Risk reduction of falls and fractures, reduction of back pain and safety in elderly high risk patients receiving combined therapy with alfacalcidol and alendronate: a prospective study

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Key words

- Alendronate
- Alfacalcidol
- Back pain
- Elderly
- Falls
- Fractures
- Muscle
- Osteoporosis

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Abstract

Efficacy and safety of a new combination package containing 4 or 12 self-explanatory one-week blisters, each with one tablet of 70 mg alendronate (CAS 260055-05-8) and 7 capsules of 1 µg alfacalcidol (CAS 41294-56-8) (Tevabone®) on muscle power, muscle function, balance and back pain was investigated in an open, multi-centered, uncontrolled, prospective study on a cohort of elderly patients with a high risk of falls and fractures.
818 practicing physicians all over Germany recruited 2579 patients for a 3-month observational trial being treated with the above combination package.
92.4 % were women [89.7 % of the women had postmenopausal osteoporosis (PMO)]. Their average age was 74.1 years and the mean body mass index 26.4 kg/m^2.
55.4 % had a history of falls. Prevalent vertebral and non-vertebral fractures were documented in 62.9 % and 61.4 % of the patients, respectively, and a creatinine clearance below 65 ml/min was documented in 65.5 %. Main outcome parameters were the Chair Rising Test (CRT), Timed Up and Go Test (TUG), back pain and safety at onset and after 3 months. In addition an evaluation of the package design was done at the end of the study.

The percentage of patients able to perform the CRT within 10 sec increased from 26.3 % to 42.9 % after 3 months (increase 63 %, $p < 0.0001$), while successful performance within 10 sec of TUG increased by 54 % ($p < 0.0001$) from 30.6 % at onset to 47.1 % after 3 months. The average overall improvement of CRT was 2.3 sec ($p < 0.0001$) and of TUG amounted to 2.4 sec ($p < 0.0001$). It was shown in another recently published study that a mean increase of 2.6 sec in the performance of TUG results in a 24 % increased risk for non-vertebral fractures. Mean back pain measured by a 0–10 visual analogue scale decreased significantly by 41 % from 5.9 to 3.5 ($p < 0.0001$).

Throughout the study, 178 adverse events (AE) were reported in 85 of the 2579 patients (incidence: 3.3 %). Only 3 patients experienced serious AE, 2 without causal relationship to the new combination pack. Patients using the new combined regimen of alfacalcidol plus alendronate achieved significant improvement in CRT, TUG and back pain already after 3 months, with a high safety profile and good compliance. This may contribute to the previously shown significant effect on reducing falls and fractures with the same regimen during a controlled long-term trial. The same trend was found in all mentioned efficacy parameters and no different trend in safety in the large subgroup of 2106 women with documented PMO.

1. Introduction

Mobility and an intact loco-motor system are of high value in advanced 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 [1–4]. Older individuals are at an increased risk of falls, mainly due to an age-related increase of muscle weakness as well as the accumulation of impairments and co-morbidities observed with aging [3, 5, 6].

An ideal treatment to prevent future fractures should increase bone mass and quality, improve muscle strength and decrease risk of falls without having a risk for major adverse events. Preclinical and clinical data suggest that the combination therapy of D-hormone analogs (alfacalcidol, calcitriol) with bisphosphonates, like alendronate, might warrant better therapeutic results than the monotherapies in bone mass, bone quality, muscle power and function and decreasing falls and fractures due to their different and complementary modes of action [7–13].

Recently two combination packages containing 4 or 12 self-explanatory one-week blisters, each with one tablet of 70 mg alendronate (CAS 260055-05-8) and 7 capsules of 1 μg alfacalcidol (CAS 41294-56-8), were developed and launched in Germany in 2009.

In this study the effect of this combination therapy on muscle power and muscle function, but also on osteoporotic back pain was investigated. The latter is the most important symptom for patients [14, 15], as it affects severely patients' quality of life, pain related immobility and further deteriorates skeletal stability [100]. Safety and patients' satisfaction with the package design are important practical issues, which influence a patients' compliance and the efficiency of treatment.

2. Subjects and methods

This is an open, uncontrolled prospective study on a cohort of elderly patients with a high risk for falls and fractures conducted from March 2009 till February 2010. The primary aim was to investigate the efficacy and safety of the combination package[1)] containing 4 or 12 self-explanatory one-week blisters, each with one tablet of 70 mg alendronate and 7 capsules of 1 μg alfacalcidol and the effects on muscle power, muscle function and back pain.

Recruitment was done by physicians from 818 private practices from all over Germany with experience in the management of patients with osteoporosis. They informed suitable patients about the purpose of this open short term study and the latter gave oral consent. None of the patients had been treated before with a combination of alfacalcidol and alendronate. If there had been a pretreatment with other anti-osteoporotic substances no wash-out interval was requested. The study medication was prescribed by the physicians. The combination package is reimbursed in Germany.

The physicians had to fill in a questionnaire on their patients, perform different muscle tests, measure some basic laboratory values, register side effects, and ask the patients to grade their back-pain as well as compliance and satisfaction concerning the package design. The questionnaire had to be completed at the beginning and after 3 months of treatment with the new combination therapy, in the presence and with the help of the respective patients. The questionnaire requested information on gender, age, weight, height, body mass index (BMI), diagnosis and type of osteoporosis, diagnosis and type of prevalent fractures, diagnosis of fall risk based mainly on the "Esslinger Fall Risk Assessment" [3], back pain, renal insufficiency, co-medication, concomitant diseases, and finally concluding with the efficacy and safety estimation of the physician, adverse events (AE), and adverse drug reactions (ADR) and patient satisfaction with the design of the combination package.

Bone mineral density (BMD) was measured with dual energy X-ray absorptiometry (DEXA) either by the study physicians themselves or in cooperating practices. The average lumbar spine BMD value before intervention was –3.1, for the proximal femur – 2.5 T-score. 72 % of patients had at least one prevalent vertebral or non-vertebral fracture. In addition, laboratory tests were performed measuring serum calcium and creatinine. Creatinine clearance (CrCl) was calculated by the Cockcroft-Gault formula [16]. Back pain was rated by the patients using a visual analog scale (VAS) ranging from 0 (no pain) to 10 (worst imaginable pain) [26]. The participating physicians received a small remuneration upon completion of the patients' records according to German regulations of post marketing studies.

