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Original Article

Prophylactic Use of Alfacalcidol in Corticosteroid-Induced Osteoporosis

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Abstract. One hundred and forty-five patients suffering from diseases requiring long-term treatment with high doses of corticosteroids (30 mg/day or greater of prednisolone) were recruited to the study. Patients had to be steroid naive on entry to the study (not more than 15 days of treatment with a corticosteroid within the previous 24 months). Patients were randomized to receive either 1 μg/day alfacalcidol or placebo capsules for 12 months. Bone mineral density (BMD) of the lumbar spine was assessed by dual-photon absorptiometry on entry and after 3, 6 and 12 months' treatment. Safety was monitored by the recording of all adverse events reported by patients and the regular screening of blood samples for hematology and serum biochemistry. Of the 145 patients, 74 were randomized to alfacalcidol and 71 to placebo. The treatment groups were well matched at baseline with no significant differences in demographic, clinical or biochemical parameters. The mean equivalent dose of prednisolone at baseline was 46.6 mg/day and 46.3 mg/day for the alfacalcidol and placebo group respectively. From the 145 patients randomized to treatment, 71 (38 who received alfacalcidol and 33 who received placebo) provided BMD data both at baseline and at 3, 6 and 12 months. The percentage change in BMD after 6 months' treatment was –2.11% in the alfacalcidol group and –4.00% in the placebo group ($p = 0.39$). After 12 months the percentage change in BMD was +0.39% (CI: –4.28 to 4.81) in the alfacalcidol group and –5.67% (CI: –8.13 to –3.21) in the placebo group, this difference (6.06%, CI: 0.88 to 11.24) being statistically significant ($p = 0.02$). An intention to treat analysis also showed a significant difference between the two treatment groups in alfacalcidol's favor (3.81%, $p = 0.01$; CI: 0.92 to 6.70). There was no significant difference between the two treatment groups in the corticosteroid dose at any time point during the study. Serum calcium was measured throughout and there were no significant differences between the two treatment groups at any visit. This study suggests that alfacalcidol can prevent corticosteroid-induced bone loss from the lumbar spine. Long-term use of alfacalcidol was not associated with any significant adverse effects in this diverse group of patients.

Keywords: Alfacalcidol; Glucocorticosteroid; Human; Osteoporosis; Vitamin D

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Introduction

Soon after the introduction of cortisone it became recognized that excess doses of exogenous corticosteroids were associated with the early development of osteoporotic fractures. The prevalence of vertebral fractures varies according to the doses used, but can be as high as 34% in patients with rheumatoid arthritis [1], although there is no increased fracture rate in this disease per se [2]. In asthmatics, where the doses of steroids used may be higher, one study has shown a vertebral and rib fracture rate of 42% [3]. Vertebrae with a high trabecular bone content seem particularly prone to corticosteroid-induced effects. It has been shown that vertebral trabecular bone density may be reduced by as much as 40% in patients receiving moderate dose of corticosteroids [4]. Bone loss associated with the use of

corticosteroids starts almost immediately after treatment has been initiated. Fractures have been reported to occur with as little as 1 month's treatment [5].

The rationale for using vitamin D or its metabolites to prevent corticosteroid-induced osteoporosis is mainly to reverse the decrease in intestinal calcium absorption by antagonizing the effects of corticosteroids on gut cells and possibly to exert a direct stimulatory effect on osteoblasts.

At present there is some evidence that alfacalcidol (1α-(OH)-D_3) may arrest bone loss in patients treated with corticosteroids [6,7]. However, these studies investigated patients who had already been receiving corticosteroids for some considerable time before entering the study; thus as it has been previously shown that the corticosteroid-induced bone loss is most marked during the first few months of treatment, these studies were not strictly of a preventive nature. For this reason it seemed reasonable to conduct a prospective study in patients suffering from diseases that required high doses of corticosteroid treatment and who were expected to need long-term treatment but had not received corticosteroid treatment in the 2 years prior to entering the study. The aim of this study was to establish whether alfacalcidol could prevent corticosteroid-induced bone loss (as measured by bone mineral density) over a period of 12 months when compared with placebo.

