Cyclical etidronate increases bone density in the spine and hip of postmenopausal women receiving long term corticosteroid treatment. A double blind, randomised placebo controlled study

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Abstract

Objective—To study the effect of cyclic etidronate in secondary prevention of corticosteroid induced osteoporosis.

Methods—A double blind, randomised placebo controlled study comparing cyclic etidronate and placebo during two years in 37 postmenopausal women receiving long term corticosteroid treatment, mainly for polymyalgia rheumatica (40% of the patients) and rheumatoid arthritis (30%). Bone density was measured in the lumbar spine, femoral neck, and femoral trochanter.

Results—After two years of treatment there was a significant difference between the groups in mean per cent change from baseline in bone density in the spine in favour of etidronate ($p=0.003$). The estimated treatment difference (mean (SD)) was 9.3 (2.1)%. Etidronate increased bone density in the spine (4.9 (2.1)%, $p<0.05$) whereas the placebo group lost bone (−2.4 (1.6)%). At the femoral neck there was an estimated difference of 5.3 (2.6)% between the groups (etidronate: 3.6 (1.4)%, $p<0.05$, placebo: −2.4 (2.1)%). The estimated difference at the trochanter was 8.2 (3.0) (etidronate: 9.0 (1.5)%, $p<0.0001$, placebo: 0.5 (2.3)%). No significant bone loss occurred in the hip in placebo treated patients.

Conclusions—Cyclic etidronate is an effective treatment for postmenopausal women receiving corticosteroid treatment and is well tolerated.

(Ann Rheum Dis 1998;57:724-727)

Continuous oral corticosteroids are extensively used in the general population, especially for rheumatic conditions.¹ Most of these patients do not take prophylaxis.¹ There is an increase in fractures in corticosteroid treated patients²⁻⁶ and the risk of hip fracture is doubled.⁷ Bone loss is most rapid during the first year of treatment and continues in the hip with long term corticosteroid treatment.⁸⁻⁹ Studies on corticosteroid induced osteoporosis (CIOP) can be arbitrarily divided in studies on prevention (started within three months of corticosteroid treatment) or treatment (started after three months of corticosteroid treatment). Double blind placebo controlled trials on primary prevention of CIOP indicate a protective effect of

calcitriol⁹ and etidronate,¹⁰ but not of calcium and vitamin D.¹¹ Double blind studies on the secondary prevention are scarce¹²⁻¹⁴ and indicate a significant effect of bisphosphonates compared with placebo¹² but not of vitamin D.¹³⁻¹⁴ Results on alendronate in CIOP show similar results.¹⁵ In a number of preliminary, open studies, increases in bone density were found with inhibitors of bone resorption, such as bisphosphonates, in the spine¹⁶⁻²⁰ and hip.¹⁶ However, no double blind studies are available on the effect of secondary prevention on bone density in the hip. Postmenopausal women were studied as they are more at risk for developing CIOP with fractures.¹⁰

We therefore studied, in a double blind placebo controlled study, the effect of cyclic etidronate and calcium on bone in the spine and hip of postmenopausal women receiving long term corticosteroid treatment mainly for rheumatological conditions.

Methods

In total, 37 patients receiving long term corticosteroid treatment were entered in the study. Figure 1 shows the trial profile. The study was approved by the local ethical committee. Patients were consecutively recruited from two university centres when they consented to participate in the study (12 placebo and 12 etidronate patients in centre 1 and 7 placebo and 6 etidronate patients in centre 2). They were randomly assigned (in blocks of two within each centre) to treatment with cyclic etidronate (400 mg/day in the morning, two hours from meals) ($n=18$) or placebo ($n=19$) for two weeks, followed by calcium 500 mg/day in the evening for 11 weeks. This three month cycle was repeated for two years. Etidronate was given in tablets and the placebo tablets were similar in taste and appearance. The code was located in the sponsor's office and was only broken after full statistical analysis. Blinding was successful among participants, doctors, data managers, and statisticians. No patients were taking hormonal replacement therapy. All patients were postmenopausal and were receiving corticosteroid equivalent to 5 to 20 mg prednisolone per day for more than three months. The duration of corticosteroid treatment before the start of the study was extremely skewed and was similar between the two groups (median 31 months (range 3-108) in the placebo treated patients and 45 months (range 3-503 months) in the

