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ORIGINAL ARTICLE

Potential of alfacalcidol for reducing increased risk of falls and fractures

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Abstract There are no general accepted strategies for combined drug treatments in osteoporosis, while in other important chronic diseases combinations of different medications are used as a rule to improve therapeutic results and reduce the risk of adverse events. It is suggested that the success of combined treatments is related to the different modes of action of the respective single therapies. On the other hand it was shown that a strong antiresorptive bisphosphonate is able to blunt at least in part the effects of anabolic parathyroid hormone peptides Calcitriol, the active vitamin D-hormone and its prodrug alfacalcidol lead to pleiotropic effects on bone remodelling (antiresorptive, anabolic and enhancing mineralization) and in addition to effects on other important target tissues (e.g. gut, parathyroid glands, muscle). With active D-analogs significant improvements in the therapeutic outcome of osteoporosis can be achieved by the resulting improvements of bone quality, calcium absorption and risk reduction of falling. The same beneficial effects cannot be achieved with plain vitamin D due to feedback controlled, limited renal activation or insufficient conversion in the elderly with impairment of renal function. Accordingly alfacalcidol, approved as a treatment for different forms of osteoporosis, is besides adoption as a mono-therapy an interesting candidate for combined therapies. There are interesting preclinical trials and clinical pilote studies in the literature proving that a parallel therapy with selectively anti-osteoclastic bisphophonates and pleiotropically acting D-analogs is able to optimize therapeutic results in osteoporosis. In the AAC-Trial (Alfacalcidol-Alendronate-Combined) we studied 90 patients with established osteoporosis (57 women, 33 men) over two years after alternate allocation to three treatment arms (alfacalcidol plus calcium, alendronate plus plain vitamin D and Ca, and alendronate plus alfacalcidol and Ca). During the 2-year-study we observed the significantly highest lumbar spine and hip BMD increases in the combined treatment group ($p < 0.001$). The number of patients with new vertebral and non-vertebral fractures after 2 years was 9 with alfacalcidol alone, 10 with alfacalcidol and plain vitamin D and 2 in the group receiving alendronate plus alfacalidol ($p < 0.02$). Furthermore there was a lower rate of falls and an earlier reduction in back pain in the patients treated with the active combination. This trial confirms the demonstrated highly significant advantages of this combined treatment regimen used in the pilote studies. Especially in patients with severe osteoporosis this interesting combination of two substances with complete different mechanisms of action should be taken into consideration.

Keyword Osteoporosis

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Introduction

Mobility and an intact locomotor system are of high value at advancing age to preserve quality of life and independence. Loss of mobility, gait disturbances and increased risk of falls are recognized as threatening changes. Falls are frequently associated with fractures leading to pain, immobility and necessity of nursing, i.e. very often a definite loss of independence in daily life. The most important determinants of the risk of suffering a fracture in the individual case however, are both risk of falling and "bone fragility" or the degree of preexisting osteoporotic changes of the skeleton [1–3].

Since reduction of fracture risk is the main goal in treating patients with osteoporosis a complete strategy against this devastating disease should always try to also reducing the risk of falls. A key role in this dual therapeutic approach today plays the pleiotropic D-hormone calcitriol or its active analog alfacalcidol.

Following we will try to give a short and comprehensive review on the potential of alfacalcidol in reducing increased risk for falls and fractures in different forms of osteoporosis [4]. For detailing however the scientific evidence of alfacalcidol and its biological and pharmacological actions, it this important to provide in parallel a clear distinction to a supplementation with cholecalciferol, the plain vitamin D [5, 6]. The basis for this in daily practice crucial distinction is the knowledge of the physiological regulation of vitamin D activation.

Activation of vitamin D

About 80% of vitamin D supply in men is produced by photo-synthesis in the skin.

