Alfacalcidol Versus Plain Vitamin D in the Treatment of Glucocorticoid/Inflammation-Induced Osteoporosis

JOHANN D. RINGE, HERBERT FABER, PARVIS FAHRAMAND, and ERICH SCHACHT

ABSTRACT. Treatment with plain vitamin D is a nutritional substitute, while the application of alfacalcidol is an active hormonal therapy. Due to strong feedback regulation, plain vitamin D is not activated in the kidney in vitamin-replete patients, while alfacalcidol, having been hydroxylated at position 1, bypasses regulation and increases available amounts of active D-hormone in different target tissues. Nevertheless, a majority of physicians still prescribe plain vitamin D plus calcium as a first-step prevention or even as therapy for glucocorticoid (GC) induced osteoporosis. This article summarizes results of our previous study comparing the therapeutic efficacy of the D-hormone analog alfacalcidol to plain vitamin D in patients with established GC induced osteoporosis with or without vertebral fracture. Patients taking longterm GC therapy were included as well-matched pairs to receive randomly either 1 µg alfacalcidol plus 500 mg calcium per day (group A, n = 103) or 1000 IU vitamin D_3 plus 500 mg calcium (group B, n = 101). The mean bone mineral density (BMD) values at baseline for the 2 groups for alfacalcidol and vitamin D_3, respectively, were: lumbar spine T score –3.26 and –3.25; femoral neck –2.81 and –2.84. Rates of prevalent vertebral and nonvertebral fractures were not different between groups. In the 3 year study we observed in the alfacalcidol group as compared with the plain vitamin D group, respectively: a 3 year median percentage increase of BMD at the lumbar spine of 2.4% versus –0.8% ($p < 0.0001$); a median increase at the femoral neck of 1.2% versus 0.8% ($p < 0.006$). Likewise observed in the alfacalcidol as compared to the vitamin D group, respectively: a 3 year rate of patients with ≥1 new vertebral fracture of 9.7% versus 24.8% (risk reduction: 0.61; 95% CI 0.24 to 0.81; $p = 0.005$); a 3 year rate of patients with ≥1 new nonvertebral fracture of 15% versus 25% (risk reduction: 0.41; 95% CI –0.06 to 0.68; $p = 0.081$); a 3 year rate of patients with ≥1 new fracture of any kind of 19.4% versus 40.6% (risk reduction: 0.52; 95% CI 0.25 to 0.71; $p = 0.001$). In accordance with the observed fracture rates, the alfacalcidol group showed a substantially larger decrease in back pain than the plain vitamin D group ($p < 0.0001$). Generally, side effects in both groups were mild, and only 3 patients in the alfacalcidol group and 2 patients in the vitamin D group had moderate hypercalcemia. We conclude that alfacalcidol plus calcium is highly superior to plain vitamin D_3 plus calcium in the treatment of established GC induced osteoporosis, and the latter should no longer be used as monotherapy. (J Rheumatol 2005;32 Suppl 76:33-40)

Key Indexing Terms:
ALFACALCIDOL VITAMIN D_3 GLUCOCORTICOIDS
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INTRODUCTION

Glucocorticoids (GC) are widely used in daily practice since they play a major role in the treatment of a number of chronic diseases with high socioeconomic impact. Despite their indisputable therapeutical advantages, longterm GC use is overshadowed by several relevant side effects that can produce morbidity comparable to that of the original illness. The most important of these is secondary osteoporosis, which is known to arise not only as a consequence of longterm GC administration but also due to deleterious effects of the underlying disease on bone metabolism. The bone loss is highest in the initial 3 to 6 months of therapy and the fracture incidence in GC induced osteoporosis (GIOP) is estimated to be between 30% and 50% among patients receiving this immunosuppressive therapy over longer times. Therefore, an early, efficient, and cost-effective treatment is mandatory.

The early and rapidly increasing risk of fractures cannot be explained by the respective loss of BMD alone. It is suggested, however, that negative influences on bone quality and muscle metabolism and therefore increased risk of falls contribute to this rapid increase in fracture risk. GC affect bone through multiple mechanisms. Pathogenetic effects of GC on bone and calcium homeostasis include decrease in intestinal calcium uptake, enhancement of renal excretion of calcium, increase in osteoclastic bone resorption, impairment of osteoblast function, promotion of osteocyte apoptosis and (directly and indirectly) development of myopathy. Recent work demonstrates GC upregulation of myostatin, a negative regulator of muscle mass[1]. It has been recently confirmed in vitamin D receptor (VDR) gene-deleted mice that absence of VDR causes muscle abnormalities independently of secondary metabolic changes, e.g., hypocalcemia or hyperparathyroidism, and that treatment with D-hor-

From the Klinikum Leverkusen, Medizinische Klinik 4, University of Cologne, Cologne, Germany; and the Department of Rheumatology and Rehabilitation, University Clinic Balgrist, Zurich, Switzerland.

