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ORIGINAL ARTICLE

Alfacalcidol in men with osteoporosis: a prospective, observational, 2-year trial on 214 patients

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Abstract Due to pleiotropic-synergistic actions on bone, muscle, gut, brain and different other non-skeletal tissues, alfacalcidol is an interesting drug for treating osteoporosis. In studies on glucocorticoid-induced osteoporosis, men have always been treated with calcitriol or this active D-hormone prodrug, but there is no study of male patients only in the literature. The AIM-Trial (Alfacalcidol In Men) is an extension of the control group ($n = 158$) of our former risedronate study in male osteoporosis (Ringe et al. in Rheumatol Int 29:311–315, 2009). In that study, we treated daily those controls with prevalent vertebral fractures with 1 µg alfacalcidol + 500 mg calcium (group A) and those without prevalent vertebral fractures with 1,000 IU plain vitamin D (Vit. D) + 1,000 mg calcium (group B). Subsequently, we added an additional 56 pairs of patients to these two groups: 28 with and 28 without prevalent vertebral fractures, reaching a total of 214 cases. That means with this design, we are comparing two groups with a different risk at onset. Due to the prevalent vertebral fractures and lower average bone mineral density (BMD) values, there was a higher risk of incident fractures in group A. After 2 years, we found significantly higher increases in lumbar spine BMD (+3.2 vs. +0.8 %) and total hip BMD (+1.9 vs. −0.9 %) in group A and B, respectively. Eighteen incident falls were recorded in the alfacalcidol group and 38 in the group treated with Vit. D ($p = 0.041$). There were significantly lower rates of patients with new vertebral and non-vertebral fractures in group A than in group B. Back pain was significantly reduced only with alfacalcidol. Concerning the incidence of new non-vertebral fractures, we found that there was a relation to renal function in the two groups. The advantage for alfacalcidol was mainly due to a higher non-vertebral fracture-reducing potency in patients with a creatinine clearance (CrCl) below 60 ml/min ($p = 0.0019$). There were no serious adverse events (SAE), and the numbers of mild-to-moderate adverse events (AE) were not different between groups. Despite the higher initial fracture risk in the alfacalcidol group, 2-year treatment with this active D-hormone prodrug showed a higher therapeutic efficacy in terms of BMD, falls and fractures. One important advantage of alfacalcidol may be that it is effective even in patients with mild-to-moderate renal insufficiency.

Keywords Male osteoporosis · Treatment · Vitamin D · Alfacalcidol

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Introduction

Among postmenopausal women, osteoporosis-related fractures (FX) are acknowledged as a common and important cause of disability and death [2]. In recent years, however, they have become recognized as an important public health concern in men as well. It is estimated that today approximately 20 % of all patients affected by osteoporosis (OST) are men [3–5]. Although bone loss begins later in men and advances more slowly, this percentage is expected to rise as lifestyle risk factors and life expectancy in men will further increase.

The most common fractures associated with osteoporosis occur at the hip, spine and wrist. The incidence of these

fractures, particularly at the hip and spine, increases with age in both women and men [6, 7]. Vertebral fractures can result in serious consequences, including loss of height, severe back pain, vertebral deformity and disability. Hip fracture in general requires surgery and may result in a loss of independent living. While the rate of hip fracture is two to three times higher in women than men, 1-year mortality is greater for men than for women: 20.7 % for men vs. 7.5 % for women with hip fracture over the age of 75 years [4].

Besides a change in lifestyle, pharmacological therapy is the key to reducing fragility fractures in both women and men. However, while a range of therapies are available for the prevention and/or treatment of postmenopausal osteoporosis, only few studies on the treatment of osteoporosis have been performed exclusively with men, and only the bisphosphonates alendronate, risedronate and zoledronic acid as well as the anabolic agent teriparatide are currently approved for the treatment of male osteoporosis. The target of these drugs is to change bone remodeling and to increase bone strength by either reducing bone resorption or stimulating bone formation. Alfacalcidol is approved for prevention and treatment of osteoporosis in both sexes and has a dual effect on fracture risk and falls by influencing bone turnover and muscle strength [8]. The scientific question of this trial was whether alfacalcidol plus calcium is also effective in a male only population with osteoporosis and thereby superior to Vit. D with calcium.