In Europe only during the months May to September UVB-radiation of sunlight is strong enough to support the conversion of dehydro-cholesterol to cholecalciferol. This plain vitamin D is biologically inactive and has to be activated by two steps of hydroxylation, at first in the liver at position 25 to become 25 hydroxycholecalciferol (25-OH-D3), and subsequently in the kidney at position 1α to 1α,25-dihydroxy-cholecaciferol (1α,25-(OH)2-D3). The latter is calcitriol or active D-hormone. In case of intermittent high vitamin D supply 25-OH-D3 will be stored in fat tissue (as a depot for the rest of the year with insufficient UVB-radiation) or will be hydoxylated by a renal 24-hydroxylase to become 24,25-(OH)2-D3 which will be excreted by the kidneys [7].

The first step of activation, hepatic 25-hydroxylation occurs quantitatively and uncontrolled. An insufficiency of hepatic 25-hydroxylase occurs only in cases of very advanced, terminal liver disease. It was shown that the enzyme 25-hydroxylase is not only expressed by hepatozytes but also by other tissues or cells, e.g. osteoblasts. It is suggested that this local activation is biologically not very important since 25-hydroxy-vitamin D is relatively inactive. The osteoblastic expression of 25-hydroxylase is however very important when adopting alfacalcidol. Since this active D-hormone analog is already hydroxylated at the crucial 1α-postion, it can be directly activated in the liver or locally in the osteoblasts to 1α,25-dihydroxycholecaciferol, i.e. active D-hormone. That means when treating with alfacalcidol systemic effects can be achieved through hepatic activation besides local intraosseous, autokrin or parakrin effects.

The second activation step on the other hand, renal 1α-hydroxylation is strongly regulated by a negative feedback mechanism. If there is sufficient D-hormone and serum calcium is close to the upper normal level no further D-hormone will be produced. This regulation makes sense, since otherwise all vitamin D produced after one extensive sun-bathing in summertime would lead to uncontrolled high values of D-hormone leading to hypercalcemia. There is another important point limiting renal activation. In contrast to the abundant availability of hepatic 25-hydroxylase the renal capacity for 1α-hydroxylation is limited. Already with a creatinine clearance (CrCl) of <65 ml/min it is significantly reduced. As a consequence there is an early deficiency of D-hormone in patients with renal insufficiency leading to malabsorption of calcium, secondary hyperparathyroidism and increased bone resorption. Since impairment of kidney function is very frequent in the elderly with corresponding insufficiency of final vitamin D activation, elderly patients with osteoporosis are very often resistant to plain vitamin D supplementation.

The consequence of the above described mechanism of regulation of vitamin D activation is that a supplementation with plain vitamin D in vitamin D replete patients with normal D-hormone plasma levels can have no therapeutic effect. Since plasma levels of 25-OH-D3 are about 1000-fold higher than the levels of 1α,25-(OH)2-D3 (ng versus pg) even with very low values of 25-OH-D3, 1α,25-(OH)2-D3 levels may still be kept within the normal range.

The efficacy of a treatment with plain vitamin D is limited through both the negative feedback regulation of the final activation in the kidneys and the fact of the very frequent impairment of renal function with increasing age. The fundamental differences between a nutrional substitution of plain vitamin D and the therapeutic use of the D-hormone analog alfacalcidol (Table 1) can be easily deduced from the physiological activation of vitamin D and its regulation [4, 5].

Pleiotropic effects of the D-hormone

Vitamin D3 (cholecalciferol) was detected in the first decades of the 20th century within the research efforts to clarify the etiology of rickets [8, 9]. Only in the sixties it became clear that this "vitamin", able to heal rickets, by itself has no biological activity and has to be activated in the above explained manner [10]. That means vitamin D does not fulfil the criteria of the definition of a vitamin, but is a pro-hormone, which is produced in the skin and will be transformed in liver and kidney to become an metabolically highly active steroid hormone [7].