Patients and Methods

This was a multicenter, prospective, randomized, double-masked, placebo-controlled, parallel group study to determine the efficacy of alfacalcidol 1 μg/day in the prevention of corticosteroid-induced bone loss in patients receiving high doses of corticosteroids. Regulatory permission was obtained from the two countries involved and approval from the appropriate ethics committees was obtained for all centers. All patients gave informed consent. The study was performed between 1987 and 1989. Unfortunately frozen samples for measurement of bone markers were lost, due to prolonged storage. The study was conducted according to the Declaration of Helsinki (Venice 1983).

Patients

The inclusion criteria required that patients (aged 21–80 years) had a disease requiring treatment with high doses of corticosteroids (minimum starting dose of 30 μg/day of prednisolone or the equivalent dose of a methylprednisolone derivative [8]), and that this treatment be expected to continue for at least 6 months with the dose after 6 months being not less than 7.5 mg/day. The equivalent prednisolone dose was calculated for all randomized patients at each visit and calculated separately for all patients who provided bone mineral density (BMD) data. Patients were excluded if they had received more than 15 days' treatment with a corticosteroid within the previous 24 months, or if they were suffering from conditions known to interfere with calcium and phosphate metabolism. Patients with fractures that could be due to disorders of calcium or phosphate metabolism were also excluded. A total of 145 patients were recruited from 25 centers in Belgium and France. Seventy-four were randomized to alfacalcidol (1 μg/day) and 71 to placebo.

Study Medication

Patients were randomized to receive treatment with either alfacalcidol (Onc. Alpha®) 1 μg/day or placebo capsules for 12 months, together with a calcium supplement (Effical; daily dose 405 mg elemental calcium) to insure that the daily calcium intake in these patients was sufficient. Randomization was according to a computer-generated random numbers table. Study medication was randomized in balanced blocks of 4. If hypercalcemia occurred then study medication and calcium supplements were stopped until serum calcium levels (corrected for albumin) returned to within the normal range. The dose of study medication could then be decreased by 0.25 μg/day decrements until the patient was stabilized on a non-hypercalcemic dose.

Concomitant Medication

Patients were permitted to have intravenous corticosteroids during the study provided they continued with their oral corticosteroid treatment. Treatments for indigestion and mucosal protection were allowed with the exception of Cortalugel® (prednisolone sodium sulfobenzoate + aluminium phosphate gel). Other concomitant treatments were permitted with the exception of drugs which interfered with either calcium or phosphate metabolism (e.g., thiazides).

Protocol

Patients attended the clinic on eight occasions during the 12 months of the study (at entry, monthly for 4 months, then after 6, 9 and 12 months). At the first visit demographic details were recorded. Blood samples were taken at each visit with analysis of serum calcium, phosphate and albumin performed at every visit and serum biochemistry and hematology performed at baseline and after 6 and 12 months' treatment. BMD of the lumbar spine was assessed by dual-photon absorptiometry on entry to the study and after 3, 6 and 12 months' treatment. Evaluation of bone pain using a 4-point scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe) was performed at all visits. Adverse events were recorded at all treatment visits. The protocol included neither BMD of the femoral neck nor radiography of the lumbar spine.

