

Deflazacort versus Prednisone in Patients with Giant Cell Arteritis: Effects on Bone Mass Loss

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ABSTRACT. Objective. To compare bone mass loss due to deflazacort versus prednisone in longterm treatment of patients with giant cell arteritis (GCA) in a randomized double blind comparative trial.

Methods. Seventy-four patients were included in a prospective multicenter study. Half received deflazacort (DFZ) and the other half prednisone (PR) for a minimum of 12 months. Calcium and vitamin D supplements were also provided to all subjects. Our intent was (1) to evaluate bone mineral density, using dual energy x-ray absorptiometry, at baseline and comparatively at 3, 6, and 12 mo; vertebral fractures by Meunier score and size variations after 12 mo treatments were also analyzed; (2) to assess calcium/phosphate metabolism modifications in both groups at baseline and after 12 mo.

Results. No significant difference was observed between the 2 groups in terms of treatment efficacy. Patients taking PR were slightly older on average versus the DFZ group (74 vs 70 yrs). Bone mass loss between entry and month 12 was not statistically different in the PR group (-0.026 ± 0.007 g/cm²) compared to the DFZ group (-0.03 ± 0.005 g/cm²). No significant difference was found in Meunier score variations (0.77 and 1.18 in the PR and DFZ groups, respectively; $p = 0.3$), nor in vertebral size variations (-0.4 and -0.2 in the PR and DFZ groups, respectively; $p = 0.4$). There was no difference in calcium/phosphate metabolism evaluations at month 12.

Conclusion. In older patients taking longterm glucocorticoids who are at risk of osteoporosis, deflazacort did not result in less bone loss than prednisone. (J Rheumatol 2001;28:2474-9)

Key Indexing Terms:

GIANT CELL ARTERITIS
BONE MASS LOSS

DEFLAZACORT
OSTEOPOROSIS

PREDNISONE
GLUCOCORTICOIDS

Corticosteroid induced bone loss is the major side effect of longterm glucocorticoid therapy¹. In its guidelines, the American College of Rheumatology (ACR) recommends that glucocorticoid induced osteoporosis and its complications (mainly vertebral or hip fractures) can be prevented by administration of osteoclastic activity inhibitors, vitamin D and/or calcium supplements, and estrogen replacement therapy in postmenopausal women². Deflazacort (DFZ), a prednisolone derivative component, has been suggested to have fewer adverse bone effects than prednisone (PR) at

doses with equivalent antiinflammatory activity³. The aim of this randomized multicenter double blind study was to compare the effects of PR versus DFZ on bone mass loss in patients treated for giant cell arteritis (GCA) for 12 months.

MATERIALS AND METHODS

Patients. Seventy-four hospitalized patients who provided written informed consent, aged between 40 and 85 years, and who presented either clinically evident or histologically verified GCA, were enrolled in a 12 month study. The diagnosis of GCA included one of the 4 clinical criteria: (1) abnormality of the temporal artery on examination, (2) visual abnormality (if present, CGA was considered as severe), (3) intermittent jaw pain, (4) compatible headaches, and at least one biological inflammatory sign including: erythrocyte sedimentation rate > 40 mm/h, C-reactive protein more > 3-fold the normal value, haptoglobin, orosomucoid or fibrinogen more than twice the normal value.

Exclusion criteria were: bedridden patients, glucocorticoid therapy given during the 12 months before entering the study or given previously for more than one month, uncontrolled infectious disease, pregnancy or breast feeding, creatinine blood level > 120 μ mole/l, peptic ulcer, gout, acute hepatitis, psychotic state, severe hepatic disease, cancer, Paget's disease, heparin, fluoride, calcitonin, bisphosphonates, estrogen or hormone replacement therapy in the 3 months before study entry, and medications that could lead to hypokalemia. Nonsteroidal antiinflammatory drugs (NSAID) were not permitted except for salicylic acid at dosages < 300 mg per day.

Study design. In this double blind multicenter controlled study, subjects were randomly assigned to receive either 0.7 mg/kg/day of PR or the corresponding prednisone equivalent dose (PReq) of DFZ. The potency ratio of

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DFZ is 1.2/1 compared with PR^{4,6}. Patients presenting with severe GCA received one intravenous infusion of 500 mg methylprednisolone on the day of entry. Indistinguishable tablets containing 30 mg DFZ or 25 mg PR, 6 mg DFZ or 5 mg PR, 1 mg DFZ or 1 mg PR were prepared for the study (Marion Merrel Dow, France). The initial full dose of corticosteroid (0.7 mg/kg/day PReq) was maintained until there was clinical improvement and normalization of at least 2 of the following inflammation tests: erythrocyte sedimentation rate (ESR), C-reactive protein, fibrinogen, haptoglobin, and orosomucoid. The daily dose of corticosteroid was then decreased by 10% of the initial dose per week until a 50% reduction, which was then maintained for one month. If no relapse occurred, the dose was progressively reduced by 1 mg PReq every 2 weeks until one minimal dose of 10 mg/day was achieved. Relapses were controlled by increasing the dosage of PReq and thereafter re-decreasing it with respect to the clinical and biological responses.

