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Rationale for Active Vitamin D and Analogs in the Treatment of Osteoporosis

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Abstract In 1981, Chugai Pharmaceutical succeeded in marketing alfacalcidol, a prodrug of calcitriol, as a therapeutic agent for renal osteodystrophy. In 1983, Chugai succeeded in extending the application of alfacalcidol to the treatment of osteoporosis as well. Clinicians in Japan have accepted alfacalcidol as a remedy for osteoporosis. However, the use of calcitriol and its analogs for the treatment of osteoporosis is still controversial. Some misunderstandings exist internationally about the efficacy of the active form of vitamin D for the treatment of osteoporosis. It is important to emphasize that patients with osteoporosis have intestinal calcium malabsorption and dysfunction in renal activation of vitamin D. When massive doses of parent vitamin D were administered to OVX rats, bone mass increased, but surprisingly, many porotic area were observed in the cortical bone. On the other hand, administration of alfacalcidol increased physiological bone without porotic observation. It is necessary to give the active form of vitamin D, D-hormone, with an RDA-equivalent supply of calcium. Alfacalcidol forms physiological strong bones that are hardly fractured by regulating calcium and bone metabolism. We proposed a new vitamin D analog, 2β (3-hydroxypropoxy)calcitriol [ED-71] as a therapeutic drug for osteoporosis, which is more potent than calcitriol. ED-71 is now being investigated in phase 2 clinical studies in Japan. ED-71 will appear as more improved drugs for osteoporosis until 2010. J. Cell. Biochem. 88: 381–386, 2003.

Key words: osteoporosis; alfacalcidol; calcitriol; ED-71; OCT; calcium; vitamin D; D-hormone

Vitamin D, discovered at the beginning of the 20th century, became the therapeutic agent for the treatment of rickets. In 1971, the structure of active vitamin D, calcitriol, was identified by DeLuca, and Kdicek found that 25-hydroxy vitamin D 1α-hydroxylase exist in the kidney.

In 1974, Tatsuo Suda proposed us the structure of alfacalcidol to replace calcitriol for the treatment in the vitamin D deficient patients with renal failure. In 1981, Chugai Pharmaceutical Company succeeded in marketing alfacalcidol as a therapeutic agent for renal osteodystrophy. In 1983, Chugai extended the application of alfacalcidol to cover the treatment of osteoporosis as well. I participated in the development of alfacalcidol as a project leader in Chugai from 1974.

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In 1981, Suda et al. found the differentiation-inducing activities of active vitamin D. At that time, we challenged to separate the differentiation-inducing activity from calcium activity by modifying the structure of calcitriol. Finally, We proposed two of vitamin D analogs, OCT and ED-71, as shown in Figure 1. 22-Oxacalcitriol, OCT, has a stronger effect than calcitriol in inducing differentiation activity. On the other hand, 2β (3-hydroxypropoxy)calcitriol, ED-71, has the weaker activities than calcitriol in inducing differentiation activity, and showed the stronger effect on calcium regulating activities.

In this report, the alfacalcidol and ED-71 as therapeutic drugs for osteoporosis will be focus.

ARE ACTIVE VITAMIN D AND ITS ANALOG EFFECTIVE FOR THE TREATMENT OF OSTEOPOROSIS OR NOT ?

The product name of alfacalcidol produced by Chugai is alfarol. Alfarol forms strong bones that are not easily fractured by regulating calcium and bone metabolism.

Alfarol formulations are four kinds of capsule type, three kinds of powder type which consist of

