Effects of Combined Treatment with Alendronate and Alfacalcidol on Bone Mineral Density and Bone Turnover in Postmenopausal Osteoporosis: A two-years, randomized, multiarm, controlled trial

K Ones, E Schacht, L Dukas, N Caglar

Abstract

One hundred ninety seven postmenopausal women with osteoporosis were enrolled in a prospective, randomized, single-blind, controlled trial of 24 months' duration to compare the efficacy of Alendronate 10mg + Alfacalcidol 0.5µg + 500 mg calcium (group A), Alendronate 10mg + 500 mg Calcium (group B), Alfacalcidol 0.5 µg + 500mg calcium (group C), or Calcium 500 mg (group D), on bone mineral density and bone metabolism markers. Upon inclusion, the subjects were randomized to groups A, B, C and D according to a 1.5/2/1.5/1 scheme. BMD was measured at the lumbar spine (L2-L4) and the femur neck using dual energy x-ray absorptiometry (LUNAR DPX) at baseline and after 12 and 24 months. Biochemical markers of bone metabolism including osteocalcin, urinary calcium and urinary deoxypyridinoline, were collected at baseline, 6 month, 12 month, and 24 month. Data collection and statistical analyses were performed in a single-blind fashion. SPSS 10.0 and Statistica 7.0 statistical packages were used for data encoding and analysis. The 5% level was used as threshold for statistical significance.

Upon inclusion and randomization, patients' characteristics (age, height, weight, time since menopause,) and study outcomes (osteocalcin, urinary calcium, deoxypyridinoline, and BMD values) were homogeneous between the four groups. At 2-years, and at the lumbar level, the highest significant gain in bone mass was seen for group A (+8.4%), followed by group B (+6.4%), and group C (+2.3%), while a significant decrease was seen among subjects from group D (-2.5%). A similar pattern was observed at the femoral neck level, with gains ranging from +5.3% for group A, +3.8% for group B, +1.2% (NS) for group C, and -6.4% for group D. Significant reductions of osteocalcin levels were observed among groups A (-4 %), B (-5.7%), and C (-1.7%). Urinary calcium was significantly increased in group C (+14%), while decreased in group B (-5.6%). Deoxypyridinoline significantly decreased among verum groups (A: -68%, B: -63.3%, C: -45%) and increased in the control group (+18.1%). Intergroup differences revealed a significantly higher gain in bone mass induced by treatments regimen A, B and C compared to D at both the femoral and lumbar levels, a higher decrease of osteocalcin levels in groups A and B versus D, similar variations of urinary calcium among the four groups, and a significantly higher reduction in deoxypyridinoline in group A, followed by B and C, versus D. The incidence of increased 24 h urinary calcaemia was similar between the four groups (p>0.06). No case of clinical hypercalciuria or hypercalcaemia has been recorded. Gastrointestinal side effects occurred in 4 patients in Group A, and in 5 patients in Group B, which resulted in the termination of treatment.

Data from this randomized controlled trial suggested a higher efficacy in increasing bone mineral density and a similar tolerance of combined therapy with Alendronate and Alfacalcidol compared to Alfacalcidol alone, and to Alendronate as a consistent trend. Importantly, the combined therapy resulted in lower rates of hypercalciuria, hypercalcemia, and hypocalcemia compared to monotherapies.

FUNDING

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INTRODUCTION

Postmenopausal Osteoporosis (PMO) is an important health problem, characterized by decreased bone mass, microarchitectural changes in bone tissue and consecutive increased fragility of the bone. Osteoporotic fractures, causing significant morbidity and excess mortality, induce major economic burdens on the health care systems worldwide ( ). Therefore, and given the report of a deleterious
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benefit/ratio for Hormone Replacement Therapy (HRT) (4), the search for more effective and safe therapies remains a priority. The development of recent, highly effective therapeutics, (bisphosphonates, SERM’s, strontium ranelate and PTH) has significantly extended the spectrum of osteoporosis therapy. Notwithstanding, the fracture rate reduction rates obtained from these therapies ranging from 30 to 60% make it obvious that their aetiology is multiple, and does not only involve bone mass (6), but also bone quality and neuromuscular and lifestyle factors (7).

