ASTHMA

Five year study of etidronate and/or calcium as prevention and treatment for osteoporosis and fractures in patients with asthma receiving long term oral and/or inhaled glucocorticoids

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Background: Glucocorticoids are associated with a reduction in bone density and an increased risk of fracture. Concurrent treatment with bisphosphonates reduces bone loss and may prevent fractures. A randomised study was performed to determine whether treatment with cyclical etidronate and/or calcium for 5 years prevents fractures or reverses/reduces bone loss in patients receiving glucocorticoid treatment for asthma.

Methods: A multicentre, randomised, parallel group comparison of etidronate alone, calcium alone, etidronate + calcium, and no treatment, with stratification according to level of glucocorticoid exposure was carried out in 39 chest clinics in the UK. Three hundred and forty nine postmenopausal female and male outpatients with asthma aged 50–70 years were randomised. The main outcome measures were fractures and changes in bone mineral density (BMD).

Results: Overall, 8% of the patients experienced symptomatic fractures and 17.5% developed either a symptomatic fracture and/or a semiquantitative vertebral fracture by the end of 5 years There were no significant differences between the four treatment groups. Comparing etidronate with no etidronate, the rates of new fractures were not significantly different for symptomatic fractures (OR 1.07 (95% CI 0.46 to 2.47)) or for any fractures (OR 0.82 (95% CI 0.45 to 1.47)). For the comparison of calcium with no calcium the corresponding ORs were 1.43 (95% CI 0.62 to 3.33) and 0.91 (95% CI 0.50 to 1.63). In post hoc analysis the effect of etidronate was greater in women than in men (interaction p value 0.02) with the fracture incidence roughly halved (OR 0.39, 95% CI 0.14 to 0.99). Etidronate increased BMD at the lumbar spine by 4.1% (p = 0.001) while calcium had no significant effect. At the proximal femur the effects of treatment were not significant (relative increases etidronate 1.6%; calcium 1.1%). The rate of new fractures in patients with fractures at entry (23.7%) was higher than in those without fractures at entry (14.3%): OR 1.87 (95% CI 1.06 to 3.07). No association was found between change in BMD and new fractures.

Conclusions: In patients receiving glucocorticoids for asthma etidronate significantly increased BMD over 5 years at the lumbar spine but not at the hip and had little if any protective effect against fractures, except possibly in postmenopausal women. The effects of calcium were not significant. Combination treatment had no advantage but increased unwanted effects.

It has been estimated that over 250 000 people in the UK are on long term oral glucocorticoid treatment.[1] Cross sectional and longitudinal studies show that respiratory disease is a major reason for oral glucocorticoid use, accounting for 19–40% of patients on long term treatment.[2][3] Systemic glucocorticoid treatment is associated with osteoporosis, an increased risk of fracture, and the morbidity and mortality associated with fractures.[4–7] This risk increases rapidly after the onset of treatment and is observed with doses of prednisolone of less than 7.5 mg daily.[3] Bisphosphonates increase bone mineral density (BMD) and can prevent fractures in postmenopausal women with osteoporosis who are not receiving glucocorticoids.[8][9]

Reid *et al* studied 40 patients on glucocorticoids, of whom 23 had respiratory diseases, and showed that over 2 years the oral bisphosphonate pamidronate could increase bone density as judged by quantitative computerised tomography.[10][11] Fracture rates were not reported in their study. Cyclical etidronate and calcium became generally available in the UK in 1992 and, for respiratory physicians, the question arose as to whether this treatment would help to prevent osteoporosis and fractures in patients taking glucocorticoids for asthma. In that year the Research Committee of the British Thoracic Society initiated a long term, multicentre, randomised trial of etidronate in patients with asthma who were receiving systemic and/or inhaled glucocorticoids. The aims of the study were to determine whether etidronate and/or calcium given for 5 years would reduce fracture rates and reverse or reduce bone loss in this population of patients. Patients at three different levels of glucocorticoid exposure were included in this pragmatic study which was carried out in a wide range of routine NHS chest clinics.

METHODS

Patients

The study population of 352 patients was drawn from 40 centres and consisted of male and female outpatients with asthma who had been taking oral and/or inhaled glucocorticoid treatment for at least 1 year, including those with preexisting osteoporosis and with vertebral and non-vertebral

fractures. Postmenopausal women aged 50–70 years were eligible for the study unless they had had hysterectomy. All men between the ages of 50 and 70 years were eligible.

