The Journal of Rheumatology Volume 39, no. 3

Adverse Events During Longterm Low-dose Glucocorticoid Treatment of Polymyalgia Rheumatica: A Retrospective Study

MAURIZIO MAZZANTINI, CLAUDIA TORRE, MARIO MICCOLI, ANGELO BAGGIANI, ROSARIA TALARICO, STEFANO BOMBARDIERI and OMBRETTA DI MUNNO

J Rheumatol 2012;39;552-557
http://www.jrheum.org/content/39/3/552

Adverse Events During Longterm Low-dose Glucocorticoid Treatment of Polymyalgia Rheumatica: A Retrospective Study

MAURIZIO MAZZANTINI, CLAUDIA TORRE, MARIO MICCOLI, ANGELO BAGGIANI, ROSARIA TALARICO, STEFANO BOMBARDIERI, and OMBRETTA DI MUNNO

ABSTRACT. ***Objective.*** To assess the occurrence of adverse events in a cohort of patients with polymyalgia rheumatica (PMR), treated with low-dose glucocorticoids (GC).

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

Results. We identified 222 patients who had a mean duration of followup of 60 ± 22 months and a mean duration of GC therapy of 46 ± 22 months. We found that 95 patients (43%) had at least 1 adverse event after a mean duration of GC therapy of 31 ± 22 months and a mean cumulative dose of 3.4 ± 2.4 g. In particular, 55 developed osteoporosis, 31 had fragility fractures; 27 developed arterial hypertension; 11 diabetes mellitus; 9 acute myocardial infarction; 3 stroke; and 2 peripheral arterial disease. Univariate analysis showed that the duration of GC treatment was significantly associated with osteoporosis ($p < 0.0001$), fragility fractures ($p < 0.0001$), arterial hypertension ($p < 0.005$), and acute myocardial infarction ($p < 0.05$). Cumulative GC dose was significantly associated with osteoporosis ($p < 0.0001$), fragility fractures ($p < 0.0001$), and arterial hypertension ($p < 0.01$). The adverse events occurred more frequently after 2 years of treatment. Multivariate analysis showed that GC duration was significantly associated with osteoporosis (adjusted OR 1.02, 95% CI 1.02–1.05) and arterial hypertension (adjusted OR 1.03, 95% CI 1.01–1.06); GC cumulative dose was significantly associated with fragility fractures (adjusted OR 1.4, 95% CI 1.03–1.8).

Conclusion. Longterm, low-dose GC treatment of PMR is associated with serious adverse events such as osteoporosis, fractures, and arterial hypertension; these adverse events occur mostly after 2 years of treatment. (First Release Jan 15 2012; J Rheumatol 2012;39:552–7; doi:10.3899/jrheum.110851)

Key Indexing Terms:
POLYMYALGIA RHEUMATICA GLUCOCORTICOIDS COMORBIDITY DRUG TOXICITY

Polymyalgia rheumatica (PMR) is an inflammatory condition mostly affecting older persons that is characterized by aching and morning stiffness in the shoulder and pelvic girdles and neck. Glucocorticoids (GC) are still the mainstay of PMR therapy. It has been suggested that even low-dose GC when taken chronically may lead to clinically meaningful adverse events such as fractures[1] and cardiovascular disease[2], which includes myocardial infarction (MI)[3] and stroke[4,5]. The prevalence of these effects is expected to increase significantly with time of GC exposure. However, safety data from randomized controlled clinical trials of low-dose GC treatment for 2 years in rheumatoid arthritis (RA) suggested that GC-induced adverse effects were modest and often not statistically different from those of placebo[6,7,8,9,10]. We have recently shown that 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[11]. This may be the consequence of either high disease activity or disease-related processes, or the use of GC. The uncertainty about the relative role of GC and RA itself has prompted us to assess the occurrence of adverse events that are possibly related to GC therapy in a population of patients with PMR. In fact, differently from RA, PMR *per se* seems not to increase the risk of cardiovascular disease and is not a cause of generalized bone loss and fractures. Further, the literature about this topic is sparse and conflicting[12,13,14].