2.1 Functional assessment

Muscle power and muscle function were measured by the Timed Up and Go Test (TUG) and Chair Rising Test (CRT). These tests are in line with German and International Guidelines for the assessment of the risk of falling [17, 18]. The TUG, reported by Podsialdo and Richardson [20], is a measure of functional mobility and tests muscle function, gait speed and balance. The TUG test is an effective method of assessing functional mobility efforts needed in everyday life [20–22]. The concept is appealing, because it describes realistic mobility assessment including potential fall situations, such as getting in and out of a chair, walking and turning around. The person is observed and timed while rising from an arm chair (seat height 48 cm; arm height 68 cm), walking 3 m at normal speed and going around an obstacle on the floor (i. e. a brick at 3 m distance from the chair) returning and sitting down again. Subjects are allowed to use the arms of the chair to get up. Only one trial has to be performed. The longer a patient needs to perform the TUG, the lower his/her performance and the higher the risk of falls.

Recently it was shown in a 10-year longitudinal study that the TUG is not only a measurement of functional mobility and falls but can also be used as a predictor for non-vertebral fractures: a 1 SD (= 2.6 sec) increase in TUG performance was, in

[1)] Tevabone®; Teva Pharmaceutical Industries Ltd., Petach Tikva, Israel.

this study, associated with a 24 % increase in the risk for non-vertebral fractures [23].

With the CRT for testing hip muscle power [24, 25], an individual is asked to get up and sit down 5 times from a chair of usual height as quickly as possible without using his/her arms. The arms are crossed in front of the chest. Only one trial has to be performed. An individual who is not able to sit and rise 5 times or performs the test in more than 10 sec is at special high risk to fall. The longer a patient needs to perform the CRT the lower is his/her performance.

2.2 Statistical analysis

Continuous variables were described with number of observations available, mean, standard deviation, median, quartiles, 5 % and 95 % percentiles, minimum and maximum. Descriptive statistics were also calculated for absolute changes from baseline to the last available post-baseline value. Categorical variables were displayed by absolute and relative frequencies (percentages). Percentages for categorical variables refer to the number of non-missing values. AE and ADR were analyzed on a patient and not on an event basis, i. e. the number and percentage of patients with at least one (specific) event ("incidence") were displayed.

In addition to the analyses, statistical tests were performed for the TUG, the CRT and for back pain. For continuous data the T-test was applied, for categorical data (percentage of patients with ≤ 10 sec for both TUG and CRT) the Chi-Square test was used. Two-sided p-values were presented with four decimals. All statistical tests were not adjusted for multiplicity; the tests are to be interpreted in an exploratory sense.

3. Results

3.1 Study duration and discontinuation

A total of 2579 patients were treated for 3 months with the new combination therapy. The mean study duration was 95.5 days. 7.6 % were men and of the remaining women, 89.7 % (2106) had PMO. 181 (7.0 %) discontinued during the observation period, 138 for unknown reasons, 37 were lost in follow-up, 47 stopped due to AE. As per the subgroup of PMO patients, 136 (6.5 %) discontinued. 111 discontinued for unknown reasons, 26 were lost in follow up and 32 stopped due to AE (multiple answers possible).

3.2 Demographic data and risk factors

The mean age of the 2579 patients (women 92.4 %, men 7.6 %) was 74.1 years, 26.9 % were younger than 70, 48.4 % were between 70 and 80 and 24.7 % were older than 80 years. The average height was 162.8 cm and the mean weight 69.9 kg, i. e. an average BMI of 26.4 kg/m^2.

89.7 % had a diagnosis of PMO and 14.3 % of glucocorticoid-induced osteoporosis. Concerning BMD, the mean T-score was –3.1 for the lumbar spine and –2.5 for the total femur. 55.4 % had a diagnosis of increased risk of falls, whereas 68.0 % had fallen more than once in the past year.

16.9 % had a clinical diagnosis of impaired renal function, 65.5 % a CrCl lower than 65 ml/min. Other concomitant diseases were hypertension in 67.4 %, heart failure 25.5 %, diabetes 25.1 %, depression 22.8 %, dementia 8.2 %, muscle atrophy 18.8 %, immobility 20.0 %, previous stroke 7.5 %, Parkinson's disease 3.7 %.

A history of peripheral fractures was reported from 61.4 % and vertebral fractures from 62.9 % of the patients. 61.5 % of the patients were prescribed multiple medications (more than 4) and 25.5 % used sedatives and/or hypnotics almost daily. In 84.9 % of the total initial population at least one previous or concomitant medication was documented. Previous anti-osteoporotic drugs (multiple answers possible) comprised alendronate 46.0 %, alendronate + plain vitamin D 35.8 %, ibandronate 30.6 %, risedronate 31 %, risedronate + calcium (+ vitamin D) 33.5 %, zoledronic acid 29.2 %, strontium ranelate 30.4 %, teriparatide 29.3 %, raloxifene 30.8 %, calcium 60.8 %, plain vitamin D 51.6 %, estrogens 31.2 %. In nearly all cases medications taken at baseline were discontinued. A defined wash-out phase was not requested.

Comparing the total group and the subgroup with PMO for demographic data and risk factors no significant differences could be shown.

3.3 Performance in the two muscle power and muscle function tests

The mean time used for the TUG and CRT decreased during therapy by 2.4 and 2.3 sec from initially 15.9 and 15.4 sec, respectively (Fig. 1). In the subgroup of PMO the mean time used for the TUG and CRT was reduced by 2.0 and 1.9 sec respectively (at onset 15.6 and 15.2 sec respectively).

The combined treatment with alendronate and alfacalcidol was associated with significantly improved performance in the two muscle tests ($p < 0.0001$ in both tests, N = 2356 for TUG, N = 2259 for CRT) (see Table 1).

There was a significant increase in the number of participants able to successfully perform the different tests: TUG 30.6 % at baseline to 47.1 % after 3 months (increase 54 %, $p < 0.0001$) and CRT 26.3 % at onset to 42.9 % after 3 months (increase 63 %, $p < 0.0001$).

Comparable results were found in the subgroups of patients with PMO. The rate of patients who needed up to 10 sec in the TUG increased significantly from 32.0 % to 48.9 % and from 27.3 % to 44.1 % for the CRT respectively (Fig. 2).

Table 1: Percentages of patients (total population) with successful test performance (≤ 10 sec) at onset and after 3 months of the combination therapy.

	TUG	CRT
Onset	30.6 %	26.3 %
3 months	47.1 %	42.9 %
P value*	< 0.0001	< 0.0001

*P for changes in test performance between baseline and end of the study.

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3.4 Timed Up and Go Test (TUG)

The changes in the ability to perform the TUG showed only a small dependency on the BMI, but a stronger dependency on gender, age and CrCl. While men showed a mean improvement of 3.4 sec, mean improvement for women was only 2.4 sec. While at baseline the average time for the performance for the entire patient group was 15.9 sec, patients younger than 70 years needed 13.1 sec, patients between 70 and 80 years of age 15.9 sec, and patients older than 80 years 19.2 sec. Average improvements, however, were not different across these age groups (with –2.2, –2.5 and –2.6 for the respective age groups). The average reduction of 2.4 sec for the whole group was highly significant (Fig. 1).