Another revolution was the finding that the newly detected hormone (calcitriol) is not at all only involved in

Table 1 Comparison of plain vitamin D and the active D-hormone analog alfacalcidol

Plain vitamin D
Nutritional supplementation
Larger amounts are stored in fat tissue (very long half life time, possible risk of intoxication)
Effective only in patients with vitamin D—insufficiency (25(OH)D <30 ng/ml ≤ 75 mmol/l)
In patients with normal levels of vitamin D no increase of 1,25(OH)2D (D-hormone) possible due to negative feedback regulation in the kidney
Patients with D-hormone deficiency (inhibition of 1α-hydroxylase) and/or Dhormone-receptor (VDR)-deficiency in quantity and quality are resistent to a treatment with plain vitamin D
Alfacalcidol
Pharmacological therapy (not only in patients with reduced renal function!)
Prodrug of D-hormone (calcitriol), complete activation in the liver, additional local activation in bone tissue
Effective in both, vitamin D deficient and vitamin D replete patients
Resulting increase in active D-hormone normalizes augmented PTH, reduces bone resorption with simultanous enhancement of bone formation and augmentation of muscle power
Deficit in D-hormone can be corrected by bypassing renal regulation. Vitamin D-resistence can be treated effectively by offering more D-hormone and by inducing an increasing number and activity of VDR's in different target tissues

calcium-phosphate metabolism and the skeleton. During evolution it was obviously a very early hormone responsible for a number of important basic biological processes such as cell division and differentiation. Expression of D-hormone receptors (VDRs) was proved in many tissues and organs. During recent years the list of pleiotropic effects of this wonder-hormone grew progressively [11–16]. The most important effects that have been described in the rapidly growing "Vitamin D-literature" on the skeleton and calcium metabolism as well as numerous non-osseous effects are given in Tables 2 and 3.

Of high interest are recent reports indicating that an optimal vitamin D supply may be able to significantly reduce the risk of several major types of cancer. An anti-proliferative effect of the D-hormone was shown already earlier. As an example it was shown that specific D-hormone metabolites were highly effective in inhibiting the hyper-proliferation of epidermal cells in psoriasis.

Within the complex therapeutic strategy of osteoporosis those pleiotropic effects dealing with bone remodelling, mineralization of bone matrix, muscle power and function, intestinal calcium absorption and parathyroid hormone secretion are of eminent importance. Of high interest are the effects on muscle and brain with the consequence of a lowered risk of falls and fractures. The enormous importance of the synergistic effects on bone and muscle are increasingly recognised and estimated worldwide only during recent years [6]. The anti-inflammatory and immuno-suppressive effects are of additional interest in some specific forms of secondary osteoporosis, such as glucocorticoid-induced osteoporosis (GIOP) and post-transplantation osteoporosis.

Table 2 Pleiotropic effects of the active D-hormone

Calcium-phosphate metabolism and skeleton
Mineralisation of bone matrix
Dual, antiresorptive and anabolic effect on bone turnover
Enhancement of intestinal calcium absorption
Inhibition of increased secretion of parathyroid hormone
Non-skeletal effects
Muscle (power and function)
Central nervous system (coordination, effect on risk of falling)
Anti-inflammatory-immunosuppressive effects
Cell differentation and antiprolif. effects (reduced cancer risk)
Reduction of cardiovascular mortality
Reduced risk for clinical manifestion of diabetes mellitus

Table 3 Rationale of the combined therapy of bisphosphonates + D-hormone-analogs

Stronger inhibition of increased bone remodelling and bone resorption by different mode of action
Improved efficacy on BMD
Higher rate of responders on BMD
Optimisation of "Bone Quality"! (better bone remodelling, repair of microcracks and mineralisation)
Synergism in reduction of osteoporotic vertebral and fall- related non-vertebral fractures
Bone strength ↑ + Falls ↓

Normal, physiological and optimal vitamin D levels?

For determining the vitamin D supply of an individual person or patient it is recommended to measure the liver

metabolite 25-OH-D3 [17]. The important question what are normal or physiological values of 25-OH-D3, is difficult to answer [18]. The average values found in a population can not be regarded a priori as "normal". Those mean values might also reflect an endemic insufficient supply [19]. Furthermore it has to be taken into consideration that there are enormous seasonal changes in average 25-OH-D3 values in all populations with low or even very low values in wintertime and higher values in the summer months. Additional factors influencing vitamin D supply are geographic latitude, age, skin colour, and differing habits of covering the skin by clothing.