Patients were stratified according to their use of glucocorticoids:

- Stratum A: continuous oral prednisolone and inhaled glucocorticoid.
- Stratum B: continuous inhaled glucocorticoid and intermittent prednisolone (more than 30 days ever).
- Stratum C: continuous inhaled glucocorticoid and no more than 30 days prednisolone ever.

To ensure comparability of the treatment groups according to baseline glucocorticoid use, treatment within each stratum and centre was allocated in random order in permuted blocks of length four within a factorial design so that patients received one of the following four regimens: (1) etidronate + calcium; (2) etidronate only; (3) calcium only; or (4) no treatment.

Etidronate was given in a dose of 400 mg/day orally on an empty stomach (at least 2 hours before or after food) for 2 weeks every 3 months. Calcium was given as calcium carbonate, providing a dose of 500 mg elemental calcium daily. Patients receiving etidronate + calcium received the doses as above except that calcium was omitted for the 2 week period of etidronate treatment. The drugs were obtained on NHS prescription from the hospitals' pharmacies or from pharmacies in the community, the latter usually via prescriptions by the general practitioner (GP).

Consistent with accepted practice in 1992, verbal informed consent was obtained from patients without the use of a written information sheet. Ethical approval was obtained from the appropriate local research ethics committees. All work was conducted in accordance with the Helsinki declaration of 1975 as revised in 1983.

Treatment allocation
Treatment was allocated by telephoning the coordinating office where the patient's name was entered on the next available treatment in the randomised sequence for that centre and for the appropriate category of glucocorticoid use.

Patient data
On entry to the study the age, sex, weight, number of years of treatment with inhaled glucocorticoid and with continuous oral glucocorticoid, mean daily dose of the inhaled and/or oral glucocorticoid over the previous year, assessment of physical activity on a 3 point scale (limited, normal, or regular brisk exercise), and history of osteoporosis related fracture (defined as such by the clinician) were recorded.

Lateral radiographs of the dorsal and lumbar spine were obtained. In those centres with the facilities, bone densitometry was measured at the lumbar spine and the proximal femur using dual energy x ray absorptiometry (DXA); 15 centres used Lunar DPX machines and six used Hologic QDR machines (1000, 1000W or 2000).

Because of systematic differences in absolute BMD measurements from different machines, the baseline comparisons of BMD data were standardised using published equations.[12] Quality control was performed according to local practice and no cross calibration phantoms were used. Changes in BMD from baseline were calculated after logarithmic transformation and presented as percentage change.

Information on glucocorticoid dosage, physical activity, new symptomatic fractures, and BMD was requested annually over 5 years using a review form sent from the coordinator to the physician for completion and return. The occurrence of new symptomatic fractures was based on patients' answers in response to direct questioning by the physicians. Although centres were asked to measure height in a standardised manner, this was not always done satisfactorily and the results were not suitable for analysis.

Lateral radiographs of the dorsal and lumbar spine were repeated at 5 years unless clinically indicated at other times. These radiographs were inspected for fractures and morphometric measurements were performed on the radiographs at entry and at 5 years by a single observer without knowledge of the treatments received by the patients. An incident vertebral fracture was defined by quantitative morphometry as a loss of vertebral height of 20% or more at the anterior, mid, or posterior regions of each vertebral body from T4 to L4, whether or not the vertebra was intact at baseline. All fractures so defined were validated using semi-quantitative visual identification as recommended by Genant et al.[13]

Sample size
When the study was designed, the main end point was that of new clinical fractures (vertebral and non-vertebral). Assuming clinical (symptomatic) fracture rates of 8% v 3%, it was calculated that 750 patients should yield 80% power to detect a statistically significant difference at the 5% level between etidronate and no etidronate or between calcium and no calcium. If densitometry was performed on 250 patients and if mean (SD) bone loss was assumed to be 3 (4)% in untreated patients on glucocorticoids, a reduction by 50% of the rate of bone loss would be detectable with 80% power at the 5% level of significance.

Difficulties in recruiting resulted in only 349 evaluable patients. The approximate halving of the sample size reduced the power to detect a statistically significant difference between symptomatic fracture rates of 8% and 3% to just over 50% from the original figure of 80%. In the final analysis we also looked at asymptomatic new and worsening vertebral fractures. The trial's incidence of 16.5% for any new or worsening fracture yields a post hoc power of 80% for detecting a halving of the incidence with the use of either etidronate or calcium. The number of subjects with densitometry on at least two occasions was 133, giving 80% power to detect as statistically significant a difference corresponding to 0.49 SD compared with the original figure of 0.375 SD with 250 subjects.