Statistical Analysis

The primary efficacy criterion was the percentage bone loss (or gain), at visit 6 (6 months) and visit 8 (12 months) as compared with baseline in the two groups. The baseline value was considered as 100% BMD for each patient. The sample size was based on a favorable response being defined as an estimated decrease in BMD of 1% in the alfacalcidol treated group and not less than 4% in the placebo group, assuming a standard deviation of the mean differences between the two treatment groups of 5%. It was therefore calculated that 88 patients (i.e., 44 per treatment group) would allow the detection of a 3% difference between the two treatment groups with a power of 80% and a significance level (two-tailed) of 5%. Differences between the treatment groups in terms of percentage change in BMD from baseline were analyzed using analysis of variance techniques. An intention-to-treat analysis on BMD was performed on all patients enrolled. The last available BMD measurement is carried forward, and missing baseline values are counted as 'no change'. The proportion of patients reporting bone pain as mild, moderate or severe was analyzed using the Wilcoxon test.

Results

Of the 145 patients who were randomized to treatment (74 alfacalcidol, 71 placebo), 38 were withdrawn from the study (16 from the alfacalcidol group and 22 from the placebo group). The most common reason for withdrawal was patients not fulfilling inclusion criteria (8 and 9 patients in the alfacalcidol and placebo groups, respectively). Six patients died during the study (1 in the alfacalcidol group and 5 in the placebo group). There were only 2 patients (both randomized to placebo) who failed to meet the primary inclusion criterion of having a starting corticosteroid dose of at least 30 mg/day, and in each of these cases the patient was receiving at least 20 mg/day The two treatment groups were well matched for demographic details (Table 1); there was a higher percentage of females in the placebo group (66.2% in the placebo group and 56.8% in the alfacalcidol group) but this was not statistically significant. The diseases necessitating treatment with systemic corticosteroid are shown in Table 2.

Table 1. Patient characteristics at baseline

Characteristic	Alfacalcidol (n=74)	Placebo (n=71)
Age (years)[a]	57.1±16.2	57.3±14.0
Sex		
Male (%)	32 (43.2)	24 (33.8)
Female (%)	42 (56.8)	47 (66.2)
Height (cm)[a]	164.8±9.8	164.7±7.3
Weight (kg)[a]	64.8±12.7	67.5±13.3
Prednisolone equivalent dose (mg/day)[a]	46.6±16.3	46.3±18.1
Bone mineral density (g/cm^2)[a]	0.90±0.23	0.92±0.27

Data shown are the mean ± SD.

Of the 107 patients who completed the study, 71 provided paired data at baseline and 3, 6 and 12 months for lumbar BMD. The reasons for the missing BMD data are that some patients did not have a baseline BMD or one of the later measurements performed. The percentage change in BMD at 3, 6 and 12 months is shown in Fig. 1 together with the number of patients providing data at each time point. The percentage change in BMD after 6 months' treatment was –2.11% (CI: –4.28 to 0.06) in the alfacalcidol group compared with –4.00% in the placebo group (CI: –7.70 to 0.31; $p = 0.39$). The percentage change in BMD after 12 months' treatment was 0.39% (CI: –4.27 to 4.81) in the alfacalcidol group compared with –5.67% (CI: –8.13 to –3.21) in the placebo group. The difference in the percentage change in BMD between the two groups was 6.06% (CI: 0.88 to 11.24), which was statistically significant ($p = 0.02$). The intention-to-treat analysis also showed a significant difference between the two treatment groups in alfacalcidol's favor (3.81%; $p = 0.01$; CI: 0.92 to 6.70). Analysis of variance showed that neither age nor sex had a significant effect on the percentage change in BMD.

Figure 2 shows the equivalent prednisolone dose at baseline and after 3, 6 and 12 months' treatment for patients providing BMD data. There was no significant difference in equivalent prednisolone dosages seen between the two treatment groups at any time point.