J.D. Ringe, MD, Head; H. Faber, MD, P. Fahramand, MD, Klinikum Leverkusen, Medizinische Klinik 4; E. Schacht, PhD, Department of Rheumatology and Rehabilitation, University Clinic Balgrist.

Address reprint requests to Dr. J.D. Ringe, Klinikum Leverkusen, Medizinische Klinik 4, Akademische Lehrkrankenhaus der Universität zu Köln, Dhünnberg 60, D-51375 Leverkusen, Germany. E-mail: ringe@klinikum-lev.de

mone counterbalances abnormalities in myoblastic cells and is necessary for optimal muscle cell differentiation[2]. GC reduce the number of VDR, and cytokines from underlying diseases reduce renal production of D-hormone. These results suggest that the GC/inflammation induced decline in muscle power and increase in falls could be explained in part by decreased VDR and D-hormone in serum and/or at the receptor level.

Interestingly, all these deleterious pharmacological effects of GC on bone or muscle can be counteracted directly by a biologically active form of vitamin D, calcitriol (D-hormone)[3]. Moreover, the D-hormone has recently been shown to be a potent immunomodulating agent. There is strong experimental evidence for a disease-modifying influence of calcitriol in murine models of human rheumatoid arthritis[4] and other chronic inflammatory autoimmune diseases[5], and there have been preliminary clinical investigations with alfacalcidol, a prodrug of the D-hormone, to corroborate these findings[6-8]. Accordingly, D-hormone analogs (alfacalcidol, calcitriol) are of high interest in the treatment of GIOP. Although both plain vitamin D and D-hormone analogs act through a common biologically active metabolite, the D-hormone calcitriol, there is evidence that the latter has a higher therapeutic potential, particularly in patients with higher GC dosage (> 2.5 mg prednisolone daily) and with insufficiently controlled inflammatory diseases.

Several clinical studies have shown the efficacy of D-hormone analogs, such as alfacalcidol[9-11] and calcitriol[12,13] in GIOP. In contrast, plain vitamin D has an important role as a nutritional supplement in the treatment of osteoporosis with agents such as bisphosphonates. Studies with plain vitamin D as a monotherapy have yielded unsatisfactory results[14,15] for use with higher dosages of GC. On the other hand, alfacalcidol is more expensive than plain vitamin D and might be associated with a higher incidence of side effects such as hypercalciuria and hypercalcemia.

Although it was clearly shown that calcium and plain vitamin D supplementation is not sufficient to avoid bone loss in patients starting longterm GC therapy[14], there is still a general belief among most physicians that this regimen is an adequate first step in antiosteoporotic treatment. Accordingly, there is a need for directly comparing studies to clarify the respective roles of plain vitamin D and D-hormone analogs in GIOP.

This article reviews published studies, in particular our own 3 year head-to-head trial[16], to consider the therapeutic efficacy of D-hormone analog alfacalcidol versus plain vitamin D in GC/inflammation induced osteoporosis.

It may be important to first provide additional background on the major biological and pharmacological differences of plain vitamin D_3 (cholecalciferol) and the mostly adopted D-hormone analog alfacalcidol (1α-hydroxy-vitamin D).

DIFFERENCES BETWEEN PLAIN VITAMIN D AND ALFACALCIDOL

All cholecalciferol from food or synthesis in the skin is hydroxylated in the liver to 25-OH-cholecalciferol. The hepatic 25-hydroxylation still occurs in states of chronic liver insufficiency and is only impaired in terminal stages of liver disease. There is no regulation and no feedback control of this first step of activation.

However, the second step, renal 1α-hydroxylation, is strongly feedback-regulated. In states of sufficient 1α,25-$(OH)_2$-D, the 1α-hydroxylase is downregulated and no further activation towards 1α,25-$(OH)_2$-D takes place[17]. The biologically not very active 25-OH-D stays in the circulation, is stored in fat tissue, or is excreted after 24-hydroxylation in the kidney to 24,25-$(OH)_2$-D. This adapted, controlled activation of vitamin D is a reasonable self-protection. Otherwise an abundant oral intake of vitamin D (e.g., meal of fresh sea fish) or a sunbath would be followed automatically by hypercalcemia.

Accordingly, treatment with plain vitamin D means nutritional supplementation is effective only in vitamin D-deficient patients with normal kidney function. In vitamin D-replete patients or in renal insufficiency no biological effect can be expected. Alfacalcidol (1α-OH-D) is a synthetic D-hormone analog that is already hydroxylated at the crucial 1α position, which physiologically would take place only in patients with D-hormone deficiency after hepatic hydroxylation. After oral intake and intestinal absorption, 1α-OH-D is automatically hydroxylated in the liver to 1α,25-$(OH)_2$-D, i.e., alfacalcidol is a prodrug to calcitriol[18]. The major difference from that of plain vitamin D is that by this kind of activation the above mentioned feedback regulation of the final renal activation is bypassed by direct activation in the liver. In addition there is evidence that a smaller part of 1α-OH-D is activated by a 25-hydroxylase expressed by osteoblasts, i.e., locally in bone tissue[19]. Accordingly, in addition to systemic D-hormone effects, a localized autocrine or paracrine effect in bone tissue can be achieved when using alfacalcidol.