Statistical methods
The analysis used the property of the factorial design whereby, in the absence of interaction between etidronate and calcium, all patients contribute to the evaluation of each factor. Thus, in all analyses the data were inspected and formally tested to confirm the absence of interaction before analysis of the effects of etidronate and calcium. Fracture rates and mortality were analysed using contingency table methods with the Breslow-Day test for homogeneity being used to assess interaction and the Mantel-Haenszel test used to assess the effects of etidronate and the effects of calcium. Changes in BMD were analysed using a repeated measures analysis of variance with a Toeplitz covariance structure after logarithmic transformation of the values. The pretreatment log BMD was included as a covariate in all such analyses. Possible associations between fracture rates and both BMD at baseline and changes in BMD over 5 years were investigated by dividing the patient population into two groups according to whether or not a new fracture had occurred or an existing fracture worsened. The baseline BMD values, after standardisation (to allow for machine differences) and logarithmic transformation, were then compared using a t test. Other tests applied are standard.

All analyses were based on the intention to treat principle to avoid bias and two tailed tests were used throughout.

Table 1 Characteristics of patients on entry to trial

	No treatment (n = 95)	Ca (n = 85)	Et (n = 81)	Et+Ca (n = 88)	Total (n = 349)
Stratum A (n)	46	42	41	42	171
Stratum B (n)	38	33	33	33	137
Stratum C (n)	11	10	7	13	41
% male	61.1	57.6	51.9	59.1	57.6
Weight (kg)					
Mean (SD)	72.4 (12.8)	72.4 (14.2)	74.8 (15.0)	76.3 (16.0)	73.9 (14.5)
N	94	82	76	84	336
Age (years)					
Mean (SD)	60.2 (7.6)	60.3 (6.0)	59.5 (7.5)	58.7 (7.7)	59.7 (7.3)
N	94	82	76	85	337
Activities					
Limited	40	35	40	36	151
Normal	48	42	31	41	162
Brisk	6	5	5	8	24
Missing	1	3	5	3	12
Previously diagnosed osteoporotic fractures at entry (n)	9	8	10	10	37
Semi-quantitative fractures evident on x ray at entry (n)	24	26	31	25	106
Either of above (n)	27	28	34	29	118 (34%)
Standardised BMD L2–L4 (mg/cm^2)					
Mean (SD)	1017 (196)	987 (173)	997 (152)	954 (199)	989 (182)
N	46	43	37	41	167
Standardised BMD proximal femur (mg/cm^2)					
Mean (SD)	799 (150)	795 (138)	806 (118)	794 (152)	798 (140)
N	47	42	37	41	167

BMD, bone mineral density; Ca, calcium; Et, etidronate.

Analysis of fractures was based on comparisons of those with known fractures versus the remainder, although the information was incomplete in 108 patients. A similar analysis of mortality was performed but information was incomplete in 51 patients. A more formally correct analysis based on survival methods, with allowance for loss to follow up, gave unchanged conclusions (available on request) and so the simpler presentation is made.

RESULTS

Between September 1992 and September 1995 physicians from 40 centres entered 352 patients into the study, but at one centre which had entered three patients the randomisation was consistently violated. The decision to remove these patients from the analysis was made without knowledge of their outcome, leaving a total of 349 in the three groups as follows: 171 were receiving continuous prednisolone tablets and inhaled glucocorticoid (stratum A); 137 were receiving continuous inhaled glucocorticoid and had received more than 30 days of prednisolone ever (stratum B); and 41 were receiving continuous inhaled glucocorticoid but had had no more than 30 days of prednisolone ever (stratum C). The details of each treatment group are shown in table 1. There were no appreciable differences in sex, age, weight, physical activity, fractures, and BMD between the treatment groups. Patients in stratum A had taken oral glucocorticoids for a mean (SD) of 9.6 (5.0) years in a mean (SD) daily dose of 8.7 (7.8) mg prednisolone at study entry. Combining all three strata, inhaled glucocorticoids had been taken for a mean (SD) of 6.9 (5.3) years in a mean (SD) daily dose of 1517 (595) μg beclomethasone dipropionate (BDP) or equivalent. Overall, 34% of patients were known to have had osteoporotic fractures before entering the trial: 36% of stratum A, 34% of stratum B, and 27% of stratum C.