Patients with CrCl < 65 ml/min had higher baseline values (mean 17.2 sec) and a somewhat higher improvement (–2.7 sec) than those with CrCl ≥ 65 ml/min (baseline 15.1 sec; improvement –2.4 sec).

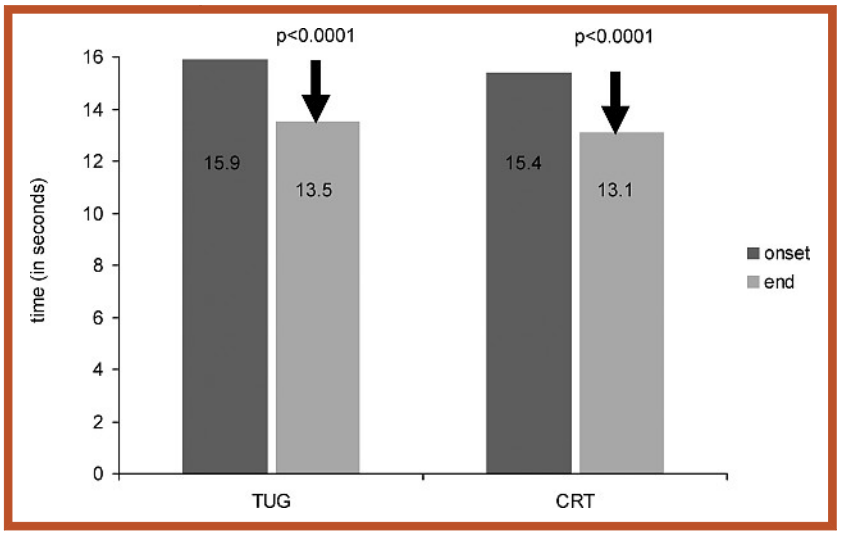

Fig. 1: Average time (s) used for the performance of the Timed Up and Go Test (TUG) and the Chair Rising Test (CRT) at onset and end of the observation. Remark: A mean increase of 2.6 s in the performance of the TUG results in a 24 % increased risk for non-vertebral fractures (Zhu et al. *J Bone Miner Res.* 2008;23:S119)

3.5 Chair Rising Test (CRT)

The changes in the ability to perform the CRT showed no dependency on BMI, but again, on gender, age and CrCl. Men showed a mean improvement of 3.2 sec, while the mean improvement for women was 2.2 sec.

At baseline the average time for the performance for the entire group was 15.4 sec.

Concerning the effect of age, patients younger than 70 years needed 13.1 sec, patients between 70 and 80 years of age 15.6 sec, and patients older than 80 years needed 17.9 sec to perform the CRT. Improvements however were not different across these age groups (with –2.1, –2.4 and –2.3 on the average for the respective three age groups). The average reduction for the whole group was significant (2.3 sec) (Fig. 1).

Patients with CrCl < 65 ml/min had higher baseline values (mean 16.3 sec) and somewhat higher improvement (–2.5 sec) compared to those with CrCl ≥ 65 ml/min (baseline 14.8 sec, improvement –2.3 sec). Similar behaviour for TUG and CRT was found in PMO patients.

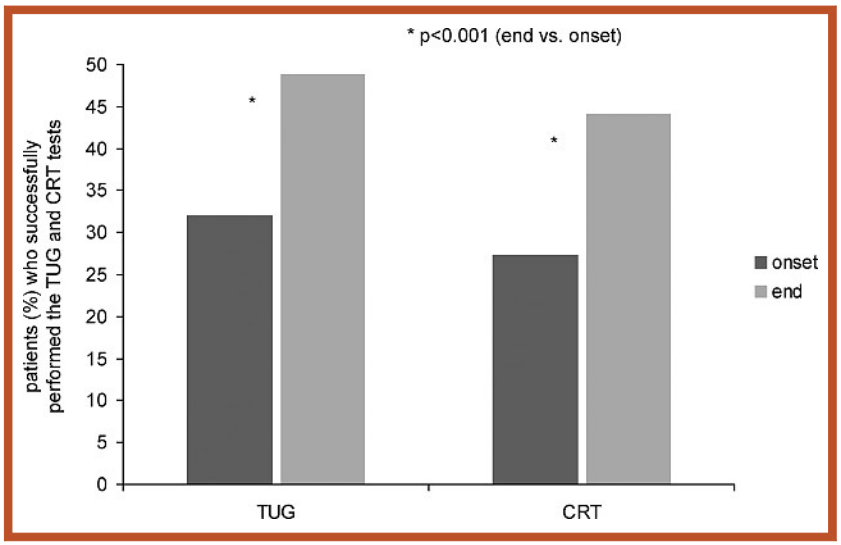

Fig. 2: Percentage of patients (%), who successfully performed the Timed Up and Go (TUG) test and the Chair Rising Test (CRT) at onset and end of the observation period.

3.6 Back pain

At the end of the observation period, back pain was reduced by 41 % from an initial average of 5.9 points to 3.5 points (p < 0.0001). Identical and significant results were found for PMO patients. While men showed a mean pain improvement of 3.0 points (onset: 6.4, end: 3.4), the mean improvement for women was 2.4 points (onset: 5.9, end: 3.5).

Mean values at baseline did not differ much across age groups. Rates of improvements, however, declined somewhat with age. BMI had little influence on initial back pain and back pain improvement. Patients with CrCl < 65 ml/min reported a significantly higher back pain level (P = 0.014) at the onset and at the end (P < 0.0001) than patients with higher CrCl (≥ 65 ml/min). The improvement in back pain was significant in both groups (Fig. 3). Similar results have been obtained in the PMO patients' subgroup.

The percentage of patients, who reported no or low pain level (0–2), increased from 5.4 % at the beginning of the observation to 28.8 % at the end. A medium pain level (3 to 6) was documented for 51.5 % of the patients at baseline and for 66.3 % at the end. The rate of patients who reported the highest pain (7 to 10) declined from 43.1 % to 4.9 % in the course of the observation (Fig. 4). A similar pattern was documented for the PMO patients.

Results grouped in categories were also analyzed for the different subgroups. In both women and men there was a marked increase in the percentage of patients in the lowest pain (class 0 to 2) when comparing the beginning and the end of observation (men: 5.7 % to 33.5 %, women: 5.3 % to 28.4 %). At the same time, there was a major decrease in the rates of patients who reported high pain (class 7 to 10): 53.1 % to 5.0 % for men, 42.4 % to 5.0 % for women.