The fundamental differences between a nutritional supplementation with plain or native vitamin D and the treatment with the active D-hormone analog or prodrug alfacalcidol are summarized in Table 1. On the basis of these biological and pharmacological differences the respective potency of vitamin D and alfacalcidol for prevention and treatment of different stages and forms can be easily explained[17]. On the other hand the possible adverse events also become obvious. There is nearly no risk of hypercalciuria and hypercalcemia even with highly increasing the vitamin D supplements above the recommended doses, while higher doses of alfacalcidol will significantly augment the respective risk. There is one rare but interesting exception: uncontrolled extrarenal activation of plain vitamin D in the granulomatous tissue

Table 1. Distinction between plain vitamin D and the D-hormone analog and prodrug alfacalcidol.

Plain Vitamin D	Alfacalcidol
• Nutritional substitute	• Pharmacological treatment
• Abundant amounts are stored in fat tissue; long half-life	• Activated in liver and bone, prodrug for 1,25-$(OH)_2$-D
• Only effective in patients with vitamin D deficiency	• Effective in vitamin D-depleted and replete patients
• In vitamin D-replete patients no further increase of 1,25-$(OH)_2$-D (D-hormone). Inactivation to 24,25-$(OH)_2$-D	• Increase in active D-hormone; decrease in PTH and bone resorption; increased bone formation and muscle power
• Patients with D-hormone deficiency (inhibition of 1α-hydroxylase) and/or VDR deficit in quantity and quality are resistant to plain vitamin D because no significant increase is achieved	• D-hormone deficiency is treated by bypassing regulation in the kidney • D-resistance is treated by inducing VDR in different target tissues

VDR: vitamin D receptor; PTH: parathyroid hormone

of sarcoidosis[20]. The increased risk of hypercalcemia with an overdose of alfacalcidol, however, is the best proof for its direct hormonal activity.

Results of our own investigation and those of others indicate that alfacalcidol plus calcium is superior to plain vitamin D_3.

ALFACALCIDOL VERSUS PLAIN VITAMIN D TRIAL IN GIOP

We compared the efficacy of D-hormone analog to plain vitamin D in patients with GC induced osteoporosis[16].

Subjects and study design. Our study included 204 patients receiving longterm GC therapy who had established osteoporosis, i.e., BMD at the lumbar spine below –2.5 standard deviations (SD) of the mean peak value in young adults (= T score). Patients were enrolled allowing only 3 underlying diseases: chronic obstructive pulmonary disease, rheumatoid arthritis, and polymyalgia rheumatica. They were grouped in matched pairs as judged by baseline variables and assigned randomly to receive either 1 μg of alfacalcidol plus 500 mg of calcium (n = 103) or 1000 IU vitamin D_3 plus 500 mg of calcium (n = 101) for 3 years.

BMD was measured at onset and at 12, 24, and 36 months by dual x-ray absorptiometry (DEXA; Lunar Corp., Madison, WI, USA) at the lumbar spine (L2–L4) and at the femoral neck. Lateral radiographic studies of the thoracic and lumbar spine were performed at onset and every year thereafter. A prevalent or new vertebral fracture was diagnosed at vertebrae on the loss of ≥20% of anterior, median, or posterior height.

Routine laboratory examinations were carried out at 6-month intervals, and patients were interviewed for adverse events and back pain.

Results

Characteristics of patients. As shown in Table 2, treatment groups were well matched for mean age, sex, mean height and weight, mean daily dose and duration of GC therapy, and percentage of patients with the 3 underlying diseases. The mean initial BMD values for the 2 groups at the lumbar spine were determined: T score –3.26 for the alfacalcidol group and –3.25 for the plain vitamin D_3 group; and at the femoral neck –2.81 and –2.84 SD, respectively (Table 2). Moreover, baseline characteristics for fracture status and bone pain did not differ substantially between the treatment groups.

A total of 89 of 103 patients in the alfacalcidol group (86.4 %) and 88 of 101 patients in the vitamin D group (87.1%) completed treatment regularly after 36 months. There was only one case of drug related discontinuation of treatment (see below).