GC therapy of PMR is well standardized[15]: usually the initial daily dose does not exceed 20 mg of prednisone or equivalent and it can be reduced every 2 weeks by 2.5–5 mg/day to 10 mg/day; thereafter, daily doses are reduced by 1.0–2.5 mg every month until the treatment is stopped, usually after 1–2 years depending on individual needs and recurrences. Since

From the Rheumatology Unit, Department of Internal Medicine; and the Epidemiology Unit, Department of Experimental Pathology MBIE, University of Pisa, Pisa, Italy.

M. Mazzantini, MD, PhD; C. Torre, MD; R. Talarico, MD, PhD; O. Di Munno, MD, Associate Professor of Rheumatology; S. Bombardieri, MD, Chief, Rheumatology Chair, Rheumatology Unit, Department of Internal Medicine, University of Pisa; M. Miccoli, PhD; A. Baggiani, MD, Epidemiology Unit, Department of Experimental Pathology MBIE, University of Pisa.

Address correspondence to Dr. M. Mazzantini, Rheumatology Unit, Ospedale S. Chiara, via Roma 67, 56100 Pisa, Italy.
E-mail: mmazzant@int.med.unipi.it

Accepted for publication October 17, 2011.

the 1970s at our Rheumatology Unit 6-methylprednisolone (6-MP) has been used as the first-choice GC in patients with PMR in order to improve symptoms and reduce disease activity. The duration of the biological effect of 6-MP (about 24 hours) and its plasma half-life (< 2 hours) make this compound appropriate for longterm therapy[16]. To limit the suppression of the hypothalamic-pituitary-adrenocortical (HPA) axis to once daily, morning doses of 6-MP (i.e., usually not exceeding 6 mg/day) are used. Consequently, after > 30 years a large number of patients with PMR have been treated chronically with 6-MP in a single morning dose. Thus it is now possible to assess in this population the association between longterm GC use and some clinical events known to be possibly related to chronic exposure to GC. The aim of our study was to assess retrospectively the occurrence of comorbidity known to be the possible consequence of GC therapy in a cohort of patients with PMR who have been followed continuously in our institution.

MATERIALS AND METHODS

We carried out an analysis by review of the medical documentation of all the patients with a diagnosis of PMR[17] at the end of 2009. We selected only the patients who had been followed continuously in our institution from the time of diagnosis; the minimum followup required for inclusion into the analysis was 6 months. Patients with giant cell arteritis (either early or later in the clinical course of PMR) were excluded. For each patient, we calculated cumulative duration of GC therapy and cumulative dose of GC either at the most recent visit registered in clinical records or at the time of adverse event occurrence. Patients with PMR were further divided into 2 subgroups based on the cumulative duration of GC therapy: < 2 years and > 2 years. All the patients were treated with 6-MP. The starting daily dose ranged from 12 to 20 mg for 2 weeks; subsequently, individual dose was tapered on the basis of clinical improvement and normalization of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values. At each visit, disease was classified as remitting or persisting, based on both pain and stiffness assessment and ESR or CRP values. Patients were classified as being in remission if pain and stiffness were absent and if ESR and CRP values were below the upper normal limit (unless abnormal for another evident medical condition), at 2 consecutive visits at least 3 months apart.

We collected demographic and clinical data retrospectively, including ESR and CRP at each visit, duration of the disease at the time of the study, use of nonsteroidal antiinflammatory drugs (NSAID) or cyclooxygenase-2 (COX-2) inhibitors, and use of methotrexate (MTX) as a GC-sparing agent. 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. Traditional cardiovascular risk factors prior to the diagnosis of PMR (hypertension, dyslipidemia, diabetes mellitus) were noted, and body mass index (BMI) and family history were obtained.

We systematically examined clinical records for the following 6 categories of incident events: (1) 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[18]. If a patient had incurred subsequent fractures, only the first one was recorded for this analysis. When there was uncertainty whether the fracture occurred because of bone fragility, the fracture was excluded from the analysis. Vertebral fractures identified by radiographs of the spine without a clinical association or precise indications of the time of occurrence (prevalent fractures) were excluded. Patients with prevalent fragility fracture at the time of disease onset were excluded. (2) Osteoporosis, defined as a T-score < –2.5 at the lumbar spine or the hip, measured by dual-energy x-ray absorptiometry. (3) Arterial hypertension, defined by systolic pressure > 140 mm Hg and diastolic pressure > 90 mm Hg, that required pharmacological intervention. Arterial blood pressure was routinely measured at least every 6 months. (4) 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 ischemic-type chest pain, pathological Q waves, ST elevation, or depression. (5) Transient ischemic attack, stroke, and peripheral arterial disease; diagnosis had to be confirmed by examination of the clinical records of the event. Peripheral arterial disease was defined by the presence of any of the following: intermittent claudication or ischemic pain with documented absence of arterial pulses; peripheral artery surgery or lower extremity amputation due to peripheral artery disease. (6) Diabetes mellitus (World Health Organization definition) that required pharmacological intervention (oral antidiabetic drugs and/or insulin). Fasting blood glucose levels were routinely evaluated at each visit.