Seven patients (five receiving etidronate alone and two receiving etidronate + calcium) were found after randomisation not to have fulfilled the eligibility criteria for the trial but were analysed in accordance with intention to treat. Thirty

Table 2 Outcome at 5 years

	No treatment (n = 95)	Ca (n = 85)	Et (n = 81)	Et+Ca (n = 88)	Total (n = 349)
Died (n)	15	20	8	14	57
Untraceable (n)	12	14	11	15	51
Alive at 5 years (n)	69	51	62	59	241
New symptomatic vertebral and non-vertebral fractures (n)	7	7	5	9	28
New semi-quantitative vertebral fractures detected on spine radiographs (n)	15	11	9	7	42
Either of above	19	15	13	14	61 (17.5%)
New fractures in those with fractures at entry	8/27	7/28	8/34	5/29	28/118 (23.7%)
New fractures in those without fractures at entry	11/68	8/57	5/47	9/59	33/231 (14.3%)
New fractures					
Stratum A	8/46	8/42	7/41	9/42	32/171 (18.7%)
Stratum B	10/38	3/33	5/33	4/33	22/137 (16.1%)
Stratum C	1/11	4/10	1/7	1/13	7/41 (17.1%)

Ca, calcium; Et, etidronate.

one patients did not complete treatment because of intolerable unwanted effects (nine in the etidronate only arm, five in the calcium arm, and 17 in the etidronate + calcium arm). A further 48 (eight in the etidronate only arm, 16 in the calcium arm, 14 in the etidronate + calcium arm, and 10 in the no treatment arm) did not complete treatment or follow up as planned: 27 were not compliant with follow up, four were not compliant with medication, six had moved away, four developed other illnesses, one was withdrawn for unspecified reasons, and in six the hospital pharmacy or the GP refused to issue the prescriptions for budgetary reasons.

Radiographs of the thoracolumbar spine were obtained both at entry and at 5 years in 205 patients. At the end of the follow up period 170 patients had been seen and recorded at each of the five annual reviews as having received treatment according to the protocol (41/81 (51%) etidronate only, 36/85 (42%) calcium only, 36/88 (41%) etidronate + calcium, and 57/95 (60%) no treatment).

Deaths

Fifty seven of the 349 patients had died at 5 years (table 2), eight (9.9%) in the etidronate only arm, 20 (23.5%) in the calcium only arm, 14 (15.9%) in the etidronate + calcium arm, and 15 (15.8%) in the no treatment arm; these mortality rates were not significantly different. There was no suggestion of an interaction between etidronate and calcium (Breslow-Day test $\chi^2 = 0.01$, p = 0.93). The estimate of the odds ratio (OR) for death during treatment with etidronate compared with no etidronate was 0.60 ($\chi^2 = 2.4$, p = 0.12; 95% CI 0.34 to 1.08). The corresponding OR for calcium was 1.68 ($\chi^2 = 2.6$, p = 0.11; 95% CI 0.94 to 2.99). The cause of death was chronic obstructive airways disease in 13, cardiorespiratory failure in six, ischaemic heart disease in four, acute asthma in four, cardiac failure in three, pneumonia in three, pulmonary embolus in two, adenocarcinoma of the colon in two, and one each with cancer of the prostate, spontaneous pneumothorax, lung cancer, viral laryngitis, Alzheimer's disease, intracerebral haemorrhage, carcinoma of the ethmoid sinus, and liver disease. In 12 patients the coordinator could not ascertain causes of death from the physicians or GPs.

New fractures

Overall, 8% (28/349) of the subjects experienced a symptomatic fracture during the study with no significant differences between the treatment groups. Of the total study population, 61 (17.5%) developed either a symptomatic fracture and/or a semi-quantitative vertebral fracture by the end of 5 years (table 2) with no statistically significant differences between treatments ($\chi^2 = 0.7$, df = 3, p = 0.88) or

between strata. There were no significant interactions of strata with either treatment or fractures at entry. Thirty three (14.3%) of the 231 patients without fractures at entry developed new fractures compared with 28 (23.7%) of the 118 patients with fractures at entry ($\chi^2 = 4.2$, p = 0.04; OR 1.87, 95% CI 1.06 to 3.27).