Bone mineral density. At the lumbar spine, a gain in BMD was observed in both treatment groups after 12 months (Figure 1). However, while median percentage gain in BMD continued to increase moderately in the alfacalcidol group during the course of the study (+2.4% at the end of study), the initial increase in the vitamin D group was neutralized by subsequent loss during months 12 and 24, which remained almost steady until the end of the study (–0.8% at 36 mo). The Wilcoxon-Mann-Whitney directional test for the criterion "percent change from baseline" showed a more than small superiority of alfa-

Table 2. Baseline characteristics of patients*. With permission, courtesy of Springer Science and Business Media, from Ringe, *et al.* Rheumatol Int 2004;24:62-70

	Alfacalcidol	Vitamin D_3
Number	103	101
Male/female	38/65	36/65
Mean age, yrs (SD)	60.1 (9.78)	60.3 (9.91)
Mean weight, kg (SD)	64.2 (9.74)	64.3 (9.44)
Mean height, cm (SD)	164.5 (8.74)	164.7 (7.82)
Underlying disease		
Chronic obstructive lung disease	53 (51.5%)	52 (51.5%)
Rheumatoid arthritis	30 (29.1%)	27 (26.7%)
Polymyalgia rheumatica	20 (19.4%)	22 (21.8%)
Median duration of glucocorticoid therapy, yrs	3.0	3.0
Median daily glucocorticoid dose, mg	8.0	7.5
Mean BMD, T-score (SD)		
Lumbar spine	–3.26 (0.57)	–3.25 (0.39)
Neck of femur	–2.81 (0.73)	–2.84 (0.58)
Previous vertebral fractures		
No. of patients with fractures (%)	54 (52.4)	52 (51.5)
Average no. of fractures per patient	1.4	1.2
Previous non-vertebral fractures		
No. of patients with fractures (%)	34 (33.0)	33 (32.7)
Average no. of fractures per patient	0.5	0.5

*No significant difference in each criterion between groups.

calcidol at month 12, and a large superiority of alfacalcidol was detected at months 24 and 36 (test result for month 36: Mann-Whitney 0.8675; 95% CI 0.7806 to 0.9543; $p < 0.0001$). Concerning BMD at the neck of femur, no noteworthy median change was observed in the vitamin D group. There was, however, a steady gain in BMD until month 12 and between months 24 and 36 (+1.2% at the end of study) denoting medium superiority of alfacalcidol (Mann-Whitney 0.6394; 95% CI 0.5596 to 0.7193; $p < 0.006$).

A stratified analysis of the BMD measurements with respect to the underlying diseases gave the same treatment effect as the unstratified analysis.

Fracture rates. In 35 of the 204 patients included in the study we documented one or more new vertebral fractures. At the end of the study 16 new vertebral fractures had been observed in 10 patients in the alfacalcidol group and 35 in 25 patients in the vitamin D group. The 3 year rate of patients with at least one new vertebral fracture was 9.7% for the alfacalcidol group versus 24.8% for plain vitamin D group (relative risk, RR: 0.39; 95% CI 0.20 to 0.76; $p = 0.005$ / risk reduction: 0.61; 95% CI 0.24 to 0.81; $p = 0.005$) (Figure 2).

The 3 year rate of patients with at least one new non-vertebral fracture was 14.6% in the alfacalcidol group versus 24.8% in the vitamin D group (RR: 0.59; 95% CI 0.32 to 1.06 / risk reduction: 0.41; 95% CI 0.06 to 0.68; $p = 0.081$). This difference was not statistically significant even in a descriptive sense, which might have been caused by the small sample size.

At end of study, 32 new fractures of any kind had occurred in 20 patients in the alfacalcidol group and 68 in 41 patients in the vitamin D group. The 3 year rate of patients with at least one new fracture was 19.4% for the alfacalcidol treated versus 40.6% for those treated with

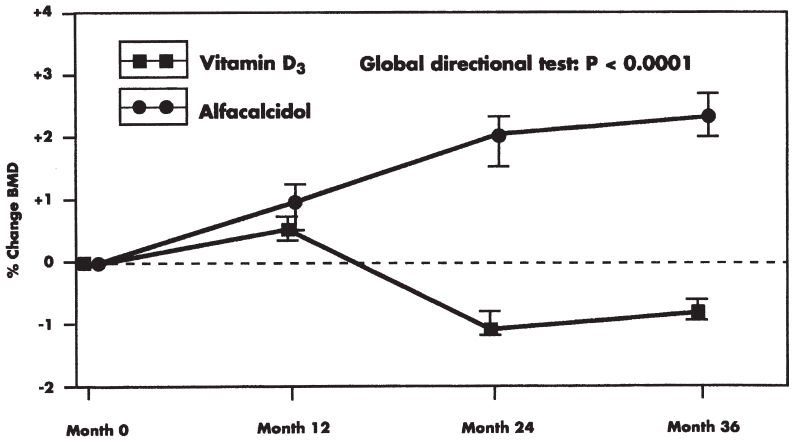

Figure 1. Bone mineral density at lumbar spine (percentage change from baseline). With permission, courtesy of Springer Science and Business Media, from Ringe, *et al.* *Rheumatol Int 2004*;24:63-70.