Throughout the study patients of both groups received calcium supplement 1 g/day (Cacit 1000[®], Procter & Gamble) and calciferol 0.025 mg/day (Dedrogy[®], Roussel Diamant).

The primary objective was to evaluate and compare lumbar spine bone mineral density (BMD) at baseline (day = 0), month 3, month 6, and month 12. BMD was measured by dual energy x-ray absorptiometry (DXA) (Hologic QDR 1000; Hologic Inc., Waltham, MA, USA; coefficient of variation 1%). The number of vertebral fractures was also assessed at entry and month 12 on radiographic film using the Meunier score, which includes end plate collapses, wedging, and complete crushes⁷.

A secondary objective was to compare phosphate and calcium metabolism under PR versus DFZ treatments. Plasma 25-hydroxyvitamin D was measured by the method of Preece, *et al*⁸, plasma 1,25 hydroxyvitamin D by a competitive protein binding method, serum parathyroid hormone by immunometric assay, and serum osteocalcin by immunoradiometric assays. Twenty-four hour urine collections were used for calcium/phosphate excretion analysis. All data regarding calcium/phosphate metabolism were collected at entry and 12 months. Glucose metabolism (glucose, insulinemia, C peptide) was also assessed.

The study protocol was approved by the ethics committee of La Pitié-Salpêtrière Hospital, Paris.

Statistical analysis. The sample size was chosen to provide the study with an 85% power with a 2 sided level of significance of 5% for the detection of a 50% reduction of BMD loss in the DFZ group compared with PR group. Clinical characteristics were compared using chi-square test. Changes in hip and lumbar spine BMD, Meunier scores, total glucocorticoid doses in the 2 treatment groups were assessed by t test, analysis of variance, and Fisher's exact test.

RESULTS

For the 12 month inclusion period 74 patients were randomly assigned, half to the PR group and half to the DFZ group. Baseline characteristics of patients in each group are detailed in Table 1. There was no difference between the groups in terms of sex ratio, GCA manifestations, medical history, or BMD. Patients taking PR were slightly older (74.6 vs 70.6 yrs; $p = 0.02$) and polymyalgia rheumatica was more frequently found than in the DFZ group [22/37 (59%) vs 9/37 (24%); $p = 0.046$]. The number of patients with biopsy proven temporal arteritis was greater in the DFZ (28/37 = 76%) than in the PR group (18/37 = 49%), but this result was not significant. At baseline, patients in the DFZ group had slightly lower BMD than those of the PR group, but differences were not significant.

Three patients in the PR group and 4 in the DFZ group did not complete the study. In the PR group the reasons were

Table 1. Baseline characteristics of the patients. Values are expressed as number of patients (%) or mean \pm SD.

	Prednisone, N = 37	Deflazacort, N = 37	p
Male	13 (35)	11 (30)	NS
Age, yr	74.6 \pm 1.1	70.7 \pm 1.3	0.02
Body mass index	14.7 \pm 2.1	18.1 \pm 2.4	NS
Fever > 38°C	18 (48)	21 (56)	NS
Weight loss > 10 %	26 (70)	29 (78)	NS
Headache	36 (97)	36 (97)	NS
Altered general status	35 (94)	32 (86)	NS
Polymyalgia rheumatica	22 (59)	9 (24)	0.046
Visual loss	2 (5)	9 (24)	NS
ESR, mm/h	70.2 \pm 4.5	80.1 \pm 5.5	NS
C = reactive protein, mg/l	61.8 \pm 10.5	68.8 \pm 9.4	NS
Results of temporal artery biopsy			
Positive/ total	18/37	28/37	NS
L2–L4 bone mineral density, g/cm ²	0.932 \pm 0.197	0.874 \pm 0.161	NS
Left hip bone mineral density	0.815 \pm 0.150	0.800 \pm 0.151	NS

gastrointestinal bleeding at month 1, diagnostic error (polyarteritis nodosa) at month 2, and personal reasons unassociated with a potential adverse event at month 4. In the DFZ group the reasons were: a cutaneous adverse event at month 2, 2 therapeutic failures at months 3 and 4, and one death due to cancer at month 7.