Table 3 shows the fracture rates over 5 years in the patients receiving etidronate containing regimens compared with those not receiving etidronate. For new symptomatic fractures the OR was 1.07 (95% CI 0.46 to 2.47) and for any fractures the OR was 0.82 (95% CI 0.45 to 1.47). None of the differences was significant at the 5% level. However, etidronate had an apparent protective effect in women (nine new fractures in 75 women given etidronate compared with 19 in 73 women on regimens not containing etidronate: OR 0.39, 95% CI 0.14 to 0.99), while in men the fracture rates were marginally higher in those receiving etidronate (18/94 v 15/107). The interaction between sex and etidronate was statistically significant (Breslow-Day test, $\chi^2 = 5.19$, p = 0.02).

The results of the comparison of calcium and no calcium are shown in table 4: no significant effect was found. For new symptomatic fractures the OR was 1.43 (95% CI 0.62 to 3.33) and for any fractures the OR was 0.91(95% CI 0.50 to 1.63).

Bone mineral density (BMD)

At entry to the trial patients known to have previously diagnosed fractures (vertebral and/or non-vertebral) had markedly lower BMD at both L2–L4 and the proximal femur than patients who entered the trial without a previously diagnosed osteoporotic fracture (table 5). Similar but less marked effects were seen in those who had vertebral fractures on spinal radiographs at study entry.

The mean percentage changes from baseline in BMD (L2–L4) at each of the 5 years for each of the four regimens are shown in fig 1. For measurements on the lumbar spine an initial repeated measures analysis of variance on the log-transformed BMDs (incorporating terms for sex, stratum of glucocorticoid use, and baseline BMD) showed a highly significant effect of treatment (p = 0.0009) with no significant effect of time (p = 0.20) or treatment × time interaction (p = 0.49). Closer examination of the treatment effects and treatment × time interaction was made by replacing the treatment term by separate effects of etidronate, calcium, and the interaction between them. The beneficial effect of etidronate was highly significant (p = 0.001) but there was no significant effect of calcium (p = 0.20) or etidronate × calcium interaction (p = 0.85). The interactions of all of these three terms with time were non-significant (p = 0.13, 0.88 and 0.50, respectively). From the model, over the course of the trial BMD levels at the lumbar spine were 4.1% higher in

Table 3 Number of patients experiencing fractures within 5 years in strata A, B and C combined: effect of etidronate

	Et and Et + Ca (n = 169)	No treatment and Ca (n = 180)	Statistics
No of patients with new symptomatic fractures	14 (8.3%)	14 (7.8%)	$\chi^2_c = 0.0$, p = 1.00
No of patients with new* semi-quantitative vertebral fractures detected on spine radiographs	16 (9.5%)	26 (14.4%)	$\chi^2_c = 1.6$, p = 0.21
Either of above	27 (16%)	34 (18.9%)	$\chi^2_c = 0.3$, p = 0.57
No of fractures in: (a) those with fractures at entry	13/63 (20.6%)	15/54 (27.8%)	Breslow-Day interaction test:
(b) those without fractures at entry	14/106 (13.2%)	19/125 (15.2%)	$\chi^2_c = 0.1$, p = 0.73

*New = either a new vertebral fracture or an extension of an existing vertebral fracture.
Et, etidronate; Ca, calcium.

Table 4 Number of patients experiencing fractures within 5 years in strata A, B and C combined: effect of calcium

	Ca and Et + Ca (n = 173)	No treatment and Et (n = 176)	Statistics
No of patients with new symptomatic fractures	16 (9.3%)	12 (6.8%)	$\chi^2_c = 0.4$, p = 0.52
No of patients with new* semi-quantitative vertebral fractures detected on spine radiographs	18 (10.4%)	24 (13.6%)	$\chi^2_c = 0.6$, p = 0.45
Either of above	29 (16.8%)	32 (18.2%)	$\chi^2_c = 0.04$, p = 0.84
No of fractures in:			
(a) those with fractures at entry	12/56 (21.4%)	16/61 (26.2%)	Breslow-Day interaction test:
(b) those without fractures at entry	17/116 (14.7%)	16/115 (13.9%)	$\chi^2_c = 0.4$, p = 0.55

*New = either a new vertebral fracture or an extension of an existing vertebral fracture.
Et, etidronate; Ca, calcium.

patients treated with etidronate than in the remaining patients (95% CI 2.0 to 6.2) with comparable figures for calcium of 1.3% (95% CI −0.7 to 3.4). At the proximal femur the treatment effects on BMD were non-significant overall (p = 0.29) with no significant treatment × time interaction (p = 0.18, fig 2). The estimated increase in BMD with etidronate compared with controls was 1.6% (95% CI −0.4 to 3.1) and for calcium was 1.1% (95% CI −1.7 to 2.7). In none of the models considered was there any indication that changes in BMD levels differed according to the stratum of glucocorticoid use (smallest, p = 0.39). There was also no significant effect of sex although at the lumbar spine the levels in men, adjusted for baseline level, were 2.0% higher (95% CI − 0.1 to 4.2).