Patients and methods

This is an open-label, prospective, single-center, controlled, observer-blind, 24-month study. Patients in this study were mainly taken from the control group ($n = 158$) of our former risedronate study in male osteoporosis [1]. In that open prospective controlled 2-year trial, the control group patients had been treated within two different subgroups: control cases with prevalent vertebral fractures received 1 μg alfacalcidol + 500 mg calcium per day (group A) and those without fractures at onset were treated with 1,000 IU vitamin D + 1,000 mg calcium per day (B). The hypothesis for this ethical procedure was that alfacalcidol would be superior in fracture protection in the high-risk group with prevalent vertebral fractures and was based on former results in postmenopausal and glucocorticoid-induced osteoporosis [9–11].

Using the same protocol, we extended this male patient cohort by adding another 56 pairs of patients to these two groups, 28 with and 28 without prevalent vertebral (total ITT population, $n = 214$). That means we are comparing the two groups with a different risk at onset. Due to the prevalent vertebral fractures and lower average BMD values, there is a higher risk of incident fractures in group A. Men were eligible for this study if they were aged 45–75 years with a diagnosis of primary or secondary osteoporosis, BMD-T-Score values of <-2.5 at the lumbar spine (LS) and <-2.0 at the total hip (TH) with or without prevalent vertebral and non-vertebral fractures. Men who had used antiosteoporotic treatments (bisphosphonates, strontium ranelate, parathyroid hormone) during the previous 6 months were excluded.

Primary endpoints of the study were the changes in LS- and TH-BMD from baseline to 12 and 24 months. Secondary endpoints included number of patients with new falls, with new vertebral or non-vertebral fractures and change in average back pain score. Adverse events were assessed, and physical examinations and laboratory tests were performed to evaluate safety. BMD was evaluated using dual-energy X-ray absorptiometry (DXA; Lunar Expert, Madison, WI, USA). To ensure standardization and accuracy of BMD results, the same operator, who was unaware of the patients' identity and treatment, determined all BMD values, using the same machine. To confirm new fractures, X-ray films were evaluated by an experienced radiologist who was blinded to patient treatment. Back pain was assessed using a score based on four categories of pain: 0 = none, 1 = mild, 2 = moderate and 3 = severe.

The expected differences in the baseline characteristics between the two groups (Table 1) are highlighted by the p values of the Wilcoxon–Mann–Whitney Test. The analysis of the efficacy data was based on the intention-to-treat principle. All men, in whom BMD was measured at baseline and after 12 and 24 months, were included in the evaluation, independent of drug compliance. Two sample t tests were used to assess percentage change in BMD after the first and second year. To compare differences between the two treatment groups, data were analyzed using the t test for continuous variables and the χ^2 test for ordinal or nominal variables. The chosen level of significance was 0.05.

Results

Baseline characteristics

The demographic and baseline clinical characteristics of the 214 patients are shown in Table 1. According to the recruitment of the patients, there were differences between group A and B. Patients from group A treated with alfacalcidol had significantly lower average BMD values at LS and TH, prevalent vertebral fractures and related to the latter a higher loss of height versus young adulthood (former height). Correspondingly, there was also a non-significant tendency of greater age, more non-vertebral fractures, more prevalent falls and a lower creatinine clearance (CrCl).

Table 1 Baseline characteristics of patients

	Alfacalcidol	Vit. D	Wilcoxon–Mann–Whitney test (*p* value)
Number of male patients (*n*)	107	107	–
Mean age (years) (patients older than 65 years)	60.4 (42)	57.8 (35)	0.097
Mean height (cm)	174.3	175.0	0.345
Former height (cm)	177.6	176.5	0.194
Loss of height (cm)	3.3	1.5	**0.046**
Prim./sec. OST	63/44	64/43	1.000
BMD-LS			
g/cm^2	0.817	0.876	**<0.001**
T-score	−3.57	−3.00	
BMD-TH			
g/cm2	0.725	0.754	**0.008**
T-score	−2.83	−2.60	
Vert. Fx			
Total	233	0.0	**<0.0001**
Mean/pat	2.2	0.0	
N-vert. Fx			
Total	84	56	0.137
Mean/patients	0.8	0.5	
CrCl			
(ml/min)	78.0	85.4	0.979
</>60 ml/min	33/74	24/83	
Falls within last 2 years	51	44	0.126