When analyzing back pain levels in regard to age groups, there was a marked increase in the percentage of patients in the lowest pain class when comparing the beginning and the end of observation. In patients younger than 70 years it rose from 6.1 % to 36.1 %, in patients between 70 and 80 years from 4.9 % to 26.5 %, and in patients older than 80 years from 5.8 % to 25.1 %. Thus, the younger the patients the more ended up in the lowest pain class. There was also a major decrease in the rates of patients in the highest pain class (patients < 70 from 40.5 % to 4.1 %, 70–80 from 43.2 % to 3.9 %, > 80 from 44.8 % to 7.7 %). The percentage of patients still remaining in the highest pain class was highest in the elderly (Fig. 5).

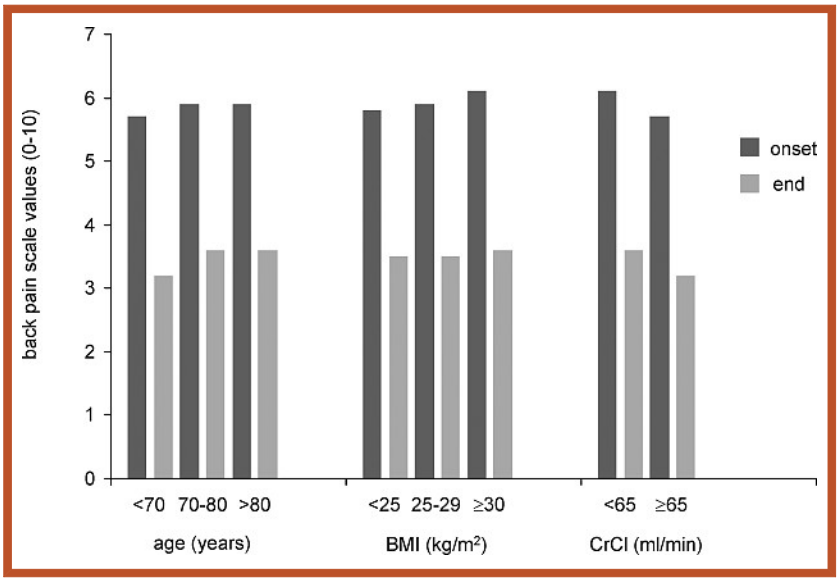

Fig. 3: Back pain scale values according to age, body mass index (BMI) and creatinine clearance (CrCl) reported by the patients at onset and end of the observation period.

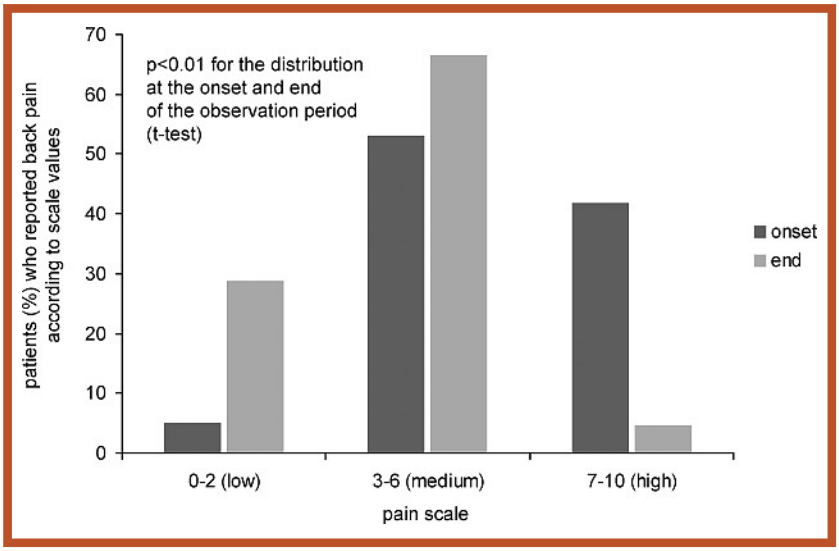

Fig. 4: Percentage of patients according to their reported back pain scale values at onset and end of the observation period.

3.7 Patients' evaluation of pack design

At the end of the observation, patients were asked to evaluate several aspects regarding the packaging design of the combination product. 94.4 % of the patients rated handling in general as very good or good, 91.8 % thought the clarity of the intake schedule was very good or good, and 91.2 % considered the ease with which tablets could be pushed through the blister foil to be very good or good.

Compliance was rated by the patients as very good or good in 93.4 % of the patients.

3.8 Adverse events and adverse drug reactions

Throughout the study for 85 out of the total 2579 patients and for 62 out of the 2106 PMO patients at least one AE was documented (total incidence 3.30 % and 2.94 % for PMO). Overall 178 AE were reported (for PMO subgroup 128). 2494 patients of the total group and 2044 of the PMO subgroup reported no AE at all. One PMO patient and 2 patients with glucocorticoid-induced osteoporosis experienced serious AE that required hospitalisation. The average initial serum calcium level was 2.40 mmol/l and there was no case of hypercalcaemia at the end of the trial.

No causal relationship with the combination therapy was assumed

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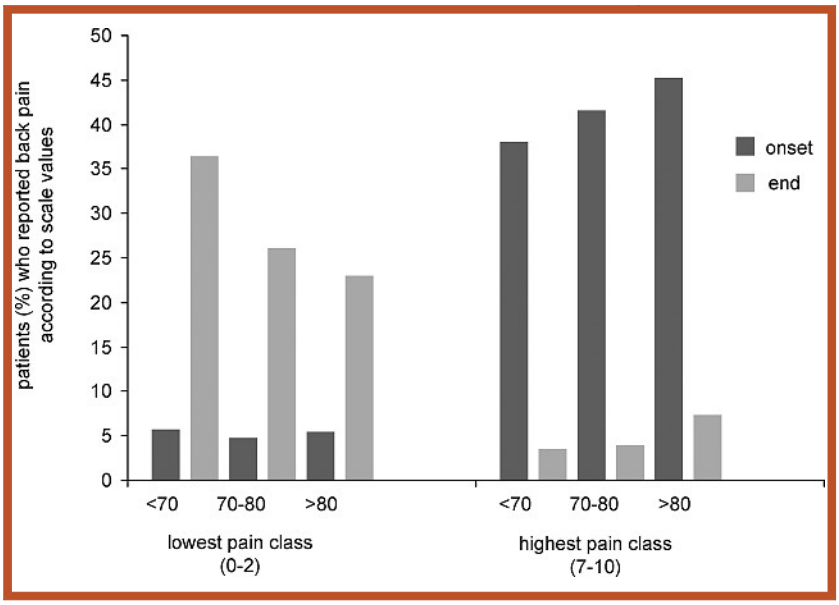

Fig. 5: Percentage of patients, subdivided by their age groups, according to their reported back pain scale class at onset and end of the observation period.

from reporting physicians and for 2 out of those 3 serious AE cases. For 1 patient, however, the causal relationship of the serious AE was assessed to be related to treatment (dizziness, asthenia, vomiting, nausea and diarrhoea). Full recovery was achieved after hospitalisation.