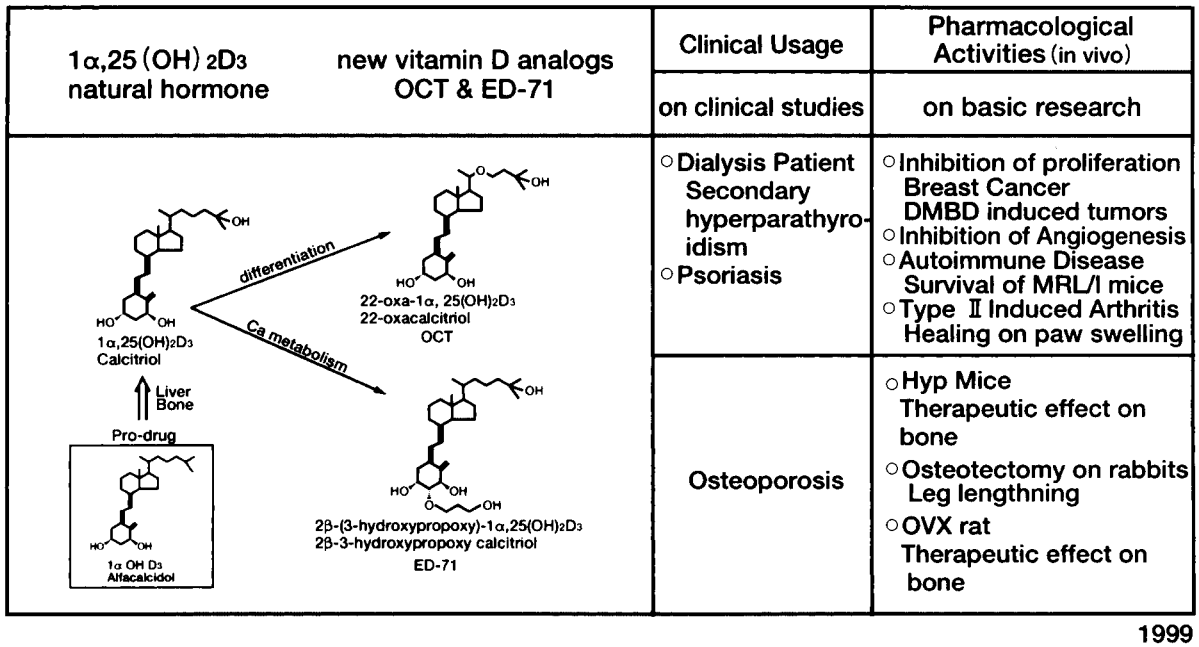

Fig. 1. Chemical structure of $1\alpha,25(OH)_2D_3$, $1\alpha OHD_3$, OCT and ED-71, and pharmacological activities and clinical directions of OCT and ED-71.

0.25, 0.5, and 1 mcg/each package, and a liquid type.

At first, Fukushima et al. [1974] demonstrated in 1975 alfacalcidol metabolized to calcitriol in liver using liver perfusion test. Thus, alfacalcidol shows its biological effects after conversion to calcitriol without kidney function. In 1998, Koike et al. [1998] reported alfacalcidol is also converted to calcitriol in the bone itself. This means alfarol is a prodrug of calcitriol.

Alfacalcidol is effective of increasing of BMD and bone strength in ovariectomized (OVX) rats, and also shows the same observations in micro QCT. Alfacalcidol inhibits bone resorption and stimulates bone formation in OVX rats.

There are many clinical reports in Japan, which show the efficacy of alfacalcidol.

Hayashi et al. [1992] have clarified that alfacalcidol can lower the incidence of vertebral fractures caused by decreasing bone loss in randomized clinical trials. Shiraki et al. [1993] reported the effects on bone of long-term treatment with alfacalcidol. Itoi et al. [1992] independently reported the same results.

They concluded that alfacalcidol with an adequate amount of calcium supplement is considered the safe and effective agent for long-term administration to osteoporotic patients. The post-marketing surveillance for 6 years of alfacalcidol in Japan has revealed that hypercalcemia was only 0.2%, and increases of BUN and serum creatinine was 0.15%.

Clinicians in Japan have accepted alfacalcidol as a useful drug for osteoporosis.

During the 20 years since the launch of alfacalcidol, there have been no reports of the severe adverse effects. Net sales of alfacalcidol are $200 million a year.