Bold values are statistically significant

Efficacy

Primary endpoint

The mean percent changes in lumbar spine and total hip BMD in both groups after 12 and 24 months are shown in Table 2 and Fig. 1. After 2 years, the patients on alfacalcidol showed significant mean increases of 3.2 % at the LS and 1.9 % at the TH, while the respective changes in the patients on Vit. D with LS +0.8 and TH −0.9 were not significant. Accordingly, the difference, change between group A and B, was highly significant ($p < 0.001$) after the first and second year (Table 2).

Secondary endpoints

The incidence of falls in the 2 years before and during the study is shown in Table 3 in absolute numbers and number of falls per patient-year. The average number of previous falls per patient-year was not different with 0.24 and 0.21 in group A and B, respectively. The decrease of this number to 0.09 in the alfacalcidol group was significantly lower than the average of 0.18 for the patients treated with Vit. D ($p = 0.04$).

The number of patients with and without the incidence rates of new vertebral and non-vertebral fractures for each year and group are shown in Table 4 and Fig. 2. We observed a significantly lower incidence of both fracture types in the patients treated with alfacalcidol. After 24 months, 12 and 23 patients in group A and B, respectively, had

Table 2 Primary endpoint: percent changes in LS- and TH-BMD after first and second year

	Alfacalcidol		Vit. D		*p*<
	g/cm^2	%	g/cm^2	%	
LS-BMD					
M 0	0.817	–	0.876	–	–
M 12	0.832	+1.9	0.879	+0.4	0.0001
M 24	0.842	+3.2	0.885	+0.8	0.0001
TH-BMD					
M 0	0.725	–	0.754	–	–
M 12	0.732	+1.1	0.755	+0.1	0.0001
M 24	0.740	+1.9	0.748	−0.9	0.0001

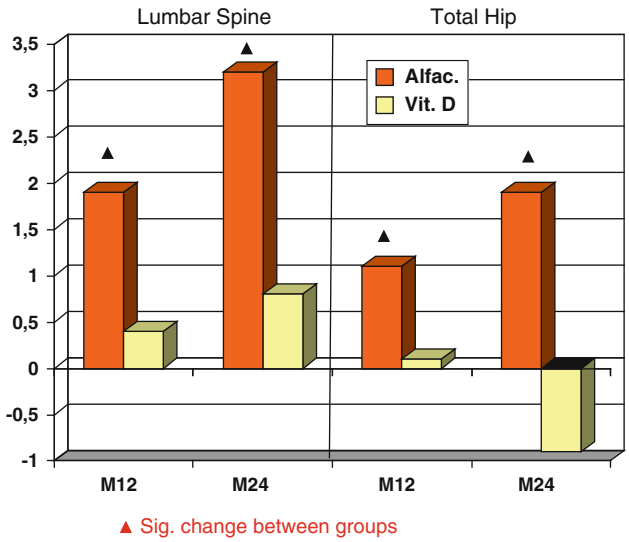

Fig. 1 Mean percent changes in BMD during treatment with Alfacalcidol or Vit. D ($p < 0.0001$)

Table 3 Incidence of falls before and during the study

	Alfacalcidol	Vit. D
Last 2 years (Av. no. falls/patient/year)	51 (0.24)	44 (0.21)
1st year study	9	16
2nd year study	9	22
Entire 2-year study (Av. no. falls/patient/year)	18 (0.09)	38* (0.18)