For 79 out of the total 2579 patients and for 58 out of the 2106 PMO patients an ADR was documented (total incidence 3.06 % and 2.75 % for PMO). Most of the events (57.14 % of all reported ADR, n = 96) were assigned to the System Organ Class (SOC) "gastrointestinal disorders": Nausea occurred in 1.16 % (n = 30) of the 2579 patients, abdominal discomfort in 0.35 % (n = 9), upper abdominal pain in 0.31 % (n = 8), diarrhoea in 0.31 % (n = 8), constipation in 0.27 % (n = 7). 22 ADR were linked to the SOC "nervous system disorders", mostly dizziness in 0.43 % (n = 11) and headache in 0.27 % (n = 7). 16 ADR are related to the SOC "skin and subcutaneous tissue disorders", mostly pruritus in 0.23 % (n = 6) of the patients. The distribution was nearly the same in PMO patients. The documented ADR in both, the total and the PMO subgroup, are consistent with the known safety profile as stated in the current Summary of Product Characteristics (SmPC) of the combination package of alendronate plus alfacalcidol.

4. Discussion

High life expectancy is an achievement of the modern era. However, longevity is inevitably associated with an increase in age-related diseases placing a heavy burden on the healthcare system. Osteoporosis-related fractures are a typical example for this problem. The consequences include financial, physical and psychosocial aspects, which significantly affect the individual as well as the family and community. Although low bone mineral density (BMD) and bone strength have been established as an important predictor of fracture risk, the results of many studies indicate that clinical risk factors related to risk of falls, such as age, low BMI, low levels of physical activity resulting in muscle weakness, central nervous system (CNS) deficiencies, often summarized as "frailty", affect fracture incidence through their effects on BMD, bone strength and propensity to fall as well as inability to absorb impact [1, 4, 5, 17, 18].

Accordingly, fracture prevention can only be approached by a multifactorial strategy and the adopted pharmacotherapy should be suitable to increase bone mass, improve bone quality and augment muscle power and neuromuscular coordination, and thereby reduce the incidence of falls.

Bisphosphonate therapy is a well established strategy to increase BMD and subsequently reduce the fracture risk [27, 28]. The modern amino-bisphosphonates, and among those alendronate in particular, are currently considered first line drug treatment for PMO [18, 29]. The approved and established dose of alendronate is either 10 mg daily or 70 mg weekly.

The mechanism of action of alendronate is based on its predominant deposition on sites of bone surface during bone resorption. It was demonstrated that alendronate is taken up specifically by osteoclasts and inhibits bone resorption by an interaction with osteoclast metabolism [19, 29–32]. The unique property of selective and complete uptake by the intended target organ, *viz.* bone, excludes major adverse events on other tissues but also beneficial effects on other risk factors, such as muscle weakness or falls [33, 34]. Interestingly, with both alendronate and risedronate it was not possible to reduce the incidence of hip fractures or other non-vertebral fractures, if patients were not recruited by low BMD but by other risk factors (e. g. muscle weakness and risk of falls) [35, 50].

The efficacy of alfacalcidol and its active metabolite calcitriol to increase BMD and reduce vertebral and non-vertebral fractures has been shown in numerous studies and was summarized in three meta-analyses [36–38]. Moreover, the active vitamin D analogues alfacalcidol and calcitriol were found to exhibit better efficacy in preventing spinal bone loss and vertebral or non-vertebral fractures in PMO compared to native vitamin D [39, 40]. Furthermore alfacalcidol was shown to significantly reduce the number of falls and fallers in elderly populations [41–44]. The superior anti-fall effi-

cacy of treatment with alfacalcidol versus native vitamin D was confirmed in two meta-analyses [45, 46].

Due to the feedback regulation of the final activation step of 25-hydroxyvitamin D (25 (OH)D) in the kidneys into the active hormone 1.25-dihydroxyvitamin D oral supplements of plain vitamin D have a limited ability to increase the D-hormone levels or vitamin D receptors (VDR) in the target tissues [47–49]. Alfacalcidol, which is already hydroxylated at the crucial 1-α-postion, is a pro-drug of the D-hormone calcitriol and is activated in the liver and in bone. That means alfacalcidol bypasses the metabolic limitations of native vitamin D pathway [47–49]. Alfacalcidol is distinguished from all other currently available anti-osteoporotic medications by its unique mode of action. The following pleiotropic actions were detected and described in the literature for alfacalcidol or the end-product calcitriol:

- Gut: induces increased intestinal calcium absorption [51, 52]
- Parathyroids: reduce hyperplasia and over-secretion of parathyroid hormone (PTH) by direct effect on parathyroid glands and by increasing serum calcium [51–53]
- Bone: antiresorptive plus anabolic effects [54–58, 77]
- Muscle: increases muscle power, muscle function and physical abilities [42, 59–63]
- Brain: improves balance and cognitive abilities [5, 6, 64–67]
- Immune system: immuno-modulation and pro- and anti-inflammatory cytokine regulation [68–73].

The pleiotropic actions on two organs are of special interest for treatment of osteoporosis and osteoporosis-related fractures: bone and muscle. The effect of alfacalcidol on bone resorption and formation was studied in ovariectomized rats, an osteoporosis model recommended by regulatory agencies [74]. Alfacalcidol increased BMD and bone strength more efficiently than native vitamin D independent of its calcium-related effects and independent of PTH [75].

While alendronate and estrogens suppress bone turnover, including bone resorption and bone formation, alfacalcidol was shown by bone histomorphometry to suppress only bone resorption and to enhance bone formation [75, 76]. Alfacalcidol inhibited osteoclastogenesis *in vivo* by decreasing the pool of osteoclast precursors in bone marrow [77] and preferentially stimulated the recruitment and differentiation of new osteoblasts from mesenchmal precursors [76]. Iwamoto *et al.* [78] compared the effects of risedronate and alfacalcidol on cortical and cancellous bone mass and bone strength in ovariectomized rats. Risedronate prevented the decrease in the cancellous bone by suppressing increases in cancellous bone resorption and formation without significant effects on the cortical bone area or bone strength. On the other hand, alfacalcidol increased cancellous bone, cortical bone and bone strength by increasing periosteal and endocortical bone formation and preventing an increase in endocortical bone resorption.