Adverse events were defined as a new diagnosis or incidence of any of these conditions first occurring after the start of GC therapy. Patients who developed 1 cardiovascular event (acute MI, transient ischemic attack, stroke, or peripheral arterial disease) were censored and only the first event was included in the analysis, e.g., if a patient had a stroke after MI, only the MI was included in the analysis.

Gastrointestinal (GI) adverse events were not the object 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. The analysis was defined by the Shapiro-Wilk test used to check normality of data distribution in order to assess whether to perform parametric tests. A statistical power analysis (ex-post) to estimate the sample size required for the specific tests gave 1 – ß value > 0.8, assuring a low risk of type II error in the study.

The univariate analysis was performed to investigate the relation between time or dosage of GC and adverse outcomes. For this purpose we used t test, Mann-Whitney U test, chi-squared test, and simple linear regression.

P values were determined with 95% CI. With regard to multivariate analysis, we performed logistic regressions adjusted for age to study the association between risk factors and adverse outcomes. Data were entered into an Excel database and were subsequently locked and imported into SPSS for Windows (SPSS Inc., version 17.0) and R-2.12.1 software.

RESULTS

At the end of 2009, our database included 1429 patients with a diagnosis of PMR. Review of the medical records revealed that, later in the followup, 81 of the patients developed RA and 152 developed giant cell arteritis; further, 148 patients had a followup of 6 months or less; 726 had sporadic visits at our institution, which would prevent an accurate retrospective analysis of the relation to GC therapy of incident adverse events; and finally, 100 patients were treated with GC different from 6-MP. As a result, 222 patients were included into the analysis (Figure 1). Table 1 shows the main demographic and clinical features of the group.

Analysis of patients' records revealed that 95 (43%), while taking GC, had at least 1 adverse event after a mean duration of GC therapy of 31 ± 22 months and a mean cumulative dose of 3.4 ± 2.4 g. In particular, 55 developed osteoporosis; 31 had fragility fractures; 27 developed arterial hypertension; 11 diabetes mellitus, 9 acute MI; and 5 stroke (n = 3) or peripheral arterial disease (n = 2). Comparing those who developed adverse events to those who did not, we found an association between a significantly longer duration of GC therapy and the

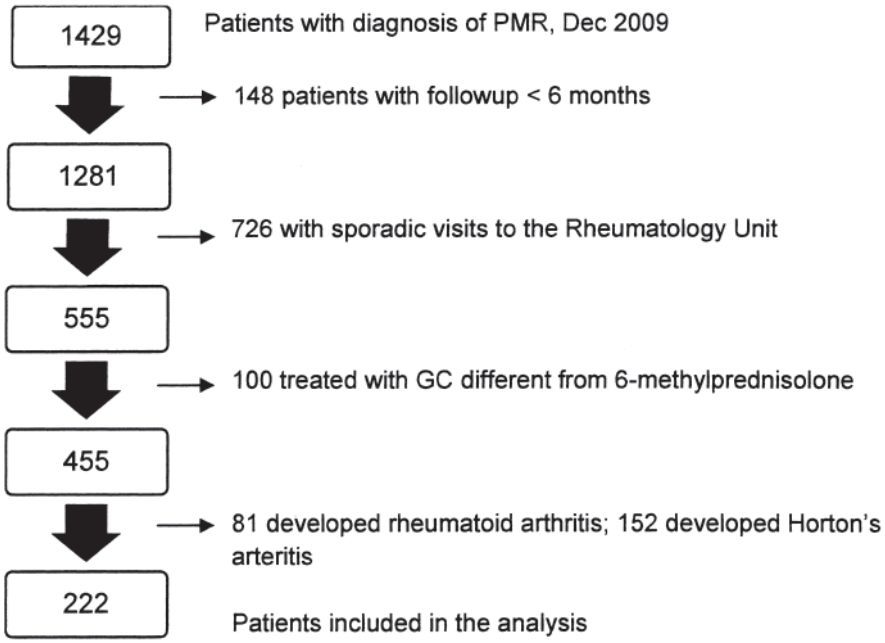

Figure 1. Summary of the exclusion criteria used in patient selection. PMR: polymyalgia rheumatica; GC: glucocorticoids.