However, the usefulness of calcitriol and its analogs for the treatment of osteoporosis is still internationally controversial. The backgrounds in Japan and United State in terms of conducting clinical studies for the treatment of osteoporosis were very different (Fig. 2). During the early development of active vitamin D under poor scientific information, Ott and Chesnut [1989] and others unfortunately failed to obtain

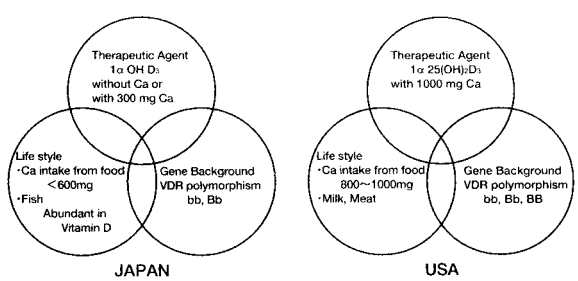

Fig. 2. The reason why differences of evaluation on the efficacy of active vitamin D_3 between Japan and USA.

positive data for active vitamin D for osteoporosis, because of clinical studies had unacceptable protocols under conditions of high total calcium intakes. These results strongly affected the evaluation of the efficacy of active vitamin D as a remedy for osteoporosis, and led to misunderstanding about active vitamin D. Tilyard et al. [1992] reported that continuous treatment of postmenopausal women with osteoporosis with calcitriol for 3 years was safe, and significantly reduced the rate of new vertebral fractures. In reliable references, the incidence of fractures in osteoporosis patients decreased to approximately half in the active vitamin D treated group compared with the control group, and the marked preventive effects on fracturing seemed to be obtained with calcium intakes at the level of 400-0800 mg. Very recently, Sairanen et al. [2000] in Finland reported the long-term effect of calcitriol treatment on bone mineral density of the femoral neck and lumbar spine. Important thing is that calcium intake of all patients was adjusted to 800 mg daily.

They concluded that calcitriol treatment increases bone mass at the femoral neck and lumbar spine, the increases being maintained for up to 4 years.

The reports compiled in Hong Kong in 1993 and in Amsterdam in 1996 currently represent the most authoritative statements on international consensus regarding the efficacy and problem of calcitriol and its analogs for the treatment of osteoporosis.

The Hong Kong report stated that vitamin D supplementation is essential for the elderly, and while recognizing that active vitamin D is effective in the treatment of osteoporosis in some cases. It pointed out the need to clarify the differences in the efficacy as compared to that of administration of vitamin D in combination with calcium. The Amsterdam consensus report stated that active vitamin D administered in combination with calcium supplementation is effective for the treatment of osteoporosis even under vitamin D replete conditions.

IS A LARGE AMOUNT OF CALCIUM SUPPLEMENT EFFECTIVE FOR OSTEOPOROSIS?

Many researchers insist that a large amount of calcium supplement is effective in inhibiting the decrease in the bone mineral density. This is true, however, it might be partially rather than the fully effective.

In Tilyard's report, a total calcium intake of 1,900 mg in the control group showed no tendency to prevent the risk of vertebral fracture.

As shown in the Rigg's report, huge amounts of calcium cause the hypercalciuria, and no effects on bone [Riggs et al., 1996].

It is well known that elderly persons and osteoporosis patients have calcium malabsorption from the intestine. Ebeling et al. [1992] showed the reduced incidence of vitamin D receptor in the intestine of elderly people.

It is well known that large amounts of calcium have no effect on increasing VDR content. Active vitamin D has up-regulation activity on VDR in the intestine.

I conclude that large amounts of calcium have little meaning to treat patients with osteoporosis.

However, in Japan as well as in China, calcium intake from food is still low to amounts of RDA equivalent. Therefore, it is necessary to supply calcium, until reaching total calcium intake to the RDA equivalent amounts.

IS PARENT VITAMIN D EFFECTIVE IN THE TREATMENT OF OSTEOPOROSIS?

The famous report by Munier's group [Chapuy et al., 1992] showed that the administration of vitamin D 800 IU was effective in preventing the risk of hip fractures in elderly women. However, it is apparent that many of these women were vitamin D deficient with low level of 25-hydroxyvitamin D in their serum. It is quite acceptable that the use of parent vitamin D is effective in those who are suffering from vitamin D deficiency.

Lips et al. [1996] conducted a similar prospective clinical trial using parent vitamin D. They selected patients with normal levels of 25-hydroxyvitamin D in the serum. As a result, parent vitamin D 400 IU had no effect on the prevention of bone fracture in elderly patients. Recently, Meyer et al. [2002] reported similar clinical results.