D-hormone is important if not essential for muscle strength [60, 62]. It has been shown in several studies that a therapy with alfacalcidol or calcitriol significantly improves muscle power and balance [79, 80]. Higher D-hormone serum concentrations in the elderly are significantly associated with increased leg extension power [81] and better muscle function [82] and lower rate of falls [83]. The cross-sectional area and number of fast-twitch (type IIA) muscle fibers has been shown to increase within 3 months under a treatment with alfacalcidol 1 μg per day in osteoporotic older women [59]. The substitution of the active D-hormone analog improves muscle strength (isometric knee extension strength) and functional ability (walking distance over 2 min) significantly after 6 months of treatment in elderly D-hormone deficient women [61]. Patients with rheumatoid arthritis, osteopenia and normal vitamin D levels who received a daily dose of 1 μg of alfacalcidol showed a significant increase in muscle power (60 %) as compared to only an 18 % increase in those patients who received a daily dose of 1000 IU of plain vitamin D [71].

In a recent study of glucocorticoid treated rats, alfacalcidol prevented not only a decrease in BMD, but also muscle atrophy [84]. Gallagher showed in the STOPIT study that physical performance, tested with the chair rising or timed walking test, declines with age [42] and that treatment with 0.5 μg D-hormone daily over three years could delay the decline of physical performance in this population. Recently, treatment with alfacalcidol over 6 months has been shown to increase muscle power, muscle function and balance as measured with three different muscle power and balance tests [97]. In a cross-sectional study it was suggested that long-term treatment with alfacalcidol could improve body sway, e. g. improve balance disorders in elderly women [66].

The dual effect on bone turnover with additional inhibition of osteoclastic bone resorption due to the effect on osteoclast precursors and on PTH and the anabolic effect on osteoblasts and on muscle metabolism and muscle action makes alfacalcidol a very interesting partner for purely anti-bone resorptive substances like alendronate and contributes to the following optimization of therapeutic results of such a combination [10, 12, 85].

A preclinical study investigated the combined effects of alendronate and alfacalcidol on bone density, bone strength and bone quality in aged ovariectomized (OVX) female rats versus the respective monotherapies [7]. The results showed that biochemical markers of bone resorption, like deoxypyridinoline, were significantly decreased when using combined treatment, as compared to respective single treatments, and confirmed the hypothesis of an increased inhibition of bone resorption. The combined treatment provided a significantly greater marked effect in terms of BMD and bone mechanical strength (mid-femur and L2-L4). Micro-CT and histomorphometric analyses showed that the density of trabecular bone, after using combined treatment, appeared to be higher than that resulting from a single

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treatment by showing better preservation of the bone micro-architecture. These results are in line with those of a study suggesting the bone anabolic effects of alfacalcidol could be enhanced when combined with alendronate [85].

Another study, featuring a similar design, compared the efficacies of risedronate and calcitriol in the prevention of bone loss among OVX rats [8]. OVX rats treated with a combination of both had higher tibial and vertebral BMD values, and significantly increased bone strength in the long bone and vertebra. In combined administration, a significantly higher cancellous bone area was noted, as compared with the groups receiving monotherapies. Authors postulated that in combined therapy, calcitriol enhanced the inhibitive effects of risedronate on osteoclast maturation and number, while partially counteracting the suppressive effects of risedronate on bone formation. The parallel administration of high doses of risedronate and calcitriol did stabilize serum calcium.

In a similar model using OVX rats risedronate was also tested with alfacalcidol [9]. The increase in vertebral strength was higher in the combination therapy than in the monotherapies. Of particular interest was that in the peripheral quantitative computertomography (pQCT) analysis the additional effect of the combination was produced in cortical and sub-cortical regions more than in the trabecular region, and this effect was mainly responsible for the marked increase in spinal strength.

We performed a prospective, randomized, actively-controlled, observer-blind study in patients with established postmenopausal or male osteoporosis [11]. Ninety patients (57 women, 33 men) with an average age of 66 years were randomly assigned to receive either 1 μg alfacalcidol daily + 70 mg alendronate weekly + 500 mg calcium daily (group A, n = 30) or 1 μg alfacalcidol + 500 mg calcium daily (group B, n = 30) or 70 mg alendronate weekly + 1000 mg calcium + 1000 IU vitamin D daily (group C, n = 30). In all patients BMD was measured at the lumbar spine (LS) and femoral neck (FN) using DEXA. Back pain was assessed using a 4 point scale.

During the 2-year study a significant mean percentage increase in BMD at LS of 9.6 % in group A, of 3.0 % in group B and of 5.4 % in group C versus baseline was observed. A significant medium increase in BMD of 3.8 % was observed at FN in group A versus baseline, of 1.5 % in group B and of 2.4 % in group C, respectively. The differences between the combined therapy and alfacalcidol and alendronate monotherapy were significant at both sites. The 2-year rates of patients with at least one vertebral fracture were 1 in group A, 5 in group B and 4 in group C. The 2-year rates of patients with at least one non-vertebral fracture were 1 in group A, 4 in group B and 6 in group C. The number of falls after 2 years was 4 in group A, 5 in group B, and 11 in group C. After 24 months, 80 % of the patients in the combination group were free from back pain, compared to 43 % in the alfacalcidol group and 30 % in the alendronate + vitamin D group. The superiority of the combined schedule was significant for BMD, total fractures and back pain. The overall safety profiles of the three treatments were not different: four cases of moderate hypercalcuria in group B and 1 in group A but no case of hypercalcaemia.

Another study in humans to assess the additive impact of alfacalcidol 1 μg daily on BMD and on bone strength in postmenopausal women treated with alendronate 70 mg weekly and 500 mg calcium daily was done by Felsenberg *et al.* [13]. In a randomized, double-blind, placebo controlled study, 279/282 postmenopausal women were recruited (ITT population) aged 73.6 ± 4.7 years who suffered from low bone mass and were treated with 70 mg alendronate weekly and 500 mg calcium daily. These patients received, in addition, either 1μg alfacalcidol or placebo daily. BMD was measured with DEXA at the LS and proximal femur and at the forearm and tibia with pQCT for 36 months.