Table 1. Demographic and clinical features of the 222 patients with polymyalgia rheumatica.

Characteristic	
Age at diagnosis, yrs, mean ± SD (range)	71 ± 8 (51–91)
Women/men	154/68
Body mass index, kg/m^2, mean ± SD	25.8 ± 4.0
Smokers	
Current	13
Past	32
Duration of disease, mo, mean ± SD (range)	49 ± 26 (8–112)
Duration of followup, mo, mean ± SD (range)	60 ± 22 (12–146)
Duration of GC* therapy, mo, mean ± SD (range)	46 ± 22 (6–111)
GC* starting dose, mg, mean ± SD (range)	15 ± 4 (12–20)
Cumulative dose of GC*, g, mean ± SD (range)	4.4 ± 2.6 (1–19)
Methotrexate users (%)	66 (30)
At start	30
At baseline, n (%)	
High cholesterol	101 (45)
High triglycerides	54 (24)
Arterial hypertension	106 (48)
Cardiovascular disease**	11 (5)
Osteoporosis	50 (23)
Fragility fractures after age 50	11 (5)
Diabetes mellitus	26 (12)

*6-methylprednisolone. **Acute myocardial infarction, transient ischemic attack, stroke, peripheral arterial disease. GC: glucocorticoids.

occurrence of osteoporosis ($p < 0.0001$), fragility fractures ($p < 0.0001$), arterial hypertension ($p < 0.005$), and acute MI ($p < 0.05$). We also found that a significantly higher cumulative dose of GC was associated with the occurrence of osteoporosis ($p < 0.0001$), fragility fractures ($p < 0.0001$), and arterial hypertension ($p < 0.01$; Table 2). In the group of patients who developed adverse events, we found that 81 patients (85%) had remission of PMR at the time of adverse event occurrence. At the end of the followup (mean 60 ± 22 months), 194 patients (87%) had remission of disease, with no significant difference between those who developed adverse events and those who did not: 89% and 86%, respectively (p = nonsignificant). Comparing the 2 groups of patients, we also found that starting GC dose, cumulative GC dose in the first 3 months, and percentage of patients in remission after 3 months of GC treatment were comparable (data not shown). Patients treated with MTX had incidence of adverse events comparable to those who were not: 47% versus 41%, respectively ($p = 0.41$). Patients who were treated with MTX, compared to those who were not, showed a higher cumulative GC dose (5.0 ± 2.6 g vs 4.1 ± 2.4 g; $p = 0.01$) and a longer duration of GC treatment (53 ± 23 months vs 43 ± 22 months; $p = 0.02$).

We compared 2 groups of different duration of GC therapy: < 2 years (n = 128) and > 2 years (n = 94). The 2 groups were comparable for age (71.7 ± 8.5 and 70.6 ± 6.7 years, respectively; $p = 0.23$), BMI (25.6 ± 3.8 kg/m^2 and 25.9 ± 4.1 kg/m^2; $p = 0.58$), duration of followup (58 ± 20 and 63 ± 23 months; $p = 0.5$), ratio of men to women, percentage of smokers, mean GC starting dose, MTX users, and prevalence of comorbidity (data not shown). Cumulative GC dose was significantly lower in the group treated for < 2 years: 2.15 ± 0.9 g and 4.8 ± 2.6 g ($p < 0.0001$). The adverse events (osteoporosis, fractures, arterial hypertension, and acute MI)

Table 2. Adverse events and duration and cumulative dose of glucocorticoids (GC). Data are mean ± SD.