Overall, there was no association between changes in BMD and fracture rates over the 5 years, nor was there any association between these variables in the population with fractures at entry to the trial. In the patients receiving calcium or no treatment there was no demonstrable relationship between the development of new fractures and BMD at baseline, nor was any significant relationship found between new fractures and changes in BMD at each year of the study.

Adverse effects
More adverse effects were reported by patients on the etidronate containing regimens than by those not receiving etidronate (29/147 v 5/161, p = 0.001). Unwanted effects attributable to etidronate were indigestion and/or nausea and/or vomiting and/or diarrhoea and/or abdominal pain (n = 10), headaches (n = 2), and non-specifically unwell (n = 2). Unwanted effects attributable to calcium were indigestion and/or nausea and/or diarrhoea (n = 4), hypercalcaemia (n = 1), and headache (n = 1). Eleven patients in

the group receiving etidronate + calcium reported unwanted effects of the type described above, but it was uncertain which drug had caused the problems. One further patient in this group reported worsening epilepsy, one developed pain in the shoulder, and another felt he was taking too many tablets. The comparison of calcium containing regimens with non-calcium containing regimens showed more unwanted effects with calcium (24/150 v 10/158, p = 0.01). Nineteen of those allocated to the combination treatment group experienced unwanted effects compared with 10 in the etidronate only group and five in the calcium only group.

Patients in whom follow up and treatment were recorded according to the protocol
Analyses restricted to the 170 patients fitting these criteria plus a further 10 who complied with the protocol until the time of symptomatic fracture revealed the same patterns of results as those found in the overall trial population. For fractures the ORs were much the same as those quoted earlier both for etidronate (new symptomatic fractures: OR 1.17 (95% CI 0.41 to 3.33); any fracture: OR 0.99 (95% CI 0.48 to 2.03)) and for calcium (new symptomatic fractures: OR 1.23 (95% CI 0.43 to 3.50); any fracture: OR 1.18 (95% CI 0.58 to 2.43)).

DISCUSSION
This study was designed to investigate whether treatment for 5 years with cyclical etidronate could prevent fractures in patients with asthma who were receiving long term oral and/or inhaled glucocorticoids. To date this is by far the longest randomised controlled trial of the prevention and treatment of glucocorticoid induced osteoporosis, with the largest number of patient-years of follow up. Overall, treatment for

Table 5 Mean standardised bone mineral density (BMD, mg/cm^2) in those with or without pre-existing osteoporotic fractures

| Evidence of fracture	Site	Fracture	N	Geometric mean	95% CI for ratio	p value
Diagnosed before entry to trial	Thoracolumbar spine	Yes	14	857		
		No	153	984	0.79 to 0.96	0.006
	Proximal femur	Yes	14	663		
		No	153	799	0.76 to 0.91	<0.001
Spinal radiograph at entry to trial	Thoracolumbar spine	Yes	52	931		
		No	110	993	0.88 to 1.00	0.04
	Proximal femur	Yes	52	755		
		No	110	802	0.89 to 1.00	0.05
Either of above	Thoracolumbar spine	Yes	55	929		
		No	112	996	0.88 to 0.99	0.02
	Proximal femur	Yes	55	751		
		No	112	804	0.88 to 0.99	0.02
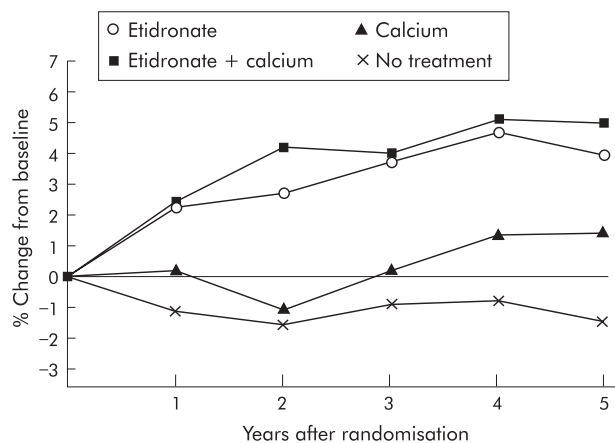
Figure 1 Mean percentage changes in bone mineral density (BMD) from baseline at L2–L4.
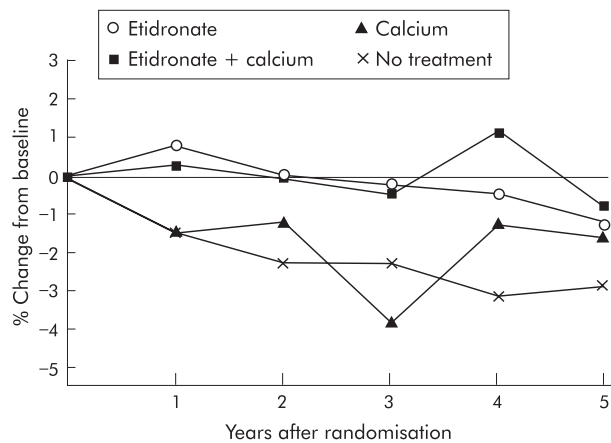