As a result of inhibiting bone resorption, Alendronate treatment in postmenopausal women increases bone mineral density (BMD) at different skeletal sites and reduces vertebral fracture incidence by 47% to 51% (8, 9). Both histomorphometric and biochemical markers studies show that Alendronate inhibits bone resorption and reduces bone remodelling quite rapidly and can prevent postmenopausal bone loss (6, 10). D-hormone analogs (alfacalcidol 1(OH) vitamin D₃, and calcitriol 1,25(OH)₂ vitamin D₃) have been proven to be potent in increasing bone mineral density (BMD) and in reducing vertebral and non-vertebral fractures in several prospective, randomized, mainly placebo-controlled studies (11, 12, 13). Recently published meta-analyses, conducted by independent research groups from the USA, Canada and Europe have demonstrated the efficacy of alfacalcidol and calcitriol versus placebo (14, 15), and over plain vitamin D (16).

The decrease in the vertebral fracture risk by D-hormone analogs reached 47%, while a slight (8%) but significant decrease in non-vertebral fracture was outlined (16) and a superiority over plain vitamin D demonstrated in this indication (17).

Initiated in the seventies with fluor salts and vitamin D, combined therapies for osteoporosis have recently been brought to the fore by the recent approval of Alendronate and vitamin D3 by both the FDA and EMEA. However, despite encouraging results obtained from a preliminary clinical study showing that calcitriol in combination with Alendronate was more active than the monotherapies together with a limited risk of hypercalcioria in osteoporosis(17), little is known about the combined efficacy and safety of vitamin D analog alfacalcidol and Alendronate.

Last but 3 para. The sentence should be reworded to:

Whereas Alendronate is mainly acting as an inhibitor of osteoclastic resorption by inducing apoptosis and inhibiting enzymes of the mevalonate pathway (18-19), Alfacalcidol increases calcium absorption, reduces the release of pro-inflammatory cytokines, decreases osteoclástogenesis in vivo by decreasing the pool of precursors in bone marrow (13) and stimulates bone formation (20).

The outcome of the combined therapy should therefore be, on one hand, a higher increase in BMD, bone quality and bone strength, on the other a further reduction of fracture risk compared to what is currently observed.

This multiarm, randomized, controlled trial was designed to compare the efficacy (BMD) and safety of the combination of Alendronate and Alfacalcidol compared to the respective monotherapies and a control group.

 MATERIALS AND METHODS

197 osteoporotic postmenopausal women were included in this randomized, open, controlled clinical trial. Women were eligible for the study if they were between the ages of 50 and 70, had been postmenopausal for at least 5 years and had a lumbar or femoral bone mineral density (BMD) with a T-score < -2.5. Patients with secondary osteoporoses, other bone diseases, significant concomitant diseases, abnormal liver and renal function tests, hypercalcemia, hyperparathyroidism, major gastrointestinal diseases, e.g. peptic ulcers, treated with drugs that influence bone metabolism (estrogens, progesterones, SERMs, calcitonins, bisphosphonates, vitamin D and calcium, glucocorticoids) were excluded. Upon inclusion, patients were randomized in a 1.5/2/1.5/1 fashion, using computer-generated random lists to either 10 mg Alendronate + 0.5 µg Alfacalcidol + 500mg Calcium (group A), 10 mg Alendronate + 500 mg Calcium (group B), 0.5 µg Alfacalcidol + 500 mg Calcium (group C) or 500 mg calcium (group D) once a day for 24 months. Alendronate therapy was applied by instructing the patients to take 1 tablet with plain water before breakfast every morning with empty stomach, emphasizing not to lie down but to walk around thereafter, while Alfacalcidol and calcium have been strictly recommended to be taken after dinner.

BMD was measured with dual energy X-ray absorptiometry (LUNAR DPX) at baseline, and after 12 and 24 months by a skilled technician blind to the therapy in all patients at the lumbar spine (L2-L4) and femoral neck levels. Serum levels of calcium, phosphorus, alkaline phosphatase, creatinine and osteocalcin and in addition calcium and deoxypiridinoline in
24 h urine were measured at 0, 6, 12 and 24 months. Serum calcium, alkaline phosphatase, phosphorus, creatinine and calcium in 24 h urine were repeated every 3 months in the alfacalcidol group to check for hypercalcemia and hypercalciuria. Hypercalcemia was defined as serum calcium levels > 11 mg/ml and hypercalciuria as > 300 mg calcium in 24 h urine.