* Alfacalcidol versus Vit. D: $p = 0.040$

Table 4 New vertebral and non-vertebral fractures during the study

	Alfacalcidol		Vit. D	
	Vert. FX	Non-vert FX	Vert. FX	Non-vert FX
1st year				
Number of patients with FX (Number of FX)	8 (9)	12 (12)	13 (18)	16 (22)
2nd year				
Number of patients with FX (Number of FX)	4 (6)	5 (10)	10 (10)	17 (19)
Both years				
Number of patients with FX (Number of FX)	12 (15)	17 (22)	23* (28)	33** (41)

Alfacalcidol versus Vit.D: * $p = 0.035$; ** $p = 0.041$

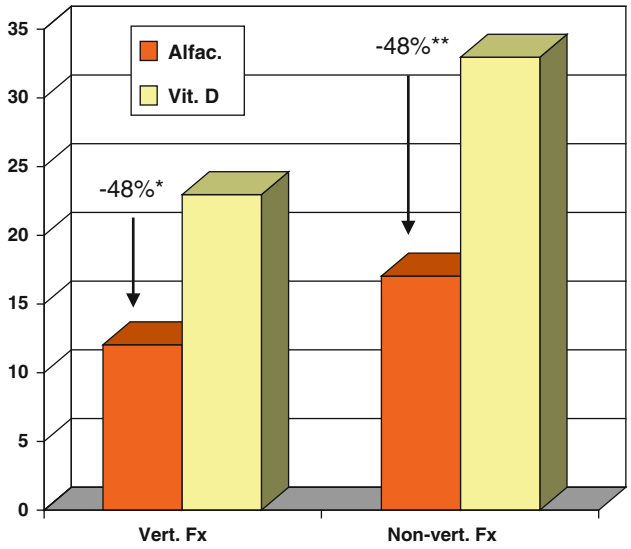

Fig. 2 New vertebral and non-vertebral fractures during the study (all fractures after 2 years: 37 vs. 69; $p < 0.003$). *$p = 0.035$; **$p = 0.041$

suffered new vertebral, and 17 and 33 new non-vertebral fractures (vertebral fractures $p = 0.035$; non-vertebral fractures $p = 0.041$).

The mean back pain score (BPS) decreased in both groups during the course of the study. In the alfacalcidol group, the mean BPS was reduced from 2.4 at baseline to 0.8 at month 24. In the vitamin D group, average BPS decreased from 1.6 to 1.1. Table 5 shows a significant higher BPS for group A at onset and a significantly lower BPS after 2 years as compared with group B, indicating no significant effect of Vit. D on back pain (Fig. 3).

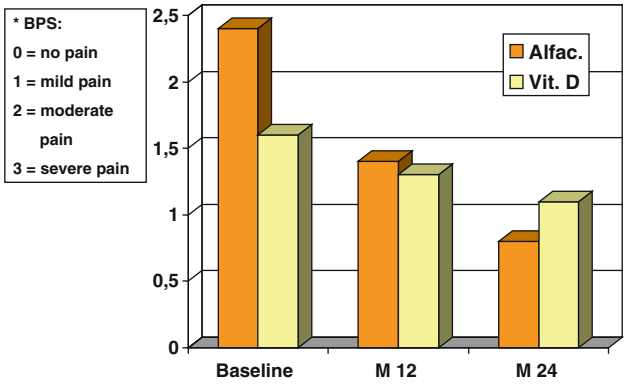

Fig. 3 Changes in average back pain scores (BPS)* during the study. Baseline: $p = 0.0001$; M 12: $p = 0.6297$; M 24: $p = 0.007$

Renal function and adverse events

In Table 5, respective numbers of patients with a creatinine clearance below or above 60 ml/min are given. There is a higher rate of patients with impaired kidney function in group A at onset, but obviously no significant deterioration of kidney function as adverse event occurred during intervention in both groups. Interestingly, we found that among all patients with a creatinine clearance below 60 ml/min, those treated with plain vitamin D showed a significantly higher incidence of non-vertebral fractures (58.3 %) than those receiving alfacalcidol (18.2 %) ($p = 0.002$; Table 6). In the subgroup of all patients with a creatinine clearance above 60 ml/min, however, the respective rates of non-vertebral fractures were not significantly different between vitamin D- and alfacalcidol-treated patients (24.3 vs. 32.5 %, $p = 0.258$). Obviously, the advantage of alfacalcidol was mainly due to a higher non-vertebral, fall-related fracture-reducing potency in patients with a creatinine clearance below 60 ml/min ($p = 0.002$) due to the fact that alfacalcidol is active and independent from kidney function.