Table 2. Comparability of treatment groups at visit 1: conditions necessitating treatment with corticosteroids

Primary condition	Alfacalcidol (n=74)	Placebo (n=71)
Cardiac transplant	8 (10.8)	10 (14.1)
Dermatomyositis	3 (4.1)	1 (1.4)
Edematous scleroderma	1 (1.4)	0
Exophthalmic goitre	1 (1.4)	0
Fasciitis	0	1 (1.4)
Pemphigoid	3 (4.1)	3 (4.2)
Polyarteritis nodosa	1 (1.4)	3 (4.2)
Polymyositis	2 (2.7)	2 (2.8)
Polymyalgia rheumatica	6 (8.1)	7 (9.9)
Pretibial myxedema	0	1 (1.4)
Primary Sjögren syndrome	1 (1.4)	1 (1.4)
Relapsing polychondritis	1 (1.4)	0
Rheumatoid arthritis	6 (8.1)	7 (9.9)
Severe inflammatory syndrome	0	1 (1.4)
Sharp's syndrome with myositis	0	1 (1.4)
Still's disease of the adult	1 (1.4)	0
Systemic granulomatosis	1 (1.4)	0
Systemic lupus erythematosus	8 (10.8)	7 (9.9)
Systemic sclerosis	1 (1.4)	1 (1.4)
T cell lymphoma	1 (1.4)	0
Temporal arteritis	7 (9.5)	5 (7.0)
Unclassified polyarthritis	6 (8.1)	3 (4.2)
Vasculitis	1 (1.4)	1 (1.4)
Unknown	15 (20.3)	16 (22.5)

Values are n (%).

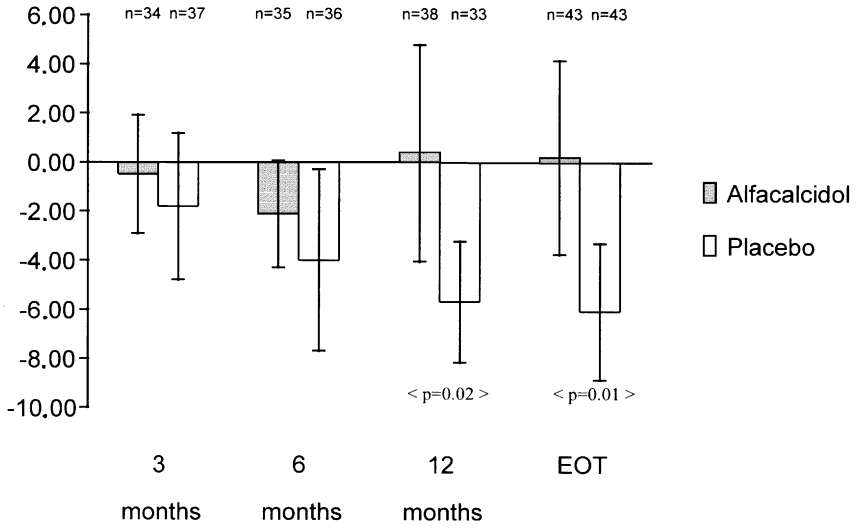

Fig. 1. Percentage change in bone mineral content over the period of the study. Upper and lower confidence limits are indicated by error bars. EOT, end of trial.

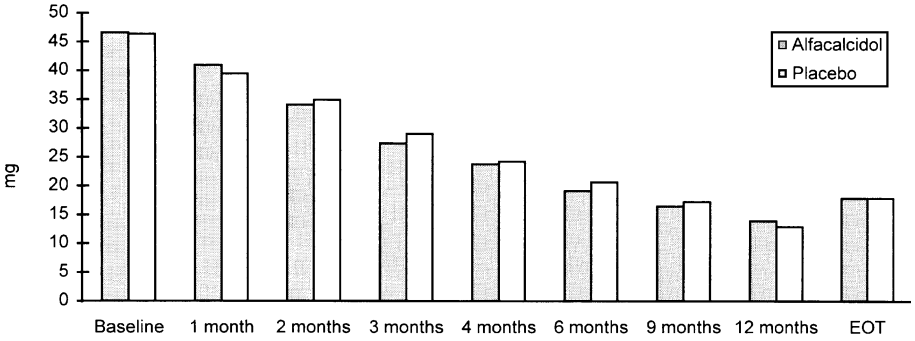

Fig. 2. Equivalent prednisolone dose over the period of the trial. EOT, end of trial.

