration of GC use 7.1 ± 6.4 years, and cumulative GC dose 9.4 ± 7.1 g. Women and men had comparable incidence of arterial hypertension: 34.4% and 28.5%, respectively (p = NS). We found no significant difference comparing NSAID/COX-2 inhibitor use in GC users who developed arterial hypertension and in those who did not: 65.6% and 74.3% (p = NS).

Thirty-nine GC users had MI: the mean age at the event was 73.7 ± 8.4 years, disease duration 14.2 ± 5.1 years, duration of GC use 10.2 ± 7.1 years, and cumulative GC dose 12.5 ± 8.0 g. Women and men had comparable incidence of MI: 13.5% and 12.4%, respectively (p = NS). Body mass index (BMI) at the time of the MI was 26.5 ± 4.2. At the time of the event, 69.2% of the patients had arterial hypertension, a significantly higher percentage than that observed (30.5%) in those taking GC who did not have MI ($p < 0.01$). We found no significant difference in NSAID/COX-2 inhibitor use and aspirin use and smoking habit between GC users who developed MI and those who did not. Percentages of NSAID/COX-2 inhibitor use were 64.1% (21 patients used NSAID and 4 used COX-2 inhibitors in the year preceding the event) and 72.1% (p = NS); aspirin use was 20.5% and 17.4% (p = NS); smoking habit 12.8% and 13.2% (p = NS), respectively. Compared to the other GC users, the patients who had MI showed a significantly higher prevalence of positive RF (74% and 59%; $p < 0.05$) and anticyclic citrullinated peptide (66% and 52%; $p < 0.02$).

Further, we divided GC users into groups of different duration of GC therapy: < 2, 2–5, and > 5 years; the mean duration of GC treatment was 1.3 ± 0.5, 3.6 ± 1.1, and 12.1 ± 5.1 years, respectively. The groups had a comparable mean age (GC nonusers 66.6 ± 12.2 years; users < 2 years 64.6 ± 13.1; users 2–5 years 65.9 ± 10.6; and users > 5 years 67.7 ± 11.5; p = NS); and comparable disease duration (years, GC nonusers 16.3 ± 6.1; users < 2 years 17.7 ± 7.3; users 2–5 years 15.1 ± 4.5; users > 5 years 17.3 ± 6.3; p = NS). GC treatment for > 5 years was associated with a significantly higher prevalence of fragility fractures, arterial hypertension, MI, and infections. GC treatment for 2–5 years was associated with a significantly higher prevalence of arterial hypertension compared to nonusers (Table 3).

Serious infections (n = 18) among GC users were tubercular pneumonia (n = 1), bacterial pneumonia (n = 7), osteomyelitis (n = 1), septic arthritis (n = 2), prosthetic infection (n = 2), herpes zoster (n = 1), and soft tissue infections (n = 4). Patients who developed serious infections had

Table 3. Prevalence of adverse events in groups with different durations of glucocorticoid treatment.

Events	Nonusers, n = 68, (%)	Users < 2 yrs, n = 52, (%)	Users 2–5 yrs, n = 60, (%)	Users > 5 yrs, n = 185, (%)
Any adverse event	32.4	28.8	47.5	62.7
Fractures	6.0	3.8	5.0	26.6*
Arterial hypertension	10.4	19.2	30.0**	36.7***
Myocardial infarction	1.5	9.6	6.6	16.1†
Diabetes mellitus	13.4	9.6	14.8	11.9
Cataract	10.4	5.8	13.3	16.2
Infections	3	0	0	9.7††

* $p < 0.001$ vs any other group; ** $p < 0.01$ vs nonusers; *** $p < 0.0002$ vs nonusers and users < 2 yrs; † $p < 0.03$ vs nonusers; †† $p < 0.005$ vs any other group.

a mean age of 65.2 ± 10.4 years, disease duration of 12.3 ± 5.5 years, duration of GC use 7.8 ± 5.4 years, and a cumulative GC dose of 13.4 ± 4.6 g. Only 1 patient was taking antitumor necrosis factor treatment (infliximab) at the time of the infection; 3 patients were not on DMARD treatment; 4 patients were on monotherapy (1 hydroxychloroquine, 3 methotrexate); and 10 were taking 2 associated DMARD. Table 4 shows the distribution of the number of adverse events in the 2 groups.

DISCUSSION

To our knowledge, we report the longest retrospective study on patients involving GC use aimed at assessing incident comorbidity. We found in patients with RA taking longterm, low-dose GC a significantly higher prevalence of fragility fractures, arterial hypertension, MI, and serious infections, using as controls patients with RA who were never treated with GC. The causative role of longterm GC use is suggested by the possibility that such adverse events are consequences of steroid treatment. However, GC treatment may represent simply a marker of disease activity: patients with more aggressive disease are treated with GC and a chronic active inflammatory condition can include *per se* rapid bone loss and accelerated cardiovascular damage.