Table 5 Renal function during the trial (no. of patients with creatinine clearance below or above 60 ml/min)

	Alfacalcidol		Vit. D	
	<60 ml/min	>60 ml/min	<60 ml/min	>60 ml/min
M 0 ($n = 107/107$)	33	74	24	83
M12 ($n = 107/107$)	31	76	22	85
M24 ($n = 100/101$)	31	69	26	75

Table 6 Renal function and number of new non-vertebral fractures after 2 years

Creatinine clearance	Treatment	Number of patients	Non-vert. fractures	Odds ratio
<60 ml/min (mean age = 69.9 years)	Alfacalcidol	33	6 (18.2 %)	5.65 ($p = 0.002$
	Vit. D	24	14 (58.3 %)	
≥60 ml/min (mean age = 55.2 years)	Alfacalcidol	74	18 (24.3 %)	1.49 ($p = 0.258$)
	Vit. D	83	27 (32.5 %)	

Table 7 Adverse events during the 2 years of observation

Adverse events	Alfacalcidol	Vit. D
Epigastric discomfort/pain	12	14
Obstipation	9	10
Nausea	6	10
Soft stool/diarrhea	5	6
Meteorism	2	3
Headache	4	3
Arthralgia	6	8
Myalgia/muscle cramps	2	3
Hypercalcuria	10	6
Hypercalcemia	2	0
Total AE	58	63

Alfacalcidol versus Vit. D, no sig. differences

Alfacalcidol is effective in both low and high CrCl level, as the incidence of non-vertebral fractures was not significantly different (18.2 vs. 24.3 %) between both subgroups. Alfacalcidol is indeed acting independent from the CrCl level.

There were no SAE, and the overall number of mild-to-moderate AE was not different between the two therapeutic regimens (58 vs. 63 in groups A and B, respectively). Importantly, we did not find significant differences in the incidence of hypercalcuria and hypercalcemia with 10 versus 6 and 2 versus 0 cases in group A and B, respectively, no renal stones and no deterioration of renal function (Table 7).

Discussion

Although no separate data have been available for men, alfacalcidol has been approved for prevention and treatment of osteoporosis without excluding male patients. This is the first study comparing head-to-head the therapeutic efficacy of the active D-hormone prodrug alfacalcidol with non-activated, native vitamin D (cholecalciferol) exclusively in men with osteoporosis. The mean increases in lumbar spine and total hip BMD that were observed at 12 and 24 months were significantly higher with alfacalcidol 1 μg/day plus 500 mg calcium compared with cholecalciferol 1,000 IU/day plus 1,000 mg calcium. The delta-gain of alfacalcidol vs. Vit. D in LS-BMD at month 24 was 2.4 % and at the TH 2.8 % (both $p < 0.001$) (Table 2). The magnitude of BMD increases with alfacalcidol is lower than with oral or intravenous bisphosphonates [12–14], but it was shown in postmenopausal osteoporosis that the relation between BMD increase and the fracture-reducing effect differs considerably when comparing antiosteoporotic drugs with different modes of action. In the PROOF study [15] with calcitonin, for example, the LS-BMD delta-gain was only 0.5 %, but the reduction in vertebral fractures was 36 %. The corresponding data for raloxifen in the MORE study [16] were +2.6 % LS-BMD and −40 % vertebral fractures and the data for risedronate in VERT-MN [17] +6.3 % LS-BMD and −49 % vertebral fractures. It should be remembered that in all these studies, Vit. D and calcium with different dosages served as "placebo". The result of this alfacalcidol study in men, a delta LS-BMD of +2.4 and −48 % of patients with vertebral fractures, is within this range of these considerably differing correlations and rather close to raloxifen. There is, however, a very important difference between this study with an active D-hormone analog and the other three above mentioned examples. They all have no or only very small effects on non-vertebral fractures, while patients with these fractures were reduced equally by 48 % in this particular male study (Fig. 2). This significantly stronger potency to reduce the incidence of both types of fractures is all the more remarkable since, due to the above mentioned special allocation of patients, there was a higher risk of fractures in the alfacalcidol-treated patients (Table 1).