The mean duration of the initial full steroid dose was lower in the PR group compared with the DFZ group (25.3 \pm 3.9 vs 38.7 \pm 4.0 days; $p = 0.02$) (Table 2). The total dose for one year of PReq was not statistically different in the 2 groups. Neither were the number of GCA relapses in either group, which were evaluated for different periods: day 15 to month 1 (7 in the PR and 4 in DFZ groups), months 3 to 6 (3 and 2), and months 6 to 12 (3 and 3). There were also no significant differences between BMD changes in the 2 groups at month 12 (Figure 1) and the frequency of vertebral fractures (Figure 2). Bone biochemical changes were not significantly different between the 2 groups (Table 3).

DISCUSSION

Reducing bone mass loss during longterm glucocorticoid

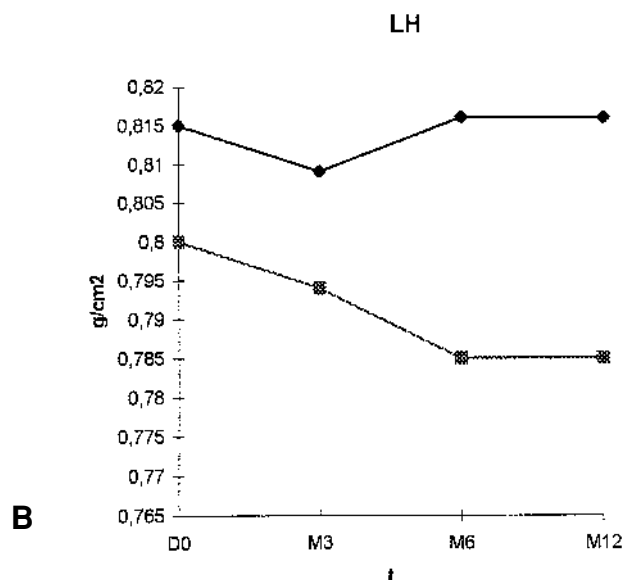
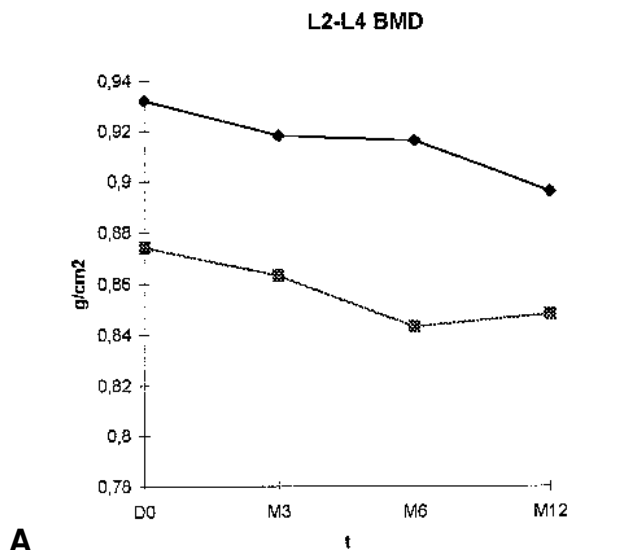
Table 2. Steroid therapy throughout the study. Values are expressed as numbers of patients or mean \pm SD.

Treatment	Prednisone, n = 37	Deflazacort, n = 37	p
Intravenous methylprednisolone at Day 1			
Yes	12	11	
No	25	23	NS
Duration of the initial full dose, days	25.3 \pm 4	38.7 \pm 4.1	0.02
Cumulative dose of PR eq received, g/kg/yr	0.11 \pm 0.04	0.12 \pm 0.005	NS

PR eq: prednisone equivalent.