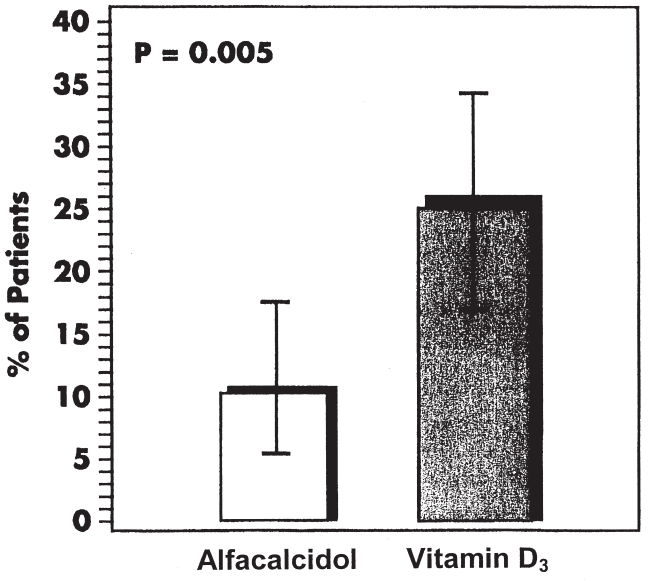

Figure 2. Three year rate of new vertebral fracture in study patients. Data are percentages of patients (95% CI). Data set: intention to treat, alfacalcidol versus vitamin D_3. With permission, courtesy of Springer Science and Business Media, from Ringe, *et al. Rheumatol Int 2004*;24:63-70.

plain vitamin D and calcium (RR: 0.48; 95% CI 0.20 to 0.75; p = 0.001 / risk reduction: 0.52; 95% CI 0.25 to 0.71; p = 0.001).

Back pain. At 36 months, the average back pain score showed a mean decrease of 1.7 points in the alfacalcidol group and 0.8 points in the vitamin D group (Figure 3). This effect was not significant for the plain vitamin D group. Concerning percentage change from baseline, a large superiority of alfacalcidol was demonstrated in the Mann-Whitney test after both 2 and 3 years (month 24: Mann-Whitney 0.7244; 95% CI 0.6523 to 0.7965; p < 0.001 / month 36: Mann-Whitney 0.7395; 95% CI 0.6683 to 0.8108; p < 0.001).

Side effects. There were no relevant differences in frequency, type or severity of side effects between treatment groups (Table 3). All side effects were mild to moderate. Epigastric discomfort was the most frequent adverse effect, which was likely related mainly to calcium supplementation. Three patients in the alfacalcidol group had moderate hypercalcemia and 2 in the vitamin D group. One alfacalcidol patient dropped out due to hypercalcemia, i.e., a treatment related adverse event. Four patients died during the course of the study (2 in each group) based on intercurrent diseases most likely unrelated to the study drugs (2 of stroke, one of cor pulmonale, one of status asthmaticus).

Table 3. Adverse events*. With permission courtesy of Springer Science and Business Media, from Ringe, *et al Rheumatol Int 2004*;24:63-70.

	Alfacalcidol n=103	Vitamin D_3 n=101
Epigastric discomfort	15	14
Constipation	5	6
Diarrhea	2	2
Nausea	5	5
Headache	3	6
Arthralgia	2	1
Hypercalciuria	3	1
Hypercalcemia	3	2
Total	38	37

*No significant difference in frequency and type of events between groups.

ROLES OF PLAIN VITAMIN D AND ALFACALCIDOL IN GIOP

Plain vitamin D is active only in patients with vitamin D deficiency. That means it may show some therapeutic effects especially at the beginning of intervention if some of the patients are vitamin D-deficient. We did not measure initial vitamin D status of patients in our study. Normal values of calcium, phosphorus, and alkaline phosphatase in serum and calcium and phosphorus in urine, however, excluded cases with relevant severe vitamin D deficiency. Nevertheless, some patients with mild insufficiency could explain the slight effect on lumbar spine BMD after the first 12 months in the group receiving plain vitamin D plus calcium (Figure 1).

Alfacalcidol, a prodrug of the D-hormone, is a pharmacological active antiosteoporotic drug, which works independently of vitamin D status[21]. D-hormone analogs such as alfacalcidol and calcitriol have been demonstrated to be useful in the therapy of GIOP. All clinical studies with these agents in GIOP have shown an increase or a stabilization of BMD in comparison to control groups. Some studies looking at prevention of GIOP by alfacalcidol in patients with different underlying diseases demonstrated an inhibition of bone loss even for very high doses of GC[10,11]. Van Cleemput, *et al* investigated the relative efficacies of alfacalcidol and etidronate in patients after cardiac transplantation under GC and and cyclosporin A therapy. Better efficacy was observed on BMD in the alfacalcidol group at both lumbar spine and femoral neck as compared to the etidronate group. In total only a small number of new fractures was observed, but there were more in the etidronate than in the alfacalcidol group[9]. This tendency was confirmed, however, by a more recent study on patients with cardiac or lung transplant, where calcitriol significantly reduced the number of vertebral fractures[13]. Prevention of bone loss after cardiac transplant has been recently shown in a 1 year prospective, randomized double-blind clinical trial comparing 0.5 µg calcitriol and 10 mg alendronate daily