Francis [1997] has reported that 40 mcg of 25-hydroxyvitamin D results in the prevention of calcium malabsorption in the intestine regarding the patients with non-vertebral fracture, while patients with vertebral fracture showed no improvement in the same test. It is clear that even the high dosages of 40 mcg of 25-hydroxyvitamin D, which is equivalent to more than 2,000 IU parent vitamin D, is not

enough to cure the intestinal calcium malabsorption in osteoporosis.

Koseisho in Japan recently decided that the RDA of vitamin D should be 400 IU, and the upper limit for parent vitamin D should be 2,000 IU.

Chugai's researchers carried out animal experiments in which the effect of alfacalcidol and vitamin D_3 on spinal bone mineral density, mechanical strength, biochemical markers, and vitamin D metabolites in ovariectomized rats were compared.

As shown in Figure 3, alfacalcidol and massive doses of parent vitamin D increased bone mineral density and mechanical strength dose-dependently. Alfacalcidol improved bone lesions in OVX rats at the same dose, which shows anti-rachitic activity. But, parent vitamin D did not show any effect at the dose which shows anti-rachitic activity.

Using vitamin D deficient rats, 2.5 mcg/kg of parent vitamin D is effective in showing anti-rachitic activity. Parent vitamin D_3 (75 mcg/kg) is equivalent to 150,000 IU for humans with 50 kg body weight.

Administration of alfacalcidol caused a dose-dependent elevation in serum calcitriol levels, whereas 75 mcg/kg of parent vitamin D caused elevation of 25-hydroxyvitamin D level, but only a slight elevation of the serum calcitriol level.

These observation suggest that 25-hydroxyvitamin D 1α-hydoxylase in the kidney might be reduced in OVX rats. When massive doses of parent vitamin D were administered to OVX rats, bone mass increased. But, surprisingly, cortical bone was observed to be porotic. On the other hand, administration of alfacalcidol increased physiological bone without porotic observation.

Slovic et al. [1981] pointed out little activation of vitamin D by continuous infusion of PTH in osteoporosis patients. Our observations in OVX rats are similar to the PTH infusion test by Slovic in 1987.

Which treatment is preferable for patients with osteoporosis who have calcium malabsorption in the intestine and renal dysfunction?

In conclusion, combination therapy of adequate amount of calcium supplementation and active vitamin D is useful for osteoporosis.