DEXA-BMD of LS (L1–4) increased significantly after 36 months in both groups, by 6.65 % ($p < 0.0001$) in the combination group vs. 4.17 % ($p < 0.0001$) in the monotherapy group. Group difference was significant after 3 years ($p = 0.026$). At the end of the study, significant differences were found in favor for the alendronate + alfacalcidol group in trabecular density (tibia) ($p = 0.002$), cortical density (mid shaft tibia) ($p = 0.043$), and bone strength ($p = 0.001$) measured by tibial strength strain index (SSI). The low incidence of non-vertebral fractures was further reduced by 38 % in osteoporotic patients treated with alendronate + alfacalcidol compared to those with alendronate alone [86]. Overall AE and SAE showed no significant difference between the groups. Hypercalcaemia was not found because all patients were treated with alendronate which has a lowering effect on serum calcium. The addition of alfacalcidol counteracted this serum calcium decreasing tendency of the bisphosphonate.

The authors concluded that alfacalcidol significantly improves the efficacy of alendronate treatment in osteopenic/osteoporotic postmenopausal women concerning DEXA-BMD of spine and trabecular BMD and especially showed a significant effect on cortical bone and bending stiffness of the tibia.

Another study showed the superiority of alfacalcidol and alendronate combined treatment over the monotherapies and calcium as control groups [87]. The combination group (10 mg alendronate + 0.5 μg alfacalcidol daily) increased LS BMD (+8.4 %) better than alendronate alone (+6.5 %) after 24 months, but the inter-group difference was not significant ($p = 0.23$) for the combination with a dose of 0.5 μg alfacalcidol.

No case of clinical hypercalcuria or hypercalcemia was recorded. 24-h urinary calcium was significantly increased by alfacalcidol monotherapy, while significantly decreased in alendronate monotherapy.

The latter findings are supported by an earlier trial comparing the combination of calcitriol and alendronate with the monotherapies [88]. An explanation is that the episodes of hypercalcuria induced by alfacalcidol or calcitriol can be reduced by alendronate. It has also been shown that the secondary hyperparathyroidism, often observed in elderly osteoporotic patients, decreases the beneficial effects of alendronate on BMD. A combination of alendronate plus calcitriol or alfacalcidol corrects the decreased response to alendronate by reduction of PTH [89]. This effect was recently confirmed by studying patients unresponsive to the combination of alendronate and native vitamin D. It was confirmed that in such non-responders, combined therapy with alendronate plus alfacalcidol increases BMD and improves the biochemical markers of bone turnover without any increase in the incidence of adverse effects [90].

A prospective, randomized study in 363 women with postmenopausal osteoporosis (mean age: 74 years) comparing the combination of alendronate (5 mg daily) + alfacalcidol (1 μg daily) with the corresponding monotherapies showed a favorable trend for the combination therapy in reducing vertebral fractures (new vertebral fractures: alendronate + alfacalcidol: 2.5 %; alendronate: 7.6 %; alfacalcidol: 7.4 %) already after 6 months of treatment [91]. Recently Orimo *et al.* confirmed in a randomized controlled trial that the rate of vertebral fractures after 6 months of treatment was significantly lower in the combination group (alendronate, 5 mg/day; alfacalcidol 1 μg/day) compared to the alendronate monotherapy in postmenopausal women with osteoporosis [114]. The further evaluation of this Japanese Osteoporosis Intervention Trial (JOINT-2) showed after 2 years of treatment a significant reduction of the rate of non-vertebral fractures in the subgroup with weight bearing bone by the combination group compared with the mono-therapy group [124].

Thus clinical trial data from combined treatment with alendronate also suggests that a daily dose of 1 μg alfacalcidol should be the dose of choice in the treatment of postmenopausal osteoporosis.

Based on the above described different and synergistic modes of action, the preclinical and clinical effects of the combination of alfacalcidol and alendronate, a new combination package of these two medications was chosen for our study. To identify elderly persons with a high risk of falls, fractures and frailty, measurements and questionnaires must be used with high sensitivity in order to characterize these risks. Individual ability to repeat specific physical activities in a defined time must be determined. The simple measurements used in the study should open up additional, quantitative possibilities for assessing the risk of falls, non-vertebral fractures and frailty. The adopted tests to measure and document the effects of the combination product were validated as useful and positive results and should motivate the patients to continue the pharmacological and physical treatments.

Successful performance in the two tests (CRT = 10 sec and TUG = 10 sec) should prove whether therapy with the combination product was effective in improvements in fall risk tests. There is no doubt that for the patients, very strong, acute back pain, but also especially strong chronic back pain and/or muscle pain is the most important symptom with strong negative influence on the quality of life and also mobility, like limitations in household and outdoor activities [92, 93]. Improvements in all three parameters should prove whether a therapy with the combination product is effective in a real world trial done by practitioners.

In this prospective, open, uncontrolled study we found that treatment with a combination of 1 μg alfacalcidol daily and 70 mg alendronate weekly in elderly osteoporotic and osteopenic patients significantly increases their muscle power, muscle function and balance and decreases their back pain. After 3 months of treatment with the combination product, participants showed a statistically significant better performance in the two muscle tests, CRT and TUG. There was a significant increase in the number of patients able to successfully perform the different tests in the whole group (Table 1), but also in a subgroup of patients with PMO (Fig. 2). At the end of the trial the mean time needed for the CRT and for the TUG was decreased by 2.3 sec and 2.4 sec (Fig. 1). In the subgroup of PMO the mean time for the CRT and TUG was decreased by 2.0 and 1.9 sec, respectively. The lower effect in the PMO subgroup could be explained by gender differences (women respond less than men) or by the fact that established osteoporosis is correlated to advanced increase in muscle weakness or frailty with less chance for a positive response.

In this context it is of great interest that a recently published 10-year longitudinal study confirmed that a one unit decrease in hip BMD T-score was associated with 33.7 %, 40.6 % and 36.2 % increase of the risk of non-vertebral, vertebral and any fracture, respectively, whereas also a 1 SD (2.6 sec) increase in TUG was associated with a 24.0 % and 16.6 % increase in the risk for non-vertebral and any fracture, respectively [23]. The results confirm the independent effects of measures of neuromuscular coordination and bone structure to incident fracture risk. Modern fracture prevention should include assessment of both neuromuscular risk and skeletal structural risk as assessed by the TUG and DEXA hip BMD.

The changes in the ability to perform CRT and TUG at baseline showed no dependency on BMI, but on gender, age and CrCl. Men showed a better improvement than women.

Elderly patients needed more time to perform the muscle power and muscle function tests at onset, but the improvements in seconds during the treatment were, interestingly, not different. Patients with CrCl < 65 ml/min had higher baseline values and a somewhat higher improvement than those with CrCl ≥ 65 ml/min.

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A low CrCl or impaired renal function is associated with lower calcium absorption, lower availability of D-hormone in the target tissues, lower physical performance, increased risk of osteopenia and osteoporosis, falls and fractures and increased risk of frailty [94–96]. The efficacy of alfacalcidol or calcitriol in reducing falls is especially pronounced in patients with low CrCl [43, 44].