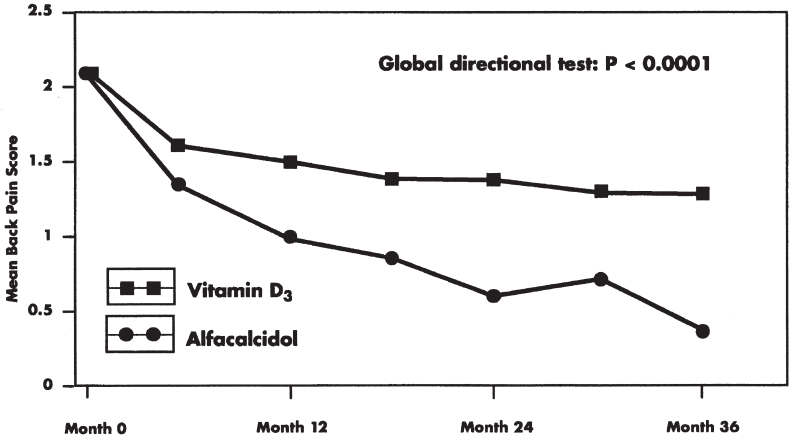

Figure 3. Average back pain score in study patients (mean score values indicate change from baseline). With permission, courtesy of Springer Science and Business Media, from Ringe, *et al. Rheumatol Int 2004*;24:63-70.

with a nonrandomized untreated control group. Bone loss was minimal in the 2 actively treated groups and did not differ between calcitriol and alendronate. New vertebral fractures occurred in 6.8% of alendronate subjects, 3.6% of subjects treated with calcitriol, and 13.6% of controls[22].

Taken together, there is very good evidence that treatment with D-hormone analogs can also maintain bone mass in patients with very high dosages of GC. This view was taken into account in the guidelines of the American College of Rheumatology[23] and confirmed by meta-analysis[24].

While there is ample evidence that alfalcalcidol and calcitriol are effective in reducing vertebral and nonvertebral fracture incidence in age-related and postmenopausal osteoporosis[25-28], fracture data for GIOP have largely been uninformative and discrepant due to the relatively small sample size of the respective studies mentioned above.

Thus, our study was the first large enough to statistically evaluate the effect of alfacalcidol not only on BMD, but also on fracture risk in patients with established GIOP. Our results corroborate previous findings that alfacalcidol is capable of significantly increasing the BMD at both lumbar spine and femoral neck in comparison to a control group. These results are of special interest, because our control group received a standard basic supplementation therapy with vitamin D and calcium. Alfacalcidol treatment led to a significant 61% risk reduction of vertebral fractures and 52% of all fractures, vertebral and nonvertebral combined, in comparison to the vitamin D group. The study patients also had a risk reduction of 41% for new nonvertebral fractures, which did not reach statistical significance.

The superiority of alfacalcidol with respect to the occurrence of vertebral fractures was reflected by a significantly higher efficacy of alfacalcidol in back pain reduction as compared with vitamin D.

It is not clear whether the advantageous symptomatic efficacy is related to only the lower vertebral fracture rate or if special effects on muscle metabolism[2,29] and/or on the immune system[5,8] are involved. Although the vitamin D dose of 1000 IU used in this study is a well established standard supplementation in osteoporosis management, it might be argued that the amount administered was too low to fully exert its antiosteoporotic potential. However, another study on GIOP has shown no therapeutic efficacy of a dose of vitamin D as high as 7000 IU per day[14].

Why the 2 agents differ so strongly in their therapeutic potency in osteoporosis was explained above (Table 1). In GIOP additional factors may play a role. Recent research has shown that GC reduce the amount of VDR on effector cells, thereby decreasing *de facto* the activity of this hormone. Interestingly, this effect might still be aggravated in chronic inflammatory diseases, where high levels of circulating proinflammatory cytokines such as tumor necrosis factor-α (TNF-α) or interleukin 1, (IL-1) IL-6, and IL-12 prevail in target tissues or serum. Experimental data suggest that TNF-α inhibits renal 1α-hydroxlase[30]. This is in accordance with clinical findings that inflammatory diseases are associated with low serum calcitriol levels[31,32] related to disease activity[31]. In GC/inflammation induced osteoporosis the fracture risk is higher than expected due to loss of BMD, because an early destruction of the trabecular architecture occurs, e.g., a decrease of bone quality and bone strength. In animal trials it has been shown that alfacalcidol increases bone strength more effectively than plain vitamin D[33]. The incidence of falls and nonvertebral fractures increases rapidly after the first 3 months and reverses sharply toward baseline levels after discontinuation of oral GC

treatment[34]. D-hormone analogs are promising candidates for a pharmacological intervention with positive effects on muscle function and falls[28,35,36]. Taken together these potential reasons suggest superiority of alfacalcidol over vitamin D in GIOP therapy, and the most important may be the greater availability of D-hormone in target tissues.