There were no significant differences in either the incidence or the severity of bone pain reported by the patients at any visit.

Significant increases in serum total calcium from baseline were seen in both groups during the study with the maximum increase after 3 months' treatment. There was a significant difference between the two treatment groups after 1 month's treatment. However, the total number of patients with total serum calcium above 2.6 mmol/l and 2.8 mmol/l was low (Table 3) and no significant differences were seen between the two groups. Only 5 of the 74 patients who received alfacalcidol 1 μg/day had to have their dose adjusted by the doctor due to hypercalcemia.

Table 3. Serum calcium levels above 2.6 mmol/l and 2.8 mmol/l by month

	Alfacalcidol (*n*=74)		Placebo (*n*=71)	
	>2.6 mmol/l	>2.8 mmol/l	>2.6 mmol/l	>2.8 mmol/l
Baseline	0	0	0	0
1 month	3	0	1	0
2 months	3	1	1	0
3 months	6	0	3	3
4 months	0	0	0	0
6 months	1	0	0	0
9 months	0	0	0	0
12 months	2	0	0	0

Treatment was well tolerated in both groups, with 23 patients reporting 51 adverse events in the alfacalcidol group compared with 25 patients reporting 62 adverse events in the placebo group. The two most common types of adverse events that were reported were musculoskeletal and gastrointestinal disorders. This was to be expected as one of the most common conditions necessitating treatment with high doses of corticosteroids were musculoskeletal disorders and high doses of systemic corticosteroids are known to have gastrointestinal side-effects. There were 6 deaths during the study: 1 in the alfacalcidol group and 5 in the placebo group. These were mostly due to the patients' underlying diseases and none of the deaths was associated with the study treatment.

Discussion

This is the first prospective double-masked, placebo-controlled study in a sufficiently large randomized population to investigate whether alfacalcidol (and calcitriol) has a role to play in the prevention of corticosteroid-induced osteoporosis. Previous studies

with alfacalcidol have suffered from low numbers of patients, low doses of corticosteroids and the duration of treatment being too short [6,7]. Also, previous studies have invariably included patients who had been receiving corticosteroids for varying periods of time prior to entering the study, and as there is strong evidence to suggest that corticosteroid-induced bone loss is most marked during the first 6–12 months of treatment, these studies were not really of a preventive nature [6,7]. The present study insured that patients were corticosteroid 'naive' by excluding those who had received more than 15 days' treatment with a corticosteroid in the previous 24 months and also those receiving intermittent long-acting steroid treatment (e.g., subcutaneous injection). However, some of the patients included suffered from rheumatoid arthritis, which is a disabling disease and a cause of osteoporosis [9].

The primary efficacy criterion in this study was the comparison of the percentage change from baseline in BMD. After 6 months' treatment there was a reduction in BMD for both groups, showing that alfacalcidol 1 μg per day seems able to prevent bone loss only when the prednisolone dose is below 30–20 mg per day. After 12 months' treatment with alfacalcidol there was no significant change from baseline while in the placebo-treated group there was a further reduction in BMD.

The results from the present study are in agreement with previous studies in both animal models and clinical studies. In ovariectomized and corticosteroid-treated rats, alfacalcidol had a strong preventive and curative effect on bone mass and mechanical strength [10,11]. Sambrook et al. [12] investigated the preventive effect on bone loss of calcitonin, calcitriol and calcium as compared with calcitriol plus calcium or calcium alone in patients receiving 25 mg prednisolone per day as a starting dose tapered to a mean daily dose of 13.5 mg. The patients were treated for 1 year and followed for a second year without treatment. Calcitriol 0.5–1 μg per day with or without calcitonin prevented more bone loss from the lumbar spine than did calcium alone. Bone loss at the femoral neck and distal radius was not significantly affected by any treatment. Calcitriol did not completely prevent bone loss but significantly reduced it. When comparing this result with that of Adachi et al. [13], who obtained an increase in BMD using intermittent etidronate, it should be noted that our study and the study by Sambrook et al. are both preventive studies, where treatment is started before bone loss starts, whereas the etidronate study was an intervention study, starting at a time when bone had already been lost. The patients in the etidronate study should therefore be expected to gain bone mass in order to compensate for the loss, in contrast to the prevention studies where a zero change or even a minor decrease may be considered as a positive result.