The study was not powered to evaluate the effect of treatment on fracture incidence; however a vertebral column x-ray was taken at onset and again at the end of the study. A vertebral fracture was defined with 20% or more loss of anterior, median or posterior height. Adverse events were prospectively recorded at each visit.

The intergroup homogeneity of the subjects from the four groups for baseline demographic, biochemical and clinical characteristics has been assessed using one-way ANOVA for demographic variables while clinical outcomes have been compared using unpaired Kruskal-Wallis’s ANOVA since the hypotheses of variances heterogeneity and distribution normality between groups could not be fulfilled. Intragroup variations have been assessed using paired Friedman’s ANOVA. Intergroup comparisons have compared the group-specific changes from baseline and t=6, 12 and 24 months using Kruskal-Wallis’s ANOVA. The incidences of new cases of hypercalciuria and fractures have been compared between groups using Pearson’s chi square. The 5% level of statistical significance has been used for all assessments. Statistical analysis has been performed using SPSS (10.0) and Statistica 7.0 statistical packages.

RESULTS

Baseline clinical, densitometric and biohumoral characteristics of the subjects of the four treatment groups were not statistically different (ANOVA, p>0.25). 50 patients were assigned to alfacalcidol + alendronate +calcium (group A), 49 to Alendronate + calcium (group B), 68 to the alfacalcidol + calcium group (group C), and 30 to the calcium-control (group D). 5 patients in the alendronate group and 4 patients in the combined treatment experienced gastrointestinal side effects and were excluded. 188 patients completed the study. As shown in table 1 treatment groups were well matched with regard to mean age, height, weight, time since the onset of the menopause, baseline biochemical, and calcium values. No statistically significant difference was observed in initial BMD T-score values neither at lumbar spine nor at femoral neck between the 4 groups (table 1).

Table 1: Baseline Characteristics

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Alendronate + Alfacalcidol (%)</th>
<th>Alendronate (%)</th>
<th>Alfacalcidol (%)</th>
<th>Control (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time since Menopause (years)</td>
<td>56.3 (7.2)</td>
<td>56.4 (8.7)</td>
<td>57.9 (6.1)</td>
<td>59.1 (8.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>1.29 (4.20)</td>
<td>1.65 (3.26)</td>
<td>1.52 (5.83)</td>
<td>1.79 (4.36)</td>
<td>NS</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>65.5 (3.2)</td>
<td>66.5 (5.3)</td>
<td>64.4 (3.4)</td>
<td>67.3 (4.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Phosphorus (mg/dl)</td>
<td>9.20 (0.22)</td>
<td>9.19 (0.19)</td>
<td>9.17 (0.21)</td>
<td>9.14 (0.21)</td>
<td>NS</td>
</tr>
<tr>
<td>Alkaline Phosphatase (mg/dl)</td>
<td>7.36 (0.29)</td>
<td>7.37 (0.31)</td>
<td>7.34 (0.29)</td>
<td>7.30 (0.05)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean BMD T-score (ED)</td>
<td>-0.0 (0.30)</td>
<td>-1.5 (0.31)</td>
<td>-1.0 (0.30)</td>
<td>-2.9 (0.22)</td>
<td>NS</td>
</tr>
<tr>
<td>- Femoral neck</td>
<td>2.4 (0.18)</td>
<td>2.4 (0.20)</td>
<td>2.4 (0.16)</td>
<td>2.4 (0.20)</td>
<td>NS</td>
</tr>
</tbody>
</table>

BONE MINERAL DENSITY

At the lumbar spine (L2-L4) level, and at one year, subjects from group A experienced a mean increase of 6.2% (p<0.0001) in their BMD, and there was an additional gain of +2.2% during the second year (figure 1), for a total gain of 8.4% (p<0.0001). Subjects from group B experienced a mean increase of 4.71% in their BMD during the first year (p<0.0001), and there was an additional gain of 1.76% during the second year (figure 1), for a total of 6.47% (p<0.0001). Subjects from group C experienced a mean increase of 1.29% (p=0.67) in their BMD during the first year, and there was an additional gain of +1.03% during the second year (figure 1), for a total of +2.32% (p<0.0001). Subjects from group D has a borderline significant decrease of -0.74% (p=0.052) in their BMD during the first year, and a further loss of 1.79% during the second year of the trial, for a total of 2.53% (p<0.0001) over two years. Significant intergroup differences in the BMD changes were observed for Groups A, B and C versus control after 12 and 24 months. Groups A (combined therapy, +8.4%) and B (Alendronate, +6.47%) provided similar gains in lumbar BMD at 24 month (p=0.23 or NS). At 24 months, the mean T-scores observed in groups A and B were statistically different (p=0.036), although those groups were comparable at baseline, outlining a higher efficacy of combined therapy over Alendronate alone.