	Patients Experienced Adverse Events					
	Yes	No		Yes	No	
	Mean Duration of GC, mo		p	Mean Cumulative Dose of GC, g		p
Osteoporosis	47 ± 27	25 ± 17	< 0.0001	5.1 ± 3.2	2.9 ± 1.7	< 0.0001
Fragility fractures	55 ± 29	27 ± 18	< 0.0001	6.1 ± 3.8	3.0 ± 1.7	< 0.0001
Arterial hypertension	43 ± 24	29 ± 21	0.004	4.5 ± 2.5	3.3 ± 2.3	0.01
Acute myocardial infarction	47 ± 25	30 ± 22	0.03	4.6 ± 1.8	3.4 ± 2.4	0.12

occurred significantly more frequently in those patients who were treated for > 2 years (75 of them had at least 1 adverse event; 79.8%) compared to those treated for < 2 years (20 had at least 1 adverse event; 15.6%): in particular, osteoporosis occurred in 42.6% and 11.7% of the patients, respectively ($p < 0.0001$); fragility fractures in 26.6% and 4.6% ($p < 0.0001$); arterial hypertension in 20.2% and 6.25% ($p = 0.0017$); and acute MI in 7.4% and 1.6% ($p = 0.028$).

Multivariate analysis was performed using age- and sex-adjusted logistic regression to test the association between risk factors (duration of GC therapy and cumulative GC doses at the time of adverse event, and traditional risk factors) and adverse outcomes. For this purpose, cases of first acute MI, stroke, transient ischemic attack, and peripheral arterial disease were considered collectively as a group. Traditional risk factors placed in the multivariate models were as follows: for osteoporosis, smoking and BMI; for fragility fractures, smoking, osteoporosis at baseline, and fragility fractures after age 50 years; for arterial hypertension, family history, use of NSAID/COX inhibitors, and BMI; and for cardiovascular events, BMI, preexisting diabetes mellitus, dyslipidemia, and arterial hypertension. The results of the multivariate analysis are summarized in Table 3. GC therapy, either as duration of therapy or cumulative dose, was the only factor that showed a significant association with adverse events (osteoporosis, fractures, and arterial hypertension) in multivariate analysis. In particular, the analysis showed that osteoporosis was significantly associated with the duration of GC ($p < 0.05$); fragility fractures were significantly associated with cumulative GC dose ($p < 0.05$); arterial hypertension was significantly associated with the duration of GC ($p < 0.05$); and GC were not significantly associated with cardiovascular events, although they showed the strongest association among the factors entered into the analysis ($p = 0.1$).

Table 3. Multivariate analysis.

	OR (95% CI)	p
Osteoporosis		
GC, duration	1.02 (1.02–1.05)	0.04
GC, cumulative dose	1.24 (0.99–1.6)	0.10
Smoking	0.97 (0.5–2.0)	0.90
BMI, kg/m^2	1.01 (0.9–1.1)	0.80
Fractures		
GC, duration	1.02 (0.99–1.05)	0.10
GC, cumulative dose	1.4 (1.03–1.8)	0.04
Smoking	1.7 (0.7–4.7)	0.30
Preexisting osteoporosis	1.2 (0.4–3.2)	0.80
Arterial hypertension		
GC, duration	1.03 (1.01–1.06)	0.05
GC, cumulative dose	1.01 (0.76–1.3)	0.90
Family history	0.6 (0.08–2.3)	0.50
NSAID/COXIB	0.7 (0.3–1.6)	0.30
BMI	1.01 (0.9–1.1)	0.90
Cardiovascular events		
GC, duration	1.03 (0.98–1.08)	0.10
GC, cumulative dose	0.8 (0.4–1.1)	0.40
Smoking	0.4 (0.1–1.3)	0.10
BMI	1.04 (0.9–1.2)	0.50
Diabetes	0.3 (0.1–0.6)	0.90
Dyslipidemia	1.3 (0.4–4.3)	0.60

GC: glucocorticoids; BMI: body mass index; NSAID: nonsteroidal anti-inflammatory drugs; COXIB: cyclooxygenase inhibitors.