Excluding the 18 transplanted patients in this study did not essentially change the result. This was to be expected since a previous study [14] of 54 cardiac-transplanted patients receiving cyclosporine, prednisolone, 25-hydroxyvitamin D and calcium for more than 1 year showed prevention of lumbar spine bone loss.

The rapid initial bone loss seen in the present study is also known from in vivo studies in animals [15], in which an initial increase in osteoclasts and resorption surfaces was seen with a subsequent fall-off to a steady state over the course of 2–4 months [16]. From the literature it seems that the lowest mean dose that has been shown to induce significant bone loss is 6.3 mg/day [17], although as little as 5 mg/day can have minor effects on bone mass [18], induce radiographic changes [19] and lead to fractures [20]. Treatment with 5–10 mg of prednisolone per day has been shown to be associated with a decreased osteoblastic response [21–22] and it has also been found that the rate of bone loss over 12 months may be increased in those patients taking higher doses of corticosteroids [23]. Recently there has been interest in the effects of inhaled corticosteroids on bone as increasingly higher doses of inhaled corticoteroids are used in the management of moderate to severe asthma. Osteocalcin is a bone-specific γ-carboxyglutamic-acid-containing protein which is predominantly synthesized by osteoblasts, and serum osteocalcin level appears to correlate with osteoblastic function and bone formation. One study [24] has demonstrated that the decreased osteocalcin level following initiation of inhaled budesonide can be reversed by treatment with calcitriol.

The major concern about using vitamin D metabolites as long-term treatment is their potential to cause hypercalcemia. Patients who were randomized in this study to alfacalcidol started on a dose of 1 μg/day. The protocol allowed for the dose to be reduced to either 0.75 μg/day, 0.5 μg/day or 0.25 μg/day if serum calcium levels rose above the upper limit of normal. Only 5 of the 74 patients treated with alfacalcidol had to have their dose reduced by the doctor, and only a few patients had a total serum calcium above 2.6 mmol/l, with no significant difference between the two groups. Also, there were no significant differences between the two treatment groups in serum calcium levels throughout the study. Therefore, contrary to previous results this study shows that for the majority of patients a dose of 1 μg/day of alfacalcidol is safe to use for periods up to 1 year in this patient population.

Although BMD data were not available for all patients, the data available showed that alfacalcidol did have a protective effect against bone loss when compared with placebo. The current study adds further support to the use of an active vitamin D analog such as calcitriol or alfacalcidol for the prevention of corticosteroid-induced osteoporosis. At present, the other options available for the treatment of steroid-induced osteoporosis include hormone replacement therapy with estrogen in women and testosterone in men, bisphosphonates, calcitonin and fluoride therapy. The hormone deficiency that can occur during glucocorticoid therapy can be corrected by hormone replacement therapy [25–27]. However, due to recurrent bleeding in postmenopausal women and fear of cancer compliance may be

low. Bisphosphonates appear to be effective in maintaining or increasing BMD compared with untreated conditions [13]. Also calcitonin appears to be effective for the prevention of corticosteroid-induced osteoporosis [28].

Few data are available on fluoride but a study by Greenwald et al. [29] suggests that fluoride 20–30 mg/day may be effective.

Our study suggests that alfacalcidol provides a reasonable, safe and effective option for the prevention of corticosteroid-induced bone loss from the lumbar spine provided that serum calcium is monitored regularly.

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