Our study has some obvious limitations. First, we are not able to provide information about disease activity over the followup period. In RA, disease activity can directly increase the occurrence of cardiovascular disease and osteoporosis (and therefore fragility fractures); further, inhibition of the immune system by immunosuppressive drugs used as DMARD can increase the occurrence of serious infective complications. Second, in our retrospective analysis, we could not attain accurate information about risk factors for cardiovascular disease (e.g., plasma lipid levels, BMI, and family history) in the majority of the patients, making it impossible to test their relevance. Third, we performed a retrospective study only on patients who were followed continuously for at least 10 years in the same rheumatology unit, which is a selection bias: the characteristics and therefore the prevalence of comorbidity of patients who were not persistent in the followup at the same center may be different, and we cannot provide information about the subjects who may have died before completion of the 10-year followup. As a consequence we cannot draw any firm conclusion about the role of GC as major provocative agents of these adverse events.

Table 4. Number of patients with 1 or more adverse events.

No. of Adverse Events	GC Nonusers	GC Users
1	17	86
2	2	40
3	3	24
4	—	4
5	—	6
6	—	—

GC: glucocorticoid.

On the other hand, our study has characteristics that support the hypothesis that chronic GC use could lead to negative effects. The 10-year followup may have revealed adverse effects of GC that are not recognizable in shorter studies. A metaanalysis of randomized controlled trials of GC in RA has reported that GC therapy is associated with limited toxicity compared to placebo[13]: the 6 trials included in the metaanalysis lasted 2 years[2,4,5,6,14] or 3.5 years[15]. We did not find significant difference in adverse events when we compared GC users for a mean 1.3 ± 0.5 years to nonusers; and GC users for a mean 3.6 ± 1.1 years differed significantly ($p < 0.01$) from nonusers only for the occurrence of arterial hypertension (30.0% and 10.4%, respectively). By contrast, we found a significantly higher prevalence of adverse events among patients with a longer duration of GC therapy (mean 12.1 ± 5.1 years). As a result, the discrepancy of our data compared to studies reporting few GC-induced adverse effects in RA may be due to the longer followup or to the longer duration of GC exposure. A long followup period may be particularly relevant with regard, for instance, to cardiovascular adverse effects: in a longitudinal study on patients with RA followed for a median of 13 years, an association between MI, heart failure, and death from cardiovascular causes and GC treatment in RF-positive subjects was identified[16]. Similarly, use of oral GC was

found to significantly increase the risk of hip fractures (RR 3.4, 95% CI 3.0–4.0) in patients with RA compared to control subjects from the British General Practice Research Database over a median followup of 7.6 years[17]. Further, patients enrolled in randomized controlled trials may differ from patients seen in clinical practice. In this view, retrospective studies may have the ability of assessing a real-life cost-effectiveness ratio, which may be different from that derived from randomized trials. Finally, a placebo-controlled, randomized, double-blind study to assess adverse events from GC therapy in patients with RA over many years of therapy is evidently not possible, and in this case retrospective studies play a fundamental role.

Another feature of our study is that we analyzed a large population sample that has been followed continuously in a single center in which strategies to prevent GC-related or RA-related adverse outcomes have always been carried out carefully. These features support the validity of the findings of our retrospective study: patients were treated with GC, when appropriate, at doses not exceeding 6 mg/day of 6-MP in a single morning dose to avoid HPA axis suppression; all the patients received a DMARD as soon as the diagnosis of RA was established, to achieve remission; accurate prevention of the predictable complication of longterm GC treatment was undertaken; most patients received treatment to prevent osteoporosis (among those taking GC, about 80% of the patients who had fractures had been screened for osteoporosis, more than 50% were on bisphosphonate treatment for osteoporosis, and the majority took calcium and vitamin D supplements); patients were invited to semiannual visits to exclude endoocular hypertension or cataracts; and measurements of arterial blood pressure were routinely performed at each visit. This homogeneity in the patients' management makes the results of a retrospective analysis reliable.

Patients with RA who use chronic low-dose GC therapy compared to those who never use GC show a higher prevalence of comorbidity, such as arterial hypertension, acute MI, fragility fractures, and serious infections. This may be the consequence of either high disease activity or disease-related processes, or the use of GC. Data from this retrospective analysis do not allow us to confirm or exclude the role of GC. However, taking into account our results and others indicating a negative effect of longterm chronic GC in RA, the longterm safety of low-dose GC should be at least questioned. Further, the high prevalence of serious conditions such as MI and fractures suggests that a more accurate identification of risk factors and prevention measures should be adopted in patients with RA, especially when treated with GC over the long term.

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