DISCUSSION

There is no doubt that GC treatment is of great value in the management of PMR, by rapidly reducing pain and stiffness and suppressing inflammation within a few weeks. On the other hand, our study suggests that longterm treatment with low-dose GC is associated with serious adverse events. Most patients with PMR are treated for > 1–2 years. Few studies have examined serious side effects following longterm GC therapy in patients with PMR. One longterm (mean 8 years) study[12] evaluated the incidence of adverse events among a cohort of patients diagnosed with PMR (n = 232; 30 patients had giant cell arteritis during followup) and found that the use of GC and NSAID was associated with longterm morbidity; the rate of adverse events was similar in the GC-treated and in the NSAID-treated groups, but patients treated with NSAID had different types of events (e.g., arterial hypertension) compared with those treated with GC (e.g., vertebral fractures). Increasing age at diagnosis, being female, higher initial GC dose, and higher cumulative GC dose were significant risk factors associated with the development of an adverse event. Perhaps due to the 13% of patients with giant cell arteritis in the cohort, the mean daily dose was about 10.0 mg prednisone, which is higher than that generally deemed a low dose (i.e., 7.5 mg or less of prednisone). A retrospective longitudinal study[13] assessed the incidence of cardiovascular and cerebrovascular events in a cohort of 364 patients with PMR, 310 of them treated with GC at a mean daily dose of 3.5 mg after

a median of 7.6 years. Patients who received GC did not have significantly higher risk for MI, heart failure, peripheral vascular disease, or cerebrovascular disease compared to those who did not receive GC. No significant association was observed between cumulative GC dose and any of the outcomes; on the contrary, a trend for a protective effect exerted by GC was observed. A subsequent retrospective study from the same center[14] compared a cohort of patients with PMR (n = 353; 63 patients had giant cell arteritis during followup) with non-PMR subjects (n = 705) to determine whether patients with PMR are at increased risk of peripheral arterial disease. After a mean followup of 11 years, patients with PMR had a significantly higher risk for peripheral disease compared with controls (HR 2.5, 95% CI 1.53–4.08). The GC contribution to this incident comorbidity was not taken into account, a decision based on the results of a study[19] suggesting that GC were not associated with greater risk of peripheral arterial disease.

Indeed, only 1 study investigating longterm adverse events of GC during the course of PMR[12] suggested an association between GC and adverse events. Our study found that either the duration or the cumulative dose of GC was significantly associated with the occurrence of osteoporosis, fragility fractures, arterial hypertension, and acute MI in patients with PMR; these adverse events occurred more frequently after 2 years; and multivariate analysis showed that duration of GC was significantly associated with both osteoporosis and arterial hypertension, and cumulative GC dose was significantly associated with fragility fractures. The association between GC and arterial hypertension in patients with PMR is a new finding, to our knowledge; further, the risk of MI seems to be increased. This is in accord with the results of a previous retrospective study of patients with RA[11] that suggested GC as a potential cause of the high incidence of cardiovascular events and arterial hypertension.

Our study has some limitations inherent with its retrospective design. We performed a retrospective study only on patients who were followed continuously in the same rheumatology unit, which presents a selection bias: the characteristics and therefore the prevalence of comorbidity of patients who did not have continuous followup at the same center may be different. Further, we could not attain accurate information about some risk factors for cardiovascular disease over the entire period of followup, e.g., assessment of plasma lipid levels was performed irregularly and plasma levels of homocysteine were assessed only in a minority of patients. On the other hand, this study has certain strengths. First, we analyzed a population that has been followed continuously in a single center and treated homogeneously. Second, methods to prevent GC-related adverse outcomes have always been carried out carefully; patients were treated with GC in a single morning dose to avoid HPA axis suppression; an accurate assessment of the predictable complication of longterm GC treatment was made; most patients received treatment to prevent osteoporosis (about 80% of the patients who had fractures had been screened for osteoporosis; > 90% were on bisphosphonate treatment for osteoporosis, and had calcium and vitamin D supplementation); patients were invited to semiannual visits to exclude endoocular hypertension or cataracts; and measurements of arterial blood pressure were routinely performed at each visit. Third, by selecting only those patients who had continuous followup at our institution, we were able to take into account the clinical disease activity. Thus, it was possible to assess remission or persistence of PMR over the entire followup period; the analysis suggested that disease-related variables were not associated with the occurrence of adverse events. Fourth, the retrospective design allowed us to exclude from the analysis the patients with giant cell arteritis and those who had a PMR-like onset of RA. In brief, we studied a very homogeneous population. This homogeneity in the patients' management and followup makes the results of this retrospective analysis reliable.

Longterm, low-dose GC treatment of PMR is associated with serious adverse events such as osteoporosis, fractures, and arterial hypertension. These adverse events occur mostly after 2 years of treatment, and despite careful awareness of the available preventive measures.