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Accepted for publication
3 September 1998

Figure 1 Flow diagram of the trial, with numbers of patients.

etidronate treated patients, $p=0.064$ using Wilcoxon-Mann-Whitney test). The indications for corticosteroids were rheumatoid arthritis (placebo: $n=9$, etidronate: $n=3$), polymyalgia rheumatica (placebo: $n=5$, etidronate: $n=10$), osteoarthritis (placebo: $n=1$), chronic bronchitis (placebo: $n=3$, etidronate: $n=2$), inflammatory gastrointestinal diseases without osteomalacia (etidronate: $n=2$), idiopathic eosinophilia (placebo: $n=1$) and sarcoidosis (etidronate: $n=1$). Patients were examined by a rheumatologist every three months for adaptation of the dose of corticosteroid, according to the common clinical practice. Bone density was measured by dual energy x ray based absorptiometry using DPX-L (Lunar Inc) or QDR 2000 (Hologic Inc). All patients were followed

up on the same device during the study. Bone density was measured at baseline and every six months in the lumbar spine in vertebrae L2 to L4, in the left femoral neck and in the left femoral trochanter according to the manufacturer's instructions. Bone density was not evaluated in the Ward's triangle as the procedure to locate the Ward's triangle is different between the devices. Precision was $<1\%$ in the spine and $<2.5\%$ in the hip for both devices. All data were centrally collected and blindly controlled for inadequate delineation and other errors. For comparison at baseline, bone density was expressed in T scores, one T score is one standard deviation difference from the mean of healthy young women, as provided by the manufacturer and in Z scores, one Z score is one standard deviation difference from the mean of age and sex matched healthy women, as provided by the manufacturer. Manufacturer provided normal values for Z and T scores in the spine were similar for both devices compared with a local control population. In some patients Z scores (one in spine and two in the femoral neck) or T scores (one in spine and four in the femoral neck) were not available from the DEXA device at baseline. During follow up, data were expressed in per cent change from baseline, based on bone density in g/cm^2 .

Clinical symptomatic fractures that were confirmed by qualitative analysis of the radiographs of the thoracic and lumbar spine (that were taken systematically at baseline and after one and two years) were recorded. Occurrence of all adverse events was recorded regardless of relation to study drug. Daily corticosteroid intake during the study was calculated as the cumulative dose devised by the number of days of intake.

STATISTICS

Descriptive statistics were used to compare the groups at baseline with respect to patient characteristics and other baseline characteristics (age, years since menopause, daily corticosteroid use, indications for corticosteroids, bone density of spine and hip, serum and urinary bone markers). The primary analysis was a comparison between the treatment groups by an analysis of covariance of the spinal bone density per cent change from baseline at two years for the intent to treat population.²¹ The mean corticosteroid dose over the two years was used as the covariate adjustment. A term for study centre was also fitted in the ANCOVA model, correcting for the two centres and the use of different devices (DPX-L and QDR 2000). Similar analyses were performed for hip bone density. To aid analysis, within group analyses of per cent changes from baseline were performed.

Results

Table 1 shows the baseline clinical data, bone density, and biochemical data. Mean age, years since menopause, daily corticosteroid dose, and bone density (expressed in Z and T scores) were similar in both treatment groups. Z scores were different from zero in the spine and hip

Table 1 Baseline clinical and bone density data (mean (SD)). The numbers of patients for each variable are indicated