In the international vitamin D related literature there is a clear trend towards increasingly higher "normal ranges" of vitamin D during the last years. The finding that PTH begins to increase with 25-OH-D3 values below 30 ng/ml is at least a biological indicator for the lower threshold of vitamin D plasma levels. On the other hand a very recent study demonstrated that this relation of increasing PTH values with decreasing 25-OH-D3 levels is significantly influenced by other factors, e.g. kidney function [20]. In that particular study it was shown that patients with a CrCl <60 ml/min have a significantly steeper increase in PTH than patients with normal renal function.

A reasonable upper normal or even optimal level of vitamin D can not be defined today. Most experts recommendations however end up at a range of 75–80 ng/ml. An important point in this discussion however, is the fact that the final agonist, the D-hormone, is regulated and activated according to the necessity of calcium-phosphate metabolism. That means whether 25-OH-D3 values significantly higher than 30 ng/ml are better for overall human health has not been proved. It seems quite possible that some of the desirable pleiotropic effects can only be achieved by bypassing the limited renal activation of 25-OH-D3 to D-hormone. This can be realized, as detailed above, by adopting the prodrug alfacalcidol.

Differentiating alfacalcidol and calcitriol

Since alfacalcidol is a prodrug of the active D-hormone a frequent question is, why to use this pro-hormone and not adopt directly the D-hormone. Alfacalcidol has indeed after hepatic or local osteoblastic activation biological and clinical effects identical with those of calcitriol.

The advantages of alfacalcidol are due to significant differences in pharmacokinetics. After oral intake of similar doses of both substances there is a smooth, continuous increase of $1,25(OH)_2D$ towards the upper normal limit or slightly increased values with alfacalcidol while calcitriol will induce a rather short and high peak of $1,25(OH)_2D$. Furthermore calcitriol will in part bind immediately after oral intake to gastrointestinal VDRs and thereby has a higher risk for hypercalcemia than alfacalcidol. The necessary hepatic or local activation of the latter is a kind of retardation of activation and together with the subsequent binding to VDRs in numerous target tissues, a smooth and flat increase of the D-hormone plasma curve will occur (Schacht). All together the risk-benefit relation of alfacalcidol is generally regarded as advantageous versus calcitriol and therefore alfacalcidol is worldwide preferred as a treatment in osteoporosis.

Effectiveness of alfacalcidol

The therapeutic efficacy of alfacalcidol (1α-OH-D3) in prevention and therapy of the different forms of osteoporosis is often underestimated due to insufficient information about the existing clinical data and the high potential of the additively acting pleiotropic effects on clinical outcome [4, 21].

Effects on muscle, central nervous system and risk of falls

It must be supposed that the direct effects of D-hormone on muscle and on the central nervous system contribute to the significant fractures reducing effects documented in numerous studies with active D-analogs in osteoporosis. Muscle cells as well as cells of the nervous system do have specific VDRs [22], by which contraction and relaxation of muscles is reinforced in part possibly by effects calcium-influx and -efflux [23].

The VDR expression of muscle tissue decreases significantly with increasing age [24]. It was shown that the decrease in muscle strength and neuromuscular function on one side and the increase in the incidence of falls with advancing age at the other side correlate directly with the reduced expression of VDRs in myocytes as well as with the deficiency of D-hormone in serum and/or at the receptors.

This new pathogenetic concept is supported by the results of trials in elderly women and men [25, 26]. Additionally it was shown that a treatment with alfacalcidol was able to improve muscular function. A three months therapy with alfacalcidol resulted in a significant increase in number and diameter of fast twitch type II muscle fibers [27], which are responsible for fast reactions, and trials measuring "knee extension power" (M. quadriceps) proved significant augmentations in muscle power and function [15, 28].

That these clear effects on muscle tissue finally result in lowering the rates of falls and fractures was shown by two large prospective, randomized, controlled studies with either calcitriol or alfacalcidol [29, 30]. While the American study examined only postmenopausal women [29] the second trial from Switzerland comprised 191 women and

187 men (total $n = 378$). That means the decreasing effect on the risk of falls is proved also for men [30].