REFERENCES

1. Van Staa TP, Leufkens B, Abenhaim L, Zhang B, Cooper C. Use of oral corticosteroids and risk of fractures. J Bone Miner Res 2000;15:993-1000.
2. Wei L, MacDonald TM, Walker BR. Taking glucocorticoids by prescription is associated with subsequent cardiovascular disease. Ann Intern Med 2004;141:764-70.
3. Varas-Lorenzo C, Rodriguez LA, Maguire A, Castellsague J, Perez-Guttham S. Use of oral corticosteroid and the risk of acute myocardial infarction. Atherosclerosis 2007;192:376-83.
4. Sodergren A, Stegmayr B, Ohman ML, Wållberg-Jonsson S. Increased incidence of stroke and impaired prognosis after stroke among patients with seropositive rheumatoid arthritis. Clin Exp Rheumatol 2009;27:641-44.
5. Levy L, Fautrel B, Barnetche T, Schaeverbeke T. Incidence and risk of fatal myocardial infarction and stroke events in rheumatoid arthritis patients. A systematic review of the literature. Clin Exp Rheumatol 2008;26:673-9.
6. Kirwan JR. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. The Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study Group. N Engl J Med 1995;333:142-6.
7. Hickling P, Jacoby RK, Kirwan JR. Joint destruction after glucocorticoids are withdrawn in early rheumatoid arthritis. The Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study Group. Br J Rheumatol 1998;37:930-6.
8. Wassenberg S, Rau R, Steinfeld P, Zeidler H. Very low-dose prednisolone in early rheumatoid arthritis retards radiographic progression over two years: A multicenter, double-blind, placebo-controlled trial. Arthritis Rheum 2005;52:3371-80.
9. van Everdingen AA, Jacobs JW, Siewertsz van Reesema DR, Bijlsma JW. Low-dose prednisone therapy for patients with early active rheumatoid arthritis: Clinical efficacy, disease-modifying properties, and side effects: A randomized, double-blind, placebo-controlled clinical trial. Ann Intern Med 2002;136:1-12.
10. Capell HA, Madhok R, Hunter JA, Porter D, Morrison E, Larkin J, et al. Lack of radiological and clinical benefit over two years of

low-dose prednisolone for rheumatoid arthritis: Results of a randomised controlled trial. Ann Rheum Dis 2004;63:797-803.
11. Mazzantini M, Talarico R, Doveri M, Consensi A, Bazzichi L, Bombardieri S. Incident comorbidity among patients with rheumatoid arthritis treated or not with low-dose glucocorticoids: A retrospective study. J Rheumatol 2010;37:2232-6.
12. Gabriel SE, Sunku J, Salvarani C, O'Fallon W, Hunder G. Adverse outcomes of antiinflammatory therapy among patients with polymyalgia rheumatic. Arthritis Rheum 1997;40:1873-8.
13. Kremers HM, Reinalda MS, Crowson CS, Davis JM, Hunder GG, Gabriel SE. Glucocorticoids and cardiovascular and cerebrovascular events in polymyalgia rheumatica. Arthritis Care Res 2007;57:279-86.
14. Hoes JN, Jacobs JW, Verstappen SM, Bijlsma JW, Van der Heijden GJ. Adverse events of low- to medium-dose oral glucocorticoids in inflammatory diseases: A meta-analysis. Ann Rheum Dis 2009;68:1833-8.
15. Salvarani C, Cantini F, Hunder GG. Polymyalgia rheumatica and giant-cell arteritis. Lancet 2008;372:234-45.
16. Kirwan JR. Systemic corticosteroid in rheumatology. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, editors. Rheumatology. 3rd ed., vol. 1. Philadelphia: Mosby; 2003:385-92.
17. Bird HA, Esselinckx W, Dixon ASJ, Mowat AG, Wood PHN. An evaluation of criteria for polymyalgia rheumatica. Ann Rheum Dis 1979;38:434-9.
18. Guidelines for preclinical evaluation and clinical trials in osteoporosis. Geneva: World Health Organization; 1998.
19. Warrington KJ, Jarpa EP, Crowson CS, Cooper LT, Hunder GG, Matteson EL, et al. Increased risk of peripheral arterial disease in polymyalgia rheumatica: A population-based cohort study. Arthritis Res Ther 2009;11:R50.