BMD is only one determinant of bone strength, and the breaking strength is based on a combination of bone structure and properties of bone material, where cortical bone plays a more important role than the trabecular bone [18, 19]. In animal trials, a significantly better effect of alfacalcidol on bone strength was shown than with Vit. D or estrogens, and also a superior effect on cortical bone was achieved as compared with bisphosphonates [20–22]. Based on the fact that there are no great sex differences known in the efficacies of different antiosteoporotic drugs, the recently published additive impact of alfacalcidol on BMD of the spine measured by DXA and on bone strength, especially on cortical bone density, cortical cross-sectional

area and strength strain index (SSI) of the tibia measured with pQCT in alendronate-treated postmenopausal women with reduced bone mass (Alfa Study) would explain our results [23]. Furthermore, the superior efficacy in reducing non-vertebral fractures was confirmed by the JOINT-02 Study, a randomized, prospective, controlled, observer-blind study over 2 years on 2,164 postmenopausal Japanese women with established osteoporosis, showing a significantly better effect of alfacalcidol plus alendronate versus alendronate alone on reduction of fall-related, non-vertebral fractures, especially femoral fractures [24].

As a further possible explanation for the significant risk reduction in non-vertebral fractures, we suggest the fact that in contrast to cholecalciferol, alfacalcidol is able to produce all pleiotropic effects of the active D-hormone immediately after hepatic 25-hydroxylation because this activation occurs quantitatively and independently from age, kidney function, prevalent vitamin D supply and 25(OH)D serum levels. Besides the dual moderate anabolic plus antiresorptive effect on bone turnover combined with improved matrix mineralization and special effects on cortical bone parameters, the major effect explaining the reduced rate of non-vertebral fractures must be the well-established potency to improve muscle strength and function as well as balance and body sway by additional central nervous effects resulting in a reduced incidence of falls [25–32]. This view is underlined by further interesting findings in this particular study with alfacalcidol versus cholecalciferol in men. After 2 years, we documented 18 new fall events in the alfacalcidol versus 38 in the vitamin D group ($p = 0.040$). In addition, we found a relation between the incidence of new non-vertebral fractures and renal function. Within the alfacalcidol-treated group, there was a higher non-vertebral fracture-reducing potency in patients with CrCl below 60 ml/min ($p = 0.002$), suggesting that the renal-function-independent activation of alfacalcidol is a major reason for a lower rate of falls and non-vertebral fractures.

The second finding related to renal function is in accordance with results of a prospective, randomized, placebo-controlled trial in elderly, vitamin D replete women and men with calcium intake of above 500 mg daily from diet [33]. The treatment with 1 mcg alfacalcidol daily was associated with 55 % reduction in number of falls. Since impaired renal function decreases the renal 1α-hydroxylase and consecutively the serum levels of D-hormone, a daily treatment with 1 µg alfacalcidol for elderly women and men with a CrCl of <65 ml/min leads to a significantly better reduction in the number of fallers after 9 months (−74 %) in comparison with placebo [34]. Our third finding, the superiority in reduction in falls induced by alfacalcidol versus native vitamin D had been shown in a meta-analysis of randomized, double-blind, controlled studies in women and men, showing that the absolute risk reduction in falls was 3.5 times higher with D-hormone analogs (alfacalcidol, calcitriol) [35].

In this trial, both medications were well tolerated, and there were no differences in the occurrence of mild or moderate adverse events, especially in hypercalcuria or hypercalcemia. Altogether, the results of this study suggest a clear therapeutic superiority of alfacalcidol 1 µg + Ca 500 mg/day over Vit. D 1000 I.U. + Ca 1000 mg/day in the management of male osteoporosis.

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