At the femoral neck level, and at one year, subjects from group A experienced a mean increase of 3.5% (p<0.01) in their BMD during the first year, and there was an additional gain of +1.8% during the second year (figure 2), for a total gain of 5.3% (p<0.0001). Subjects from group B experienced a mean increase of 2% in their BMD during the first year (p=0.08), and there was an additional gain of 1.8% during the second year, for a total of 3.8% (p<0.0001). Subjects from group C experienced a mean increase of 0.8% (p=0.82) in their BMD during the first year, and there was an additional gain of +0.6% during the second year, for a total
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of +1.4% (p=0.23). Subjects from group D has a significant decrease of -2.5% (p<0.05) in their BMD during the first year, and a further loss of -3.9% during the second year of the trial, for a total of -6.4% (p<0.0001) over the two years. Significant intergroup differences in the BMD changes were observed for Groups A, B and C versus control after 12 and 24 months.

Groups A (combined therapy) and B (Alendronate) provided significant different gains in femoral BMD at month 24 against their respective baseline values (p=0.04), while these two groups significantly differed from group C (p<0.01), and control (p<0.0001) at the same timepoint.

FRACTURE RATES
The study was not powered to be able to clearly discriminate fracture differences in fracture incidences between the four groups. As a matter of fact, no significant difference in the incidence of fracture was observed between the 4 groups. One of the 44 patients in the alendronate group (2.27%), two of the 68 patients in the alfacalcidol group (2.94%), one of the 46 patients in the combined treatment group (2.17%) and one of the 30 patients in the control group (3.33%) had new vertebral fractures at the end of the two years observation period (p=0.76).

BIOCHEMICAL MARKERS
At 6 months, mean serum osteocalcin levels did not change in any group. At 12 months, groups A, B and C had significantly decreased osteocalcin levels versus baseline (A: p=0.002; B: p=0.0006; C: p=0.039) (Figure 3, table 2). At 24 months, all three groups experienced significantly decreased osteocalcin levels. Group B (Alendronate) featured the highest reduction (-5.8%, p<0.0001), followed by group A (-4%, p=0.001), and group C (-1.6%, p=0.005). No significant change could be observed in control group (+0.8%, p=0.53). As compared to changes observed in group D, significant decreases occurred for groups A (p=0.002) and B (p<0.0001), while changes were borderline significant for group C (p=0.052).

Table 2: Biochemical Markers at Baseline, 6, 12 and 24 month.

<table>
<thead>
<tr>
<th>Time</th>
<th>Alendronate+ Alfacalcidol (Group A)</th>
<th>Alendronate (Group B)</th>
<th>Alfacalcidol (Group C)</th>
<th>Control (Group D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6m</td>
<td>9.67 (1.66)</td>
<td>9.69 (1.42)</td>
<td>9.41 (1.49)</td>
<td>9.53 (2.69)</td>
</tr>
<tr>
<td>12m</td>
<td>9.36 (1.60)</td>
<td>9.39 (1.23)</td>
<td>9.20 (1.38)</td>
<td>9.44 (2.92)</td>
</tr>
<tr>
<td>24m</td>
<td>9.16 (1.65)*</td>
<td>9.42 (0.03)*</td>
<td>9.29 (1.46)</td>
<td>9.56 (2.87)</td>
</tr>
<tr>
<td>24h</td>
<td>9.03 (1.31)*</td>
<td>9.31 (1.30)*</td>
<td>9.23 (1.46)</td>
<td>9.56 (2.72)</td>
</tr>
</tbody>
</table>