Reduced creatinine-clearance and risk of falls

The activation of vitamin D to D-hormone is significantly impaired by the age related deterioration of kidney function. Above we mentioned already the respective influence of the CrCl on the relation between 25-OH-D and parathyroid hormone [20].

In a study on women and men of age 70 and over it was shown that a CrCl of <65 ml/min is associated with lower D-hormone levels and with a four-fold higher risk of falls as compared to study participants with normal CrCl [31]. These relations between CrCl, D-hormone and falls were proved by an interventional study showing that a 9 months treatment with alfacalcidol (1 μg/day) significantly reduces the risk of falls by 71% in elderly women and men with a CrCl <65 ml/min [32]. Taking into account the above discussed biological and pharmacological differences (Table 1) a simple supplementation with plain vitamin D would never achieve this highly significant effect on the incidence of falls in this population. In a meta-analysis evaluating the effect of "vitamin D" on the rate of falls it was possible to analyse subgroups with plain vitamin D or active D-hormone analogs [33]. It could be shown that the average 22% reduction of the risk of falls was due to those trials with alfacalcidol or calcitriol.

In a comparative meta-analysis it has been shown using double–blind data only that D-hormone analogs provided a statistically lower risk of falling compared to plain vitamin D (RR = 0.79; 95% Cl 0.64–0.96 vs. RR = 0.94; 95% Cl 0.87–1.01). The corresponding reduction in RR for falls attributable for D-hormone analogs was 3.5 times higher than that attributable to vitamin D (21 vs. 6%, respectively) and the number needed to treat to avoid a fall were 12 and 52 [34].

Study results and meta-analyses in postmenopausal osteoporosis

In several prospective, randomized controlled trials with D-hormone analogs in postmenopausal osteoporosis significant effects on BMD and a reduction in the risk of vertebral and non-vertebral fractures could be demonstrated [35–39]. The average rates of increase of BMD are moderate and in the range of those achieved with other physiologically acting drugs like calcitonin, estrogen or raloxifene. Today it is generally accepted however, that the amount of gain in BMD is only of low predictive value for the fracture reducing potency of a given drug. Microarchitecture of bone tissue and propensity of falls are other important, independent risk factors for fracturing.

The deficit of one huge pivotal fracture trial can be compensated by high quality meta-analyses. One meta-analysis made a clear distinction between trials with plain vitamin D or with the active analogs alfacalcidol or calcitriol [40]. As in the already cited trials on the risk of falls [33, 34] active D-analogs exhibited significantly stronger effects on BMD. Even more important was the finding that alfacalcidol and calcitriol reduced significantly the risk of vertebral fractures (RR = 0.64; 95% CI 0.44–0.82), while there was no effect with plain vitamin D [40]. In a second meta-analysis the results of the former concerning the vertebral fracture rate were confirmed for alfacalcidol and calcitriol (RR = 0.53; 95% CI 0.47–0.60) and additionally a reduction of non-vertebral fractures was proved for the active analogs (RR = 0.34; 95% CI 0.16–0.71) [41].

Glucocorticoid-induced osteoporosis

The efficacy of calcitriol in glucocorticoid-induced osteoporosis (GIOP) was studied in some earlier trials while alfacalcidol was adopted in several more recent studies.

Active D-hormone analogs are of special interest in this most important form of secondary osteoporosis because their pleiotropic mode of action directly counteracts the complex pathogenesis of GIOP [4, 5]. Furthermore the anti-inflammatory and immune-modulating effects of the D-hormone analogs [13, 42] may contribute to the therapeutic results in patients with GIOP by positively influencing the underlying disease or by allowing lower doses of immunesuppressants in patients after organ transplantation [43]. Another important co-factor in the pathogenesis of GIOP is the early and rapid development of muscle wasting, starting already 3 months after starting GC-therapy and leading to a significantly increased risk of falls in GIOP patients [44]. In a recent study in glucocorticoid-treated rats, alfacalcidol prevented not only the decrease of BMD, but also muscle atrophy [45].That means the positive effects of alfacalcidol on muscle mass and function and thereby on falls and fractures may play an even higher role in GIOP than in postmenopausal osteoporosis.