Variable	Placebo	Etidronate
Patients (n)	19	18
Age (y)	65 (10) (19)	63 (6) (18)
Years since menopause (y)	19 (11) (19)	13 (9) (18)
Weight (kg)	69 (11) (19)	63 (7) (18)
Height (cm)	160 (6) (19)	157 (6) (18)
Mean prednisolone dose (mg/day)	6.35 (3.58) (17)	6.27 (2.99) (18)
Z score		
Lumbar spine	-0.87 (0.89) (18)	-1.10 (1.02) (18)
Femoral neck	-0.91 (0.75) (17)	-0.98 (0.74) (18)
T score		
Lumbar Spine	-2.47 (0.60) (18)	-2.82 (1.12) (17)
Femoral Neck	-2.11 (1.22) (15)	-2.14 (0.86) (17)

Figure 2 Per cent changes (compared with baseline, mean (SEM)) bone density in the lumbar spine, femoral neck, and femoral trochanter in the etidronate (closed circles) and placebo (open circles) treated groups. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$ compared with baseline.

($p < 0.05$ in both treatment groups). Of the initial 37 patients, 11 patients were withdrawn for the following reasons: adverse events (anaphylactic shock (placebo: $n=1$), shoulder fracture (placebo: $n=1$)), protocol violation (placebo: $n=2$, etidronate: $n=2$), non-compliance (placebo: $n=2$), personal reasons (etidronate: $n=2$) and death because of a ruptured aortic aneurysm after a long history of arteritis (etidronate: $n=1$). The mean daily corticosteroid intake (mean (SD)) before the study was 6.4 (0.9) mg/day in the placebo group and 6.3 (0.7) mg/day in the etidronate group (no differences between the groups). During the study the mean daily corticosteroid intake was not significantly different between the treatment groups (5.5 (0.7) mg/day in the etidronate group and 4.7 (0.8) mg/day in the placebo group).

After two years of treatment there was a significant difference between the groups in mean per cent change from baseline in spinal bone density favour of etidronate ($p=0.003$). The estimated treatment difference (mean (SD)), adjusted for corticosteroid dose and study centre was 9.3 (2.1)%. The etidronate group increased bone density (4.9 (2.1)%, $p < 0.05$) and the placebo group lost bone (-2.4 (1.6)%, not significant) (fig 2). At the femoral neck there was an estimated difference of 5.3 (2.6)% (not significant) between the groups (etidronate: 3.6 (1.4)%, $p < 0.05$, placebo: -2.4 (2.1), not significant). The estimated difference at the trochanter was 8.2 (3.0) (not significant) (etidronate: 9.0 (1.5), $p < 0.0001$, placebo: 0.5 (2.3)%, not significant). There was no consistent relation at the different sites between corticosteroid dose and per cent change in bone density.

Clinical symptomatic and radiological confirmed fractures occurred in five (28%) patients receiving placebo (hip: $n=2$, shoulder: $n=1$, foot: $n=1$, vertebra T5: $n=1$) and in one (6%) patient on etidronate (hip: $n=1$). None of the fractures occurred as a result of excess force. In the one patient that developed acute back pain and in whom radiography of the spine was therefore performed, the 5th thoracic vertebra was decreased by >50% compared with the 6th thoracic vertebra. The relative risk for fracture was not significant for etidronate compared with placebo (0.21, 95% confidence intervals: 0.03, 1.64).

The treatment was well tolerated. Gastrointestinal side effects were reported by four patients receiving placebo (diarrhoea: $n=2$,

nausea: $n=1$, vomiting: $n=1$) and three receiving etidronate (nausea: $n=2$, vomiting: $n=1$). No differences were found in side effects reported for other organ systems (data not shown).