**Figure 2**

24h urinary calcium levels were significantly increased over time among group C after 6 month and over (p<0.001), and were significantly decreased in group B after 24 month (p=0.005). Interestingly, values for combined therapy group remained stable over time (p=0.69). The only significant intergroup difference versus control group could be observed for group B, which was very significantly decreased (p<0.0001), while the relative increase observed in group C was borderline significant (p=0.052) (Figure 4, table 2). Deoxypyridinoline levels rapidly decreased upon treatment allocation, reaching statistical significance at 6 months and over in groups A (p<0.0001), B (p<0.0001) and C (p<0.0001) while it increased steadily in group D to reach significance at 24 months (p=0.002) (figure 5; table 2). From 6 months, all changes observed in groups A, B, and C, were consistently lower than in group D (p<0.001).

**Figure 3**

Figure 1: Lumbar Spine BMD changes from baseline at 12 and 24 months.
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**SAFETY**

Serum calcium, phosphorus, creatinine levels were not significantly different between the treatment groups during the 2 year period. The incidence of new hypercalciuria cases, defined by a calcium concentration over 300 mg/l, was similar between the four groups (p>0.15). In the alfacalcidol group a significant increase of 24 h urinary calcium levels...
after 6, 12 and 24 months was observed, however it did not differ from changes obtained in the control group.
Conversely, 24h urinary calcium was significantly reduced at two years in the Alendronate group, despite the calcium supplementation provided. The 24 h urinary calcium levels remained unchanged compared to basal values in all patients treated with Alendronate plus alfacalcidol and calcium (figure 4). Gastrointestinal side effects (pain in the stomach, pyrosis) occurred in 4 patients in the combination treatment group and in 5 patients in the alendronate group which resulted in the immediate termination of treatment. No case of esophagitis has been seen. No clinically significant side effect was registered in the alfacalcidol or control group.

**DISCUSSION**

The results from this randomized controlled trial suggested that daily oral treatment with combined Alendronate (10 mg) with alfacalcidol (0.5 µg) and calcium 500mg, administered for a 2-year period in postmenopausal women with established osteoporosis was significantly superior in increasing BMD at the lumbar spine and at the femur neck in comparison to the monotherapies.

Alendronate therapies significantly decreased serum osteocalcin and urinary deoxypyridinoline reflecting an early suppressive effect on bone resorption and on bone turnover. Given the insignificant change in serum osteocalcin and the significant reduction of urinary deoxypyridinoline, Alfacalcidol had the profile of an inhibitor of bone resorption and a regulator of bone remodelling with an intermediate impact in this perspective. During the 2 year study serum calcium, phosphorus, creatinine levels did not significantly change between the treatment groups. The fact that there was no single case of clinically relevant hypercalcaemia nor hypercalciuria during the two year period in none of the groups, confirmed the safety of the combination therapy. Only the expected gastrointestinal side effects (stomach pain, pyrosis) occurred in the Alendronate-treated groups. No side effects were registered in the alfacalcidol group.

The respective decreases and increases in urinary calcium in Alendronate and Alfacalcidol treated-patients did stabilize during the second year in the first group, while remained similar to the levels observed in the control group for the latter, suggesting a limited risk of hypo or hyper calcuiaria on the long term. A remarkable finding was the fact that the 24 h urinary calcium levels remained unchanged in patients treated with alfacalcidol plus alendronate (figure 4). This could be explained by a balance between the reduction of the osteoclastic reabsorption by alendronate and the increased intestinal absorption of calcium by alfacalcidol with a consequently higher influx of calcium ions at the bone level. The increase in BMD was higher in the combined treatment group on in both skeletal segments during the first and second year. These findings support the stimulating effect of Alfacalcidol on osteoblasts, uncoupled from the osteoclastic inhibition by Alendronate, and emphasize the interest of combined therapy In long treatment period in delaying the tendency to plateau effects observed with Alendronate and other bone resorption inhibitors.