Prevention of bone loss by treating with alfacalcidol in patients with different underlying diseases and even very high doses of GCs was proved in well designed trials [46, 47]. With plain vitamin D, in contrast, even with a dosage of 50,000 IU per week (i.e. >7,000 IU per day) there was a significant loss in BMD not different from that in placebo treated patients [48].

The often rapidly developing secondary osteoporosis after organ transplantation represents a special subgroup of GIOP. The efficacy of calcitriol (2 × 0.5 μg per day) was compared with the one of alendronate (10 mg/day) in patients after heart transplantation in a one year trial. Concerning the protection against vertebral or femoral loss of

BMD there were no significant differences between the two groups, that means there was no inferiority of the active D-hormone [49]. The respective rates of new vertebral fractures were 3.6% in patients on calcitriol, 6.8% on alendronate and 13.6% in untreated controls [49].

It was the aim of an own study to compare the therapeutic effects of alfacalcidol and plain vitamin D head-to-head in 204 patients with established GIOP [50, 51]. Patients on long-term GC-therapy were recruited as matched-pairs and treated alternately with either 1 μg alfacalcidol plus 500 mg calcium per day or daily 1,000 IU plain vitamin D plus 500 mg calcium. By this pair-wise allocation the two groups were well matched without significant differences in age, sex, height, weight, daily dosage of GC, duration of GC and percentages of the different underlying pneumological or rheumatological diseases. After 3 years there was a significant mean increase in lumbar spine BMD of 2.4% in the alfacalcidol group and a decrease of 0.8% in the vitamin D treated patients ($p < 0.001$). The 3-year rate of patients with at least one new vertebral fracture was 9.7% in the alfacalcidol group and 24.8% in the patients that had been treated with plain vitamin D (RR: 0.61; 95% CI 0.24–0.81; $p = 0.005$). In accordance with this significantly stronger effect on vertebral fractures we found also a significantly steeper reduction in back pain as compared with vitamin D ($p < 0.0001$). Further proofs for the high efficacy of D-analogs in GIOP are described in two meta-analyses [41, 52].

Osteoporosis in men

In some of the alfacalcidol trials in GIOP male patients had been included. The therapeutic results were not different from those achieved in postmenopausal women exposed to GC-therapy but so far no larger studies on a pure male population has been published.

In the AIM-Trial (Alfacalcidol In Men) we studied the therapeutic potential of alfacalcidol in direct comparison to plain vitamin D on 214 men with primary or secondary osteoporosis over two years [53]. In all endpoints alfacalcidol 1 μg + 500 mg calcium was significantly superior to plain vitamin D 1,000 IU + 1,000 mg calcium. After two years BMD at the lumbar spine and hip was significantly higher in the alfacalcidol group, there was a lower rate of falls and a lower incidence of vertebral and non-vertebral fractures. That means the fall reducing efficacy of alfacalcidol from the above cited Suisse study is confirmed by our results [30].

In most countries alfacalcidol is approved in general for prevention and treatment of osteoporosis without distinction between men and women but so far a clear proof of efficacy in a pure male study was missing [53]. Taking into consideration the relevant differences between alfacalcidol and plain vitamin D given in Table 1 again the significant superiority of the active analog is not astonishing.

Alfacalcidol combined with bisphosphonates

While in other important chronic diseases combinations of different drugs are adopted as a rule (e.g. hypertension, coronary heart disease, Parkinson's disease) to improve therapeutic results and reduce the risk of adverse events, in osteoporosis no strategies for combined treatments have been established by larger studies. The most promising combinations in the past have been simultaneous or intermittent applications of antiresorptive and anabolic drugs, e.g. hormone replacement plus fluoride [54–56], bisphosphonates plus fluoride [57–60] or raloxifen plus fluoride [61]. Obviously the success of combined treatments is related to the profound differences in the mode of action of the respective mono-therapies. It was shown however, that a very strong antiresorptive bisphosphonate is able to blunt at least in part the anabolic effects of teriparatide [62, 63].