Discussion

This is the first double blind placebo controlled study on treatment of CIOP in both the spine and the hip. The effect of cyclic etidronate was studied in postmenopausal women receiving long term corticosteroid treatment who had already lost bone, as reflected by a low T score and low Z score.⁹ The low Z scores reflect the additional effect of corticosteroid and/or disease activity on bone loss in postmenopausal women. In these patients, bone density was significantly different in the spine in favour of etidronate and the same trends were found in the hip. The changes in bone density in the spine were not influenced by fracture healing, as no clinical symptomatic fractures occurred in the lumbar spine and no manifest qualitative radiological signs of fracture were found on radiographs of the spine that were performed at baseline and after one and two years. A positive effect on the hip is an important clinical finding, as the risk of hip fractures is doubled in patients treated with corticosteroids.⁷ The finding of positive effects on both femoral neck and the trochanteric region further emphasises the potential of etidronate to reduce corticosteroid induced bone loss in both cortical and trabecular bone. Also in primary prevention of CIOP etidronate inhibited bone loss in the spine and the trochanter, and this was accompanied by a significant reduction of new vertebral fractures.¹⁰ In this study, the effect of etidronate on total fracture was not significant, but this study was not designed to allow analysis of fracture rate. These results on BMD are in accordance with open studies of bisphosphonates, such as etidronate alone^{16 17 19 21} or combined with calcium and vitamin D,²³ showing an increase of bone density in the spine^{16 17 19 22} and hip.¹⁶ Pamidronate increased bone density in the spine.¹² The effects on cortical bone are contradictory.^{18 20} The increase in bone density in the spine and trochanter after etidronate was more pronounced than in primary prevention of CIOP.¹⁰ This can be attributable to the much lower dose of corticosteroids in this study (6 mg of prednisolone/day) as compared with the study of Adachi *et al* (>20 mg of prednisolone/day).¹⁷ Furthermore, bone loss is less pronounced during long term corticosteroid

treatment as compared with immediately after the start of corticosteroids⁸ and therefore possibly more modifiable as shown in this study.

Therefore, and because most patients receiving long term corticosteroid treatment do not take prophylaxis,¹ the results of treatment with etidronate are encouraging as etidronate was not only able to stop bone loss but also to increase significantly bone density in the spine and hip. The increase in bone density was similar as in postmenopausal women without corticosteroid treatment.²⁴ The patients taking calcium alone did not significantly lose bone, except after 12 months in the spine, but not in the femoral neck or trochanter. Therefore, it can be assumed that long term low dose corticosteroids in postmenopausal women is not accompanied by bone loss in the femur when calcium supplements are prescribed. However, in these patients no bone gain was achieved with calcium alone, in contrast with the effect of etidronate, which increased significantly bone density in the spine, femoral neck, and trochanter.

Placebo treated patients, taking 500 mg calcium per day in the evening, did not significantly lose bone, except during the first 12 months in the spine. Other studies have shown that calcium supplements given in the evening can diminish bone turnover in patients treated with corticosteroids,²³ and can decrease bone loss in the forearm¹³ but not in the hip.¹⁶ The results in the spine are conflicting.^{16 17 26} Although the number of patients was small, the results of this study indicate that calcium supplements alone are not accompanied by bone loss in postmenopausal women taking low dose corticosteroids.

Several aspects of the study require further discussion. Firstly, the drop out rate of 29.7% may seem high, but this figure was similar to other published studies on CIOP prevention given its duration.^{9-11 13} Secondly, the small sample size can raise concerns over the statistical power. Retrospective power calculations showed the study to have 90% power to detect 7-8% treatment differences at two years for the different skeletal sites. Therefore, the study was powered to detect clinically meaningful effects on BMD. Thirdly, biochemical parameters that are now available to monitor bone formation and resorption, such as N-telopeptides and deoxypyridinoline, were not available for this study. Fourthly, there were more patients with rheumatoid arthritis in the placebo group. Patients with rheumatoid arthritis lose bone because of the disease process itself.²⁷ However, at the dose of corticosteroids used in this study (6 mg of prednisolone/day), patients with rheumatoid arthritis are not expected to have an accelerated bone loss during corticosteroid treatment compared with patients taking corticosteroids for other diseases.²⁷

We conclude that, as compared with placebo, treatment with cyclic etidronate increases bone density in secondary prevention of CIOP in patients predominantly with rheumatic conditions and was well tolerated.

We thank S Pack and I Barton, Biostatistics and Medical Surveillance, Procter and Gamble Pharmaceuticals, UK, for statistical assistance and analysis.

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