Given the relatively high increase in BMD found in antiosteoporotic treatment with bisphosphonates such as alendronate and risedronate, the changes in BMD in this study appear rather small. On the other hand, reduction of fracture rate differs considerably between the treatment groups, at least when vertebral fractures or the combined data of all fractures are considered. The observed risk reduction for alfacalcidol of 61% for vertebral fractures is in the range of results found with bisphosphonate treatment of GIOP[37,38], where the specific drugs were also compared with a vitamin D/calcium supplementation. This phenomenon of a relatively small increase of BMD and high reduction of fracture incidence was discussed in a recent study on raloxifene[39]. In this elegant statistical analysis of a large study on postmenopausal osteoporosis, the extent of treatment-associated changes in BMD accounted only for 4% of the observed vertebral fracture risk reduction. The change in BMD seems to be a poor predictor of fracture outcome for raloxifene and alfacalcidol. Due to its protection from further destruction of trabecular microarchitecture through regulation of increased bone remodeling and bone resorption, improvement of bone quality and therefore bone strength, and reduction of falls, alfacalcidol may be more important for fracture prevention, especially in GIOP.

Our study shows alfacalcidol to be an efficient agent in the therapy of GIOP. Alfacalcidol was superior to vitamin D in terms of bone mass gain as well as fracture risk reduction. Due to pleiotropic efficacy on bone, muscles and the immune system, excellent tolerability, longterm safety, simple and patient-friendly mode of administration (which all promote longterm patient compliance), and the medium daily costs, the physiological substance alfacalcidol is an important treatment option in patients with glucocorticoid/inflammation induced osteoporosis.

Plain vitamin D plus calcium can be given in glucocorticoid induced osteoporosis together with bisphosphonates but it should no longer be used as monotherapy.

REFERENCES

1. Ma K, Mallidis C, Bhasin S, et al. Glucocorticoid-induced skeletal muscle atrophy is associated with upregulation of myostatin gene expression. Am J Physiol Endocrinol Metab 2003;285:E363-71.
2. Endo I, Inoue D, Mitsui T, et al. Deletion of vitamin D receptor gene in mice results in abnormal skeletal muscle development with deregulated expression of myoregulatory transcription factors. Endocrinology 2003;144:5138-44.
3. Schacht E. Rationale for treatment of involutional osteoporosis in women and for prevention and treatment of corticosteroid-induced osteoporosis with alfacalcidol. Calcif Tissue Int 1999;65:317-27.
4. Cantorna MT, Hayes CE, DeLuca HF. 1,25-Dihydroxycholecalciferol inhibits the progression of arthritis in murine models of human arthritis. J Nutr 1998;128:68-72.
5. DeLuca HF, Cantorna MT. Vitamin D: its role and uses in immunology. FASEB J 2001;15;2579-85.
6. Andjelkovic Z, Vojinovic J, Pejnovic N, et al. Disease modifying and immunomodulatory effects of high dose 1-alpha(OH) D3 in rheumatoid arthritis patients. Clin Exp Rheumatol 1999;17:453-6.
7. Hein G, Oelzner P. Vitamin D metabolites in rheumatoid arthritis: findings – hypotheses – consequences [German]. Z Rheumatol 2000;59 Suppl 1:28-32.
8. Scharla SH, Schacht E, Bawey S, Kamilli I, Holle D, Lempert UG. Pleiotropic effects of alfacalcidol in elderly patients with rheumatoid arthritis. arthritis+rheuma 2003;23:268-74.
9. Van Cleemput J, Daenen W, Geusens P, Dequeker J, van de Werf F, Vanhaecke J. Prevention of bone loss in cardiac transplant recipients. Transplantation 1996;61:1495-9.
10. Reginster JY, Kuntz D, Verdickt W, et al. Prophylactic use of alfacalcidol in corticosteroid-induced osteoporosis. Osteoporos Int 1999;9:75-81.
11. Lakatos P, Nagy Z, Kiss L, et al. Prevention of corticosteroid-induced osteoporosis by alfacalcidol. Z Rheumatol 2000;59;Suppl 1:I48-52.
12. Sambrook PN, Birmingham J, Kelly PJ, Kempler S, Pocock NA, Eisman JA. Prevention of corticosteroid osteoporosis: A comparison of calcium, calcitriol and calcitonin. N Engl J Med 1993;328:1747-52.
13. Sambrook PN, Henderson NK, Keogh A, et al. Effect of calcitriol on bone loss after cardiac or lung transplantation. J Bone Miner Res 2000;15:1818-24.
14. Adachi JD, Bensen WG, Bianchi F, et al. Vitamin D and calcium in the prevention of corticosteroid induced osteoporosis: A 3 year follow up. J Rheumatol 1996;23:995-1000.
15. Riggs BL, Nelson KL. Effect of long term treatment with calcitriol on calcium absorption and mineral metabolism in postmenopausal osteoporosis. J Clin Endocrinol Metab 1985;61:457-61.
16. Ringe JD, Dorst A, Faber H, Schacht E, Rahlfs VW. Superiority of alfacalcidol over plain vitamin D in the treatment of glucocorticoid-induced osteoporosis. Rheumatol Int 2004;24:63-70.
17. Lau KHW, Baylink DJ. Vitamin D therapy of osteoporosis: Plain vitamin D therapy versus active vitamin D analog (D-hormone) therapy. Calcif Tissue Int 1999;65:295-306.
18. Avioli LV. Vitamin D and the D-hormones, alfacalcidol and calcitriol, as therapeutic agents for osteoporotic populations. Calcif Tissue Int 1999;65:292-4.
19. Ichikawa F, Sato K, Nanjo M, et al. Mouse primary osteoblasts express vitamin D 25-hydroxylase mRNA and convert 1-alpha,25-dihydroxyvitamin D3. Bone 1995;16:129-35.
20. Papopoulos SG, Fraher LJ, Sandler LM, Clemens TL, Lewin IG, O'Riordan JLH. 1,25-dihydroxycholecalciferol in the pathogenesis of hypercalcemia of sarcoidosis. Lancet 1979;i:627-31.
21. Lau WK-H, Baylink DJ. Treatment of 1,25(OH)2D3 (D-hormone) deficiency/resistance with D-hormone and analogs. Osteologie 2001;10:28-39.
22. Shane E, Addesso V, Namerow P, et al. Alendronate versus calcitriol for the prevention of bone loss after cardiac transplantation. N Engl J Med 2004;350:767-76.
23. American College of Rheumatology Ad Hoc Committee on Glucocorticoid-Induced Osteoporosis. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Rheum 2001;44:1496-503.
24. Richy F, Ethgen O, Bruyere O, Reginster JY. Efficacy of alphacalcidol and calcitriol in primary and corticosteroid-induced osteoporosis: a meta-analysis of their effects on bone mineral density and fracture rate. Osteoporos Int 2004;15:301-10.