L2-L4 BMD	D0	M3	M6	M12
PR	0,932	0,918	0,916	0,896
DFZ	0,874	0,863	0,843	0,848

LH	D0	M3	M6	M12
PR	0,815	0,809	0,816	0,816
DFZ	0,8	0,794	0,785	0,785



RH	D0	M3	M6	M12
PR	0,814	0,805	0,812	0,802
DFZ	0,792	0,785	0,774	0,773

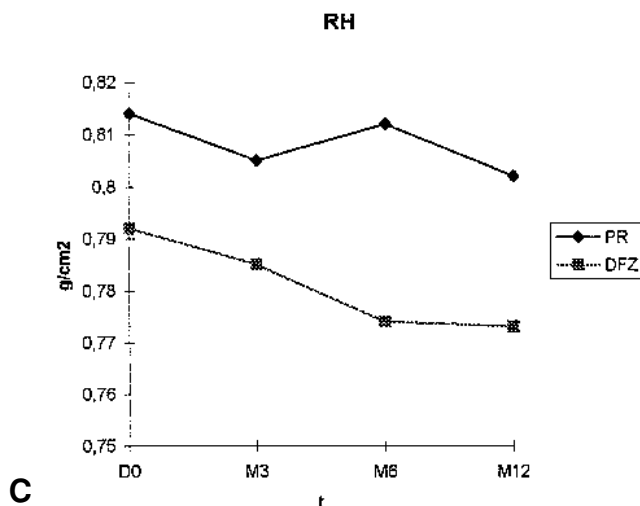


Figure 1. Bone mineral density (BMD) measurements in patients taking prednisone (PR) versus deflazacort (DFZ) at baseline (D0), 3 months (M3), M6, and M12 of (A) L2-L4, (B) left hip, and (C) right hip.

therapy appears to be the optimal goal to prevent osteoporosis and subsequent vertebral or hip fractures that substantially decrease the quality of life. A glucocorticoid capable of this goal, but with the same therapeutic efficiency as that of prednisone, would be a major advance in the management of glucocorticoid associated osteoporosis. Deflazacort's antiinflammatory capacity has been reported^{9,10}. Some preliminary studies have suggested that

DFZ results in less bone mass loss in comparison to PR when used during long periods of time. DFZ has a less deleterious effect on urinary excretion of calcium and hydroxyproline than prednisone in healthy volunteers and in patients with chronic inflammatory disease^{3,11,12}. These results have been confirmed by other studies in which DFZ is shown to reduce bone mass loss of patients requiring longterm glucocorticoids^{3,13,14}. DFZ was also shown to

Height	Baseline	M3	M6	M12
PR	159,86	159,73	159,78	159,1
DFZ	159,1	159,05	159,11	158,48

Meunier	Baseline	M12
PR	11,45	12,32
DFZ	10,97	12,14

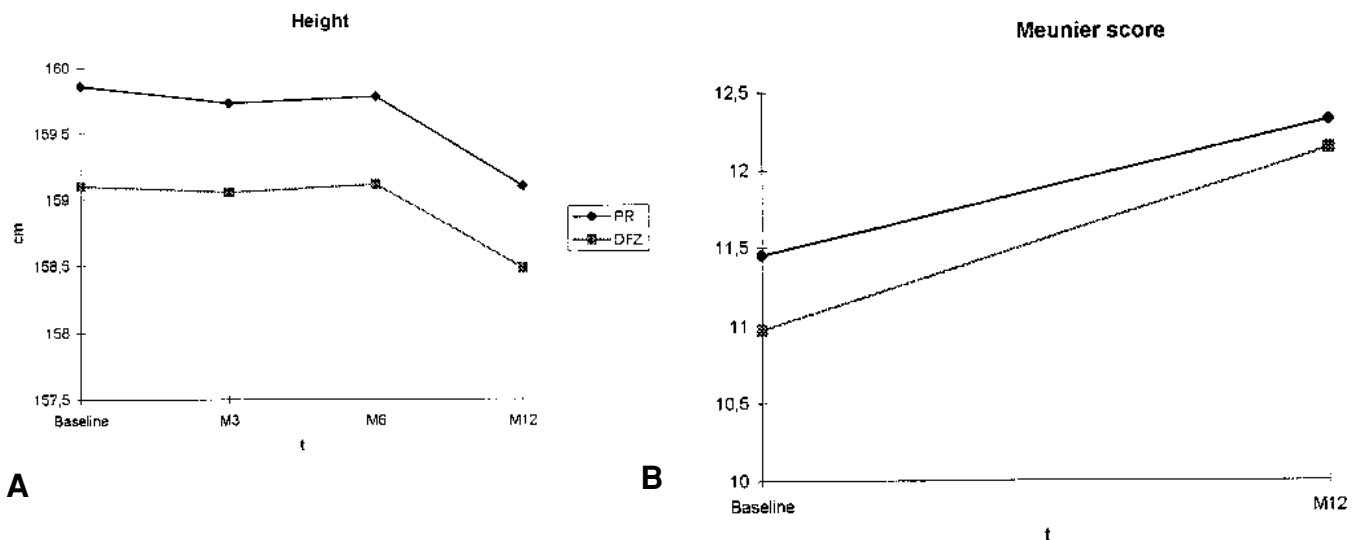


Figure 2. Number of spinal fractures, in patients taking prednisone (PR) versus deflazacort (DFZ), at baseline (D0), 3 months (M3), M6, and M12, as assessed by patient height (A) and Meunier score (B).

induce less trabecular bone loss than PR in a longterm histomorphometric comparative study¹⁵. However, one double blind study showed no difference in BMD in patients with polymyalgia rheumatica treated with DFZ or low dose PR¹⁶. To our knowledge, no double blind study has been conducted in patients with GCA, an older population at high risk of bone mass loss, receiving high dose and longterm steroid therapy. Our study was designed to test the efficacy and bone tolerance of DFZ in such patients. Unfortunately, the results suggest that this new promising compound has a generally equivalent effect on bone mass loss as prednisone.