Figure 2 Mean percentage changes in bone mineral density (BMD) from baseline at the proximal femur.

5 years with cyclical etidronate did not show a statistically significant reduction in fracture rate, but the statistical power of the study was limited by the failure to achieve the recruitment target. The study encountered more than usual difficulty with recruitment for reasons which arose from the creation of trust hospitals and of fund-holding in general practice, and because of the efforts needed to obtain the individual permission of every local research ethics committee in the era before the creation of multicentre research ethics committees (MRECs).[14]

In women, however, etidronate did appear to protect against fractures at 5 years although, when multiple statistical comparisons had been made, a significance level of p = 0.02 does not confidently exclude a chance effect, especially in a post hoc analysis.

Early studies with cyclical etidronate and a subsequent meta-analysis showed an increase in BMD and reduction in vertebral fractures in women with postmenopausal osteoporosis.[8 9 15] Studies have examined the effect of etidronate and other bisphosphonates in patients on oral glucocorticoid treatment, but these have been of short duration, lasting only 1 or 2 years.[16] Few of these have dealt exclusively with patients with respiratory disease and in none was fracture rate the primary outcome measure. Studies with etidronate published during the course of our trial have shown beneficial effects of etidronate on BMD in patients receiving long term glucocorticoids for a variety of conditions.[17–22] Follow up extended to 2 years in one of these studies[22] in a population with respiratory diseases, but in the others follow up was for only 1 year. Only two studies included more than 100 patients but very few (3–4%) in either study had asthma.[20 21] In one of these, vertebral fracture was reduced by etidronate in a post hoc analysis in a subset of postmenopausal women.[20] Reductions in vertebral fracture rates have also been observed in post hoc analyses of trials of alendronate and risedronate.[23 24]

Approximately one in six of our patients with asthma receiving inhaled and/or systemic glucocorticoids developed fractures over 5 years, with no significant differences between the three strata defined on the basis of pretrial level of glucocorticoid exposure. Thus, even exposure to systemic glucocorticoid for <30 days (stratum C) could cause fractures in patients with asthma, a period shorter than the 3 months reported previously in the analyses from the General Practice Research Database in the UK.[25] An alternative explanation is that inhaled glucocorticoids are enough to predispose to fractures. It is also possible that the major determinant of fracture in patients with asthma is the disease.

Although the present study showed no overall effect of cyclical etidronate treatment on the incidence of fracture, there was a significant increase in lumbar spine BMD and a trend towards prevention of bone loss from the proximal femur. Most of the increase in lumbar spine BMD was seen in the first 2 years of cyclical etidronate treatment, but the beneficial effect was maintained in the subsequent 3 years. This suggests that the beneficial effect of bisphosphonates on BMD observed in short term studies in patients on glucocorticoid treatment will be maintained with longer treatment.