It is obvious that based on literature data alendronate does not have any influence on the neuromuscular system. On the other hand alfacalcidol has been shown to be effective *in vitro*, and in preclinical and clinical studies effectiveness. Another proof that alfacalcidol in the combination product is responsible for the effect on muscle power and neuromuscular coordination is the fact of nearly the same outcomes in our study compared to two studies of alfacalcidol monotherapy [97, 98].

Dukas *et al.* found, after 6 months, a significant increase in the number of patients able to successfully perform the tests: 18.8 % to 39.1 % for the CRT and 29.9 % to 51.7 % for the TUG, respectively [97]. Schacht and Ringe described after 6 months a significant increase for the CRT from 21.7 % to 44.2 % and for the TUG from 24.6 % to 46.3 %, respectively [98].

The time used was decreased by –2.3 sec for the CRT and by 2.0 sec for the TUG in the first study and by –3.1 sec and by –3.0 sec in the second study, respectively.

A new and very important outcome parameter was investigated for the first time: the effect of the combination product on back pain. Using a visual analogue scale (VAS) ranging from 0 (no pain) to 10 (worst imaginable pain) a significant reduction of 41 % from 5.9 to 3.5 in the whole group and in the PMO subgroup was found. Men responded better to the therapy than women. The younger the patients the more they ended up in the lowest pain class. The percentage of patients still remaining in the highest pain class was highest in the elderly (Fig. 5). Patients with new vertebral fractures or deformities have an increased risk of back pain, physical disability caused by back pain and number of days of bed rest [92, 93]. Acute pain is usually transient. Osteoporosis treatments that reduce the incidence of new vertebral fractures also reduce the described symptoms. Chronic back pain is caused by vertebral deformations in the periost, so-called "bone pain", muscle pain by myogeloses and myotendinoses, hardening of muscles in the back, inflammation by changes of the spine statics and microfractures and their delayed healing [99, 100]. Musculoskeletal pain is a well-documented cause of functional decline and progressive disability in older adults [104].

The reduction of back pain by the combination therapy could be explained by the known reduction of vertebral fractures by alendronate [14, 15], but better by a direct and quick effect of alfacalcidol on CRT and TUG, as proven in our study and on muscle metabolism and immune system, especially on reduction of pain-inducing cytokines [11, 70, 71, 101–103].

Painful microfractures, also observed in patients without significant osteoporosis, and their potentially preferred healing by the combination of alendronate and alfacalcidol, may be another explanation [8, 9, 85, 100, 105, 116].

Last, but not least, muscle pain related to sub-clinical or overt osteomalacia and osteoporomalacia combined with femoral muscle weakness and gait disturbances could be quickly cured by alfacalcidol in the new combination strategy [106–110]. Psychological components like depression induced by increased risk of falls and fractures, increased fear of falls, decreased functional ability and quality of life are certainly other reasons for pain and might be reduced by alfacalcidol based on the correlation to disturbed vitamin D metabolism and effects of alfacalcidol [98, 108, 111–113].

The results of our study confirm the safety of a combination of alendronate and alfacalcidol shown in preclinical and clinical studies [7, 8, 11, 13, 87]. Negative interactions between both drugs have not been reported, while a risk reduction of hypercalcaemia and hypercalcuria was noted in combination therapy trials [11, 87, 88], even when using supra-physiological dosages [8, 115]. Furthermore the debated long-term side effects of alendronate, e. g. oversuppression of bone turnover with the consequences of impaired micro- and macro-facture healing and decreased bone quality ("frozen bone", "adynamic bone") might be reduced by co-administration of alfacalcidol on the basis of pre-clinical studies [7–9, 85, 105, 116]. Considering the findings that inflammation, low serum calcium or low vitamin D levels and high serum parathyroid hormone (PTH) levels play key roles in the osteonecrosis of the jaw induced by bisphosphonates, alfacalcidol could potentially even limit this low risk [117–119].

The use of drug packaging fixed or separated in one-week blisters, which explain the mode of intake as in our study, was positively judged by the patients in two other studies [120, 121]. Better compliance, improved patient convenience and reduced dispensing mistakes may be the practical advantages.

There are important limitations in this study. Since this is an open, uncontrolled, prospective study, the interpretation of our study results should be done with caution. A "study effect" by learning to improve the test performances cannot be excluded. In addition there is no information given for changes in physical activities before and during the study. An increase could partly explain the improvements in CRT and TUG.

A placebo effect on back pain is often described in controlled clinical trials in osteoporosis, especially with native vitamin D [122]. A pharmacological, true effect of alfacalcidol on chronic back pain in principle cannot be excluded [11, 101]. There is no doubt on the other hand that alfacalcidol is working in pre- and clinical osteomalacia and that the efficiency on muscle weakness and back pain depends on vitamin D deficiency or insufficiency.

Having no information about the vitamin D status in our patients is an important weakness [123]. Another weakness of our study is the fact that type and dosage of analgesics are not reported and not correlated to the responders of alfacalcidol.

In general, we could not control other important covariates such as co-morbidity, number of medications and other non assessed variables. Finally, the diagnosis of osteoporosis in the Caucasian elderly men and women was based on different radiological methods. Accordingly our findings cannot be generalized for a mixed osteoporotic population, a younger population, or to osteoporotic men and women of other races.

5. Conclusion

The basis of future optimal treatment for the prevention of fractures is to increase bone strength, improve muscle power, muscle function and balance and thereby reduce back pain in the long term, without exposing the patient to serious deleterious effects. Preclinical and clinical data featuring BMD and bone quality suggest that a combination therapy of alfacalcidol and alendronate warrants better efficacies on bone strength and fractures due to their different and complementary modes of action. Synergy may lie in the fact that the published data strongly suggest that, apart from the pleiotropic effects on musculoskeletal, immune and neurological systems, alfacalcidol in combination with alendronate is able to adjust a better osteoblastic/osteoclastic balance via distinct mechanisms. Our data showed that the new combination package of 70 mg alendronate weekly and 1 µg alfacalcidol daily improved significantly already after 3 months of treatment muscle power, muscle function and balance measured by Chair Rising Test (CTR) and Timed Up and Go Test (TUG) and significantly reduced back pain in mainly elderly patients with diagnosed PMO.

Therefore our results may contribute to the previously observed reduction of falls and fractures by this combined therapy. We conclude, based on our findings, that this innovative treatment strategy is safe and the combination package might improve compliance and reduce dispensing mistakes. There is an urgent need to confirm our results by double-blind clinical studies.

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Conflict of Interest

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