More recent pilot studies encourage to try a parallel therapy with selectively anti-osteoclastic alendronate and alfacalcidol pleiotropically acting on bone, gut and muscle [64, 65].

In the AAC-Trial (**A**lfacalcidol-**A**lendronate-**C**ombined) we studied 90 patients with established osteoporosis (57 women, 33 men) over two years after alternate allocation to 3 treatment arms [66]:

- Group A: 1 μg alfacalcidol + 500 mg calcium daily
- Group B: 70 mg alendronate 1x/week plus 1,000 IU vitamin D + 1,000 mg Ca per day
- Group C: 70 mg alendronate 1x/week plus 1 μg Alfacalcidol + 500 mg Ca per day

The average age of all patients was 66 years. The mean initial lumbar spine BMD was −3.6 and patients had an average of 3.1 prevalent lumbar and 1.9 non-vertebral fractures.

During the 2-year-study we observed significant increases of BMD at the lumbar spine of 3.0% in group A compared to baseline, and of 5.4% in group B and of 9.6% in group C respectively. The differences between the combination therapy and Alfacalcidol (6.6%) and Alendronate (4.2%) were highly significant with $p < 0.001$. There were also significant increases of the femoral neck BMD of 1.5% in group A, of 2.4% in group B and of 3.8% in group C respectively. The differences between the combination therapy and Alfacalcidol (2.3%) and Alendronate (1.4%) were again significant.

The number of patients with new vertebral fractures after 2 years was 5 in group A, 4 in group B and 1 in group C. The 2-year incidences of non-vertebral fractures was 4 in group A, 6 in group B and 1in group C, i.e. the fracture data support the view of a relevant superiority of Alfacalcidol and Alendronate combined versus either Alfacalcidol or Alendronate alone. When looking separately at each fracture type the Fligner Wolfe 1-sided test for superiority

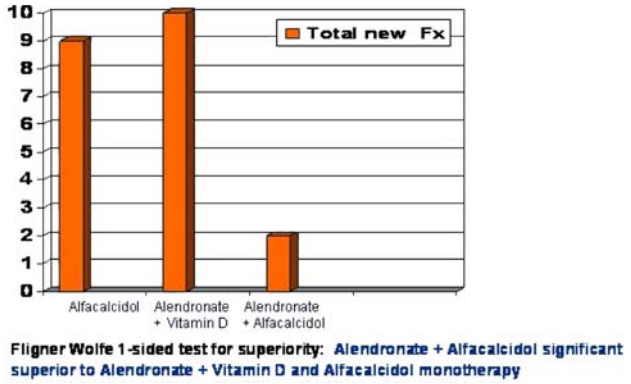

Fig. 1 AAC-trial patients with new fractures after 24 months (vertebral plus non-vertebral)

showed a small advantage for the combined group but no significant differences. Figure 1 shows the total number of new fractures (vertebral plus non-vertebral) observed in the three different treatment arms. With the same statistical test a significant superiority could be demonstrated for the combined treatment group ($p < 0.02$). Furthermore there was a lower rate of falls and an earlier reduction in back pain in the patients treated with the combination of alendronate and alfacalcidol [66, 67]. This trial demonstrates highly significant advantages of the combined treatment regimen. Especially in patients with severe osteoporosis this interesting combination of two substances with complete different mechanisms of action should be taken into consideration.

From the presented data, we conclude that alfacalcidol is efficacious in prevention and treatment of postmenopausal, senile and glucocorticoid-induced osteoporosis as well as in osteoporosis in men. The dual effect on bone strength and muscle function is unique since all other anti-osteoporotic drugs affect the fracture risk only by acting on bone turnover. It must be stressed that in patients with a high fracture risk or severe osteoporosis, in patients with increased fall risk and in patients with insufficient response to a previous antiresorptive therapy the combination alendronate-alfacalcidol is a promising new therapeutic option.

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