The preparation of cyclical etidronate licensed for the treatment of osteoporosis in the UK (Didronel PMO) comprises a 2 week course of disodium etidronate followed by 70 days of calcium supplementation. We found no evidence of benefit to BMD or fracture incidence from the addition of calcium to cyclical etidronate. We were also unable to detect any useful effect of giving elemental calcium alone (500 mg daily as calcium carbonate) on BMD or fracture incidence in patients with respiratory disease treated with glucocorticoids. Etidronate and calcium were each associated with an increased risk of unwanted effects, which increased even more in patients receiving the combination. These results indicate that the addition of calcium supplementation to cyclical etidronate is unnecessary and impairs tolerability, at least in patients aged 50–70 years on glucocorticoid treatment. Nevertheless, calcium and vitamin supplementation may be appropriate in older patients taking bisphosphonates as vitamin D insufficiency, common in this age group,[26] may attenuate the expected increase in BMD.[27]

One study suggests that the inverse relationship between BMD and fracture incidence in patients on oral glucocorticoids is similar to that in subjects not exposed to glucocorticoid treatment.[28] In contrast, other work shows that patients on oral glucocorticoids fracture at a higher BMD than untreated subjects,[29 30] suggesting that glucocorticoids may also increase the fracture risk independently of BMD. This has now been further strengthened with data from studies with risedronate.[31] In the present study, lumbar spine and proximal femur BMD was significantly lower in patients with a history of symptomatic fracture on recruitment to the study than in those without previous fractures. BMD was also lower in patients with radiological evidence of vertebral fracture.

Our study clearly shows that glucocorticoid treated patients with a prevalent fracture are at increased risk of further fractures, a relationship which has been documented previously in postmenopausal osteoporosis.[18 32 33] This provides a useful clinical marker for patients on glucocorticoids who are at a higher risk of further fractures, a fact acknowledged in the guidelines for the prevention and treatment of glucocorticoid induced osteoporosis recently published by the Royal College of Physicians.[16]

There is controversy as to the effects of inhaled glucocorticoids on BMD.[34–40] A study using the UK General Practice Research Database showed no difference in the incidence of vertebral or non-vertebral fractures in patients on inhaled glucocorticoids compared with those on bronchodilators, but both groups had higher fracture rates than the control group.[41] The authors therefore concluded that the increased risk of fracture among users of inhaled glucocorticoids was due to the underlying respiratory disease rather than an adverse effect of the medication. Using the same database, a subsequent case-control study of elderly patients who, with a mean age of 79 years were 20 years older than our population, showed a small dose related association between the recent use of inhaled corticosteroid and the risk of hip fracture. However, the analyses were not adjusted for lung function or for physical activity.[42] In patients with asthma or mild chronic bronchitis and emphysema a recent Cochrane review also found no evidence of an adverse effect of inhaled glucocorticoids at conventional doses given for 2 or 3 years on BMD or vertebral fractures.[43]

In diseases such as asthma and osteoporosis long term studies of treatment are important but, while they are in progress, there is always a chance that new products and clinical trials will make the results of such studies less directly relevant to contemporary practice. More potent bisphosphonates such as alendronate and risedronate are now commonly used in preference to cyclical etidronate because of the more convenient regimen and greater evidence of anti-fracture efficacy.[44] The use of bisphosphonates in the management of glucocorticoid induced osteoporosis is less clear cut as the benefits of etidronate, alendronate, and risedronate on fracture incidence have only been documented in post hoc analyses of short term studies lasting 1 or 2 years.[20 23 24] The present study is unique in showing the beneficial effect of cyclical etidronate on BMD over 5 years in patients with asthma treated with glucocorticoids, which occurs irrespective of the use of calcium supplementation. It also suggests that cyclical etidronate may decrease the incidence of fractures over 5 years in women taking glucocorticoids for asthma.

Further studies of bisphosphonates in glucocorticoid induced osteoporosis are necessary to show whether, in the longer term, they do indeed protect against fractures, either generally or in subgroups of patients. If they do, the mechanisms need further elucidation, if only to provide a better evidence base for their prescription than currently exists. For patients with asthma it is important to determine whether the disease itself, glucocorticoid treatment, or constitutional factors of certain patients chiefly determine the occurrence of fractures.

In summary, this 5 year trial in 349 patients receiving glucocorticoids for asthma has shown little if any protective effect of cyclical etidronate against fractures, except possibly in postmenopausal women. However, BMD at the lumbar spine did increase over 5 years with etidronate. Calcium had little if any effect, nor was there any benefit in giving calcium as part of the etidronate regimen. It remains to be seen whether the beneficial effects observed with the newer bisphosphonates in terms of reducing vertebral fractures at 1 year (risedronate) or 2 years (alendronate) are maintained beyond those time points.

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