The diagnosis of GCA was based on one of 4 clinical criteria and at least one biological inflammation marker. These criteria are not exactly the same as the ACR criteria, but if the 1990 ACR criteria were used, all the 74 patients would still have GCA¹⁷. The appropriate ratio for bioequiv-

alence between PR and DFZ is not well established to date. The initial estimation of potency ratio of DFZ to PR was between 1.28:1 and 1.0:1^{4,6}. It has been suggested that this potency ratio could depend upon the disease⁶. Although baseline characteristics showed that patients in the PR group were slightly older and sicker than those randomized to the DFZ group, the duration of the initial full dose of steroids was higher in the DFZ group (possibly explained by an underestimated antiinflammatory ratio of DFZ to PR). These results could have decreased the possible differential benefit of DFZ on bone mass loss. Our study was designed to detect a 50% BMD reduction between the 2 treatment groups, which is a large effect. It is possible that a smaller difference could have been missed because of the low power of this study. Bone mass evaluation during the study was assessed by bone densitometric analysis only. Histomorphometry by bone biopsy was not done¹⁸. Lastly, other

Table 3. Calcium/phosphate metabolism values measured at baseline and Month 12 in the prednisone (PR) versus deflazacort (DFZ) treatment group. Values are expressed as mean \pm SD.

	Baseline		Month 12	
	PR (n = 37)	DFZ (n = 37)	PR (n = 30)	DFZ (n = 29)
Serum calcium mmole/l	2.4 \pm 0.9	2.2 \pm 0.6	2.51 \pm 1.03	2.35 \pm 0.15
Serum phosphorus, mmole/l	1 \pm 0.2	1.1 \pm 0.1	1.17 \pm 0.15	1.10 \pm 0.14
Vitamin D, ng/ml	51.1 \pm 28.1	52.3 \pm 29.2	53.02 \pm 33.13	56.8 \pm 30.85
Urinary calcium, mmole/24 h	5.2 \pm 2.6	4.2 \pm 2.3	5.48 \pm 2.58	4.41 \pm 2.43
Urinary phosphorus, mmole/ 24 h	16.8 \pm 8.3	15.3 \pm 7.2	17.74 \pm 8.92	14.24 \pm 7.81
Alkaline phosphatases, IU/l	68.2 \pm 32.5	62.9 \pm 31.7	69.8 \pm 34.6	60.93 \pm 37.47
Hydroxyprolinuria, μ mol/ 24 h	152.2 \pm 65.2	143.3 \pm 72.6	154.71 \pm 68.1	140.56 \pm 14.87

biochemical markers of bone turnover such as N-telopeptide or osteocalcin were not included in our study.

The benefits of calcium and vitamin D supplements, replacement estrogen therapy, and more recently bisphosphonate administration have been proven in the prevention of corticosteroid induced osteoporosis¹⁹⁻²³. However, such preventive measures have their limitations. Bone loss depends on each patient's specific risk factors such as age, sex, hormonal status, baseline BMD, genetic predisposition, and dose and duration of glucocorticoid therapy. Thus preventive measures against BMD loss could only be based on individual evaluations.

The treatment of established osteoporosis is less effective than that of preventing bone loss, but several surveys have suggested that only a minority of patients receiving longterm glucocorticoid therapy are receiving adequate preventive treatment²⁴. Adding other longterm drugs to the glucocorticoid could easily be rejected by those patients who already take medications for other health problems. Calcium, vitamin D, and bisphosphonate need to be carefully monitored to avoid potential toxicity, and possible contraindications to estrogen therapy should be evaluated^{25,26}.

Our study reveals that deflazacort and prednisone appear to have near-equivalent deleterious effects on bone mass loss. Interestingly, after the 12 months, bone mass loss was relatively modest in both groups of these high risk older women taking high dose, longterm steroid therapy. This could be explained by the calcium and vitamin D supplements in both groups that have already been shown to help prevent bone mass loss^{27,28}. Despite our provocative findings, bone mineral density may be a relatively insensitive tool in evaluating changes in trabecular bone over a one year period. Therefore, a larger, well designed clinical trial of longer duration needs to be conducted.

APPENDIX

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