Despite the fact that in daily practise and for different types of osteoporoses, the combination therapy is actually regularly used, its positive effects have still been described in a few clinical studies. Previous clinical investigations did corroborate our findings. In a prospective, randomized, open controlled study by Frediani and colleagues, 120 women with have been treated for 24 months with calcium 500 mg, alendronate 10 mg, and calcitriol 0.25 bid or combined treatment with alendronate 10 mg+ calcitriol 0.25 µg bid (17). At the end of the follow up period, BMD was significantly higher in the group of patients receiving combined therapy compared with the group treated with alendronate or calcitriol alone. Serum calcium did not show any significant variation between the four treatment groups during the two years of treatment. 24h urinary levels of calcium were significantly increased after 3 months of therapy with calcitriol and were significantly reduced with alendronate. Both increases and decreases stabilized during the second year of treatment. Important is the fact, that the urinary calcium remained stable in the combination group. The stable urinary and serum calcium levels observed among the subjects allocated to combined therapy in that study, as in ours, strongly limits the need for periodic checks of the calcium levels, and favours a better patient compliance. Malavolta and colleagues reported that the combination of alendronate 10 mg and a lower dose of calcitriol (0.25 µg daily) was strictly equivalent, in terms of BMD, to alendronate 10 mg + calcium 500 mg after 9 months (18). Therefore for an optimal combination therapy with alendronate, 0.5 µg calcitriol or 0.5 µg – 1.0 µg alfacalcidol daily seem to be required. Masud and colleagues reported that Etidronate 400mg + Calcitriol 0.50 µg was superior to Etidronate alone in terms of BMD at the lumbar and the femoral neck levels (19), however, Iwamoto and...
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colleagues not when comparing lower doses of etidronate (200 mg) with alfacalcidol 1 µg (\(\text{dose}_1\)). Kataxaki and colleagues compared Alendronate 10mg + Alfacalcidol 0.5µg to Alendronate 10 mg + calcium 500 mg and also observed a better efficacy of the combination in maintaining BMD (\(\text{dose}_2\)). Ringe and colleagues derived the same conclusions for the combination of Alendronate 10mg, Alfacalcidol 1 µg and 500 mg calcium, together with significantly reduced risks of falls and fractures (\(\text{dose}_3\)). Shiota and colleague showed that the combination of Etidronate 200 mg and Alfacalcidol 1 µg was more potent than monotherapies in increasing LS BMD and reducing vertebral fractures (\(\text{dose}_4\)).

This study had several limitations. Whilst the limitations of an open, controlled study are recognised, the present pragmatic study was designed to reflect better actual clinical practise. However compliance was poorly recorded, although this parameter is recognized as a major determinant of treatment efficacy (\(\text{dose}_5\)). The dose of 0.5 µg alfacalcidol was lower than the normal daily dose of 1 µg, therefore the efficacy of the combined treatment may be improved with the higher dose, while the expected higher risk of hypercalcemia and hypercalciuria with higher alfacalcidol doses should be avoided by the combination with alendronate, as it was in the study by Ringe et al. (\(\text{dose}_6\)). The power to assess differences in fracture rates was too low. Therefore we could not corroborate, on a clinical perspective, the improvement in bone strength convincingly shown in preclinical trials (\(\text{dose}_7\)). The improvement of muscle power and neuromuscular coordination and consequently the reduction of falls induced by alfacalcidol (\(\text{dose}_8\)) is an important determinant of the total efficacy of the combination, while these risk factors do not appear to be neither positively nor negatively influenced by alendronate and risedronate (\(\text{dose}_9\)). As a consequence the combination may reduce more effectively non-vertebral, especially the clinically most relevant hip fractures. This hypothesis could not be tested given the above-mentioned limited statistical power and because of the relatively young age of the patients, where falls do not play a crucial role in the pathogenesis of fractures.

**CONCLUSION**

This study provides valuable evidence that simultaneous administration of 10 mg Alendronate and 0.5 µg Alfacalcidol, together with 500 mg calcium is very efficient, and provides advantages over respective monotherapies, in the treatment of postmenopausal osteoporosis. The combination is significantly more effective in increasing vertebral and femoral bone mineral density than the monotherapy with Alfacalcidol, and a consistent trend towards better efficacy than Alendronate. A remarkable finding was that combined therapy did stabilize urinary calcium over treatment time, which leads to improved compliance and easier treatment monitoring. Negative interactions between both drugs have not been reported yet. However, further large, double-blind, dose-ranging studies in postmenopausal osteoporosis and subjects with increased risk of falls are still required to confirm the synergistic efficacy of Alendronate in combination with Alfacalcidol in the reduction of falls and vertebral, non-vertebral fractures.

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