25. Orimo H, Shiraki M, Hayashi Y, et al. Effects of 1-alpha-hydroxyvitamin D3 on lumbar bone mineral density and vertebral fractures in patients with postmenopausal osteoporosis. Calcif Tissue Int 1994;54:370-6.
26. Hayashi Y, Fujita T, Inoue T. Decrease of vertebral fracture in osteoporotics by administration of 1-alpha-hydroxy-vitamin D3. J Bone Miner Metab 1992;10:184-8.
27. Tilyard MW, Spears GF, Thomson J, Dovey S. Treatment of post-menopausal osteoporosis with calcitriol or calcium. N Engl J Med 1992;326:357-62.
28. Gallagher JC, Fowler SE, Detter JR, Sherman SS. Combination treatment with estrogen and calcitriol in the prevention of age-related bone loss. J Clin Endocrinol Metab 2001;86:3618-28.
29. Boland R. Role of vitamin D in skeletal muscle function. Endocr Rev 1986;7:434-48.
30. Ebert R, Jovanovic M, Ulmer M, et al. Downregulation by nuclear factor kappa B of human 25-hydroxyvitamin D3 1-alpha-hydroxylase promoter. Mol Endocrinol 2004;18:2440-50.
31. Oelzner P, Muller A, Deschner F, et al. Relationship between disease activity and serum levels of vitamin D metabolites and PTH in rheumatoid arthritis. Calcif Tissue Int 1998;62:193-8.
32. Haug CJ, Aukrust P, Haug E, Morkrid L, Muller F, Froland SS. Severe deficiency of 1,25-dihydroxyvitamin D3 in human immunodeficiency virus infection: association with immunological hyperactivity and only minor changes in calcium homeostasis. J Clin Endocrinol Metab 1998;83:3832-8.
33. Shiraishi A, Higashi S, Ohkawa H, et al. The advantage of alfacalcidol over vitamin D in the treatment of osteoporosis. Calcif Tissue Int 1999;65:311-6.
34. Van Staa TP, Leufkens HGM, Abenhaim A, Zhang B, Cooper C. Use of oral corticosteroids and risk of fractures. J Bone Miner Res 2000;15:993-1000.
35. Gallagher JC. The effects of calcitriol on falls and fractures and physical performance tests. J Steroid Biochem Mol Biol 2004;89-90:497-501.
36. Dukas L, Bischoff HA, Lindpaintner LS, et al. Alfacalcidol reduces the number of fallers in a community-dwelling elderly population with a minimum calcium intake of more than 500 mg daily. J Am Geriatr Soc 2004;52:230-6.
37. Saag KG, for the Glucocorticoid-induced Osteoporosis Intervention Study Group. Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. N Engl J Med 1998;339:292-9.
38. Cohen S, Levy RM, Keller M, et al. Risedronate therapy prevents corticosteroid-induced bone loss – a twelve-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum 1999;42:2309-18.
39. Sarkar S, Mitlak BH, Wong M, Stock IL, Black DM, Harper KD. Relationships between bone mineral density and incident vertebral fracture risk with raloxifene therapy. J Bone Miner Res 2002;17:1-10.