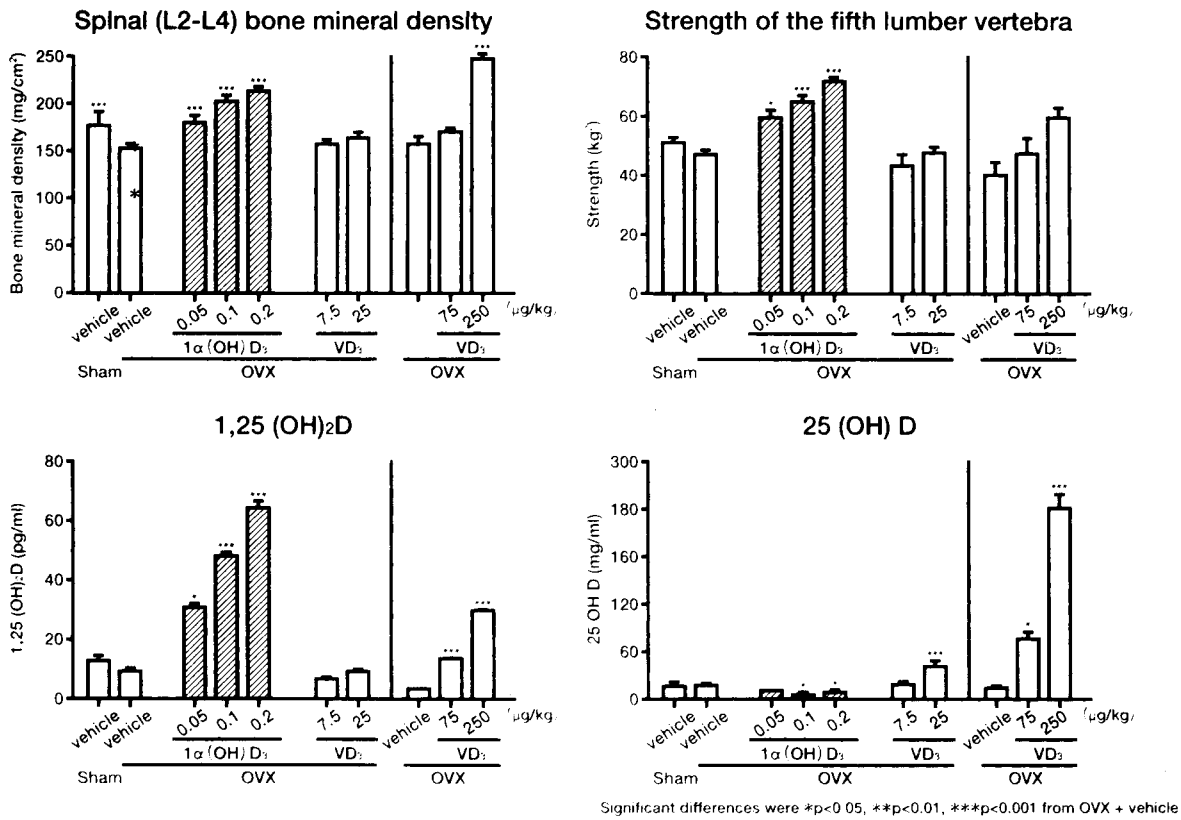

Fig. 3. Comparison of the effects of 1αOHD_3 and parent vitamin D_3 treatment on bone in OVX rats, and their effects on concentrations of serum D metabolites.

NEW CONCEPT OF D-HORMONES, AND A NEW D-HORMONE FOR OSRTEOPOROSIS

Recently, Ogata et al. showed that active vitamin D has the different activities from the stimulation effect of intestinal calcium absorption and suppression effect of PTH [Ikeda and Ogata, 1999]. Calcitriol has a narrow therapeutic window (Fig. 4), which leads to misunderstandings about the evaluation of active vitamin D. Alfacalcidol might have a wider therapeutic window than calcitriol as a drug for osteoporosis. The anabolic effects of alfacalcidol were also confirmed by the histological analysis.

If we have a new anabolic analog, which has direct effects on bone at lower doses than the suppression of PTH, this might be a more valuable candidate for osteoporosis.

The structure of ED-71 and OCT are shown in the Figure 1. ED-71 is one of the candidates, which have a stronger bone anabolic effect than calcitriol.

When I showed this slide at the Steenbock Symposium in 1989. Dr. Raisz strongly interested in this new analog and asked me to collaborate on this new analog.

First, Sato et al. [1993] examined the effect and mechanism on bone metabolism in vitro using Raisz's assay method.

The dose response curves of ED-71 on both bone resorption and collagen synthesis were quite different from those of calcitriol.

In comparison to the administration of the parent vitamin D and alfacalcidol, administration of ED-71 is extremely effective in the prevention of bone loss. When serum calcium is brought to normal levels, bone mass and bone strength increase above the value of the sham group by 20%.

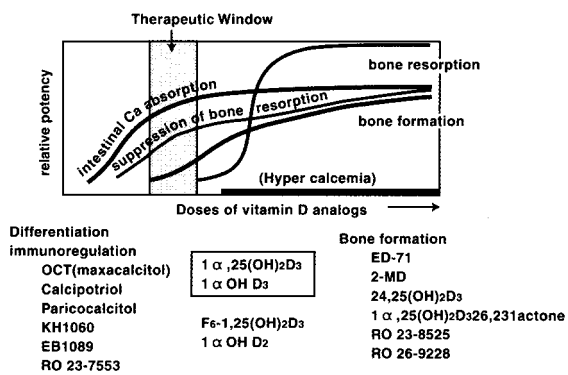

Fig. 4. Pharmacological and toxicological aspects of active vitamin D analogs.

Results of bone morphometric analysis indicated the strong effect on bone formation after administration of ED-71, compared to alfacalcidol. Also ED-71 markedly inhibits bone resorption as indicated by the finding of decreased excretion of deoxypyridinoline in the urine.

Chugai has been conducting clinical studies in Japan. It will become a new drug for osteoporosis, near future.

Treatment as therapy for osteoporosis should be clearly separated from the category of nutritional supplement.

In conclusion, Administration of calcitriol and alfacalcidol with an adequate supply of calcium to patients with osteoporosis effectively decreases the incidence of fractures as effectively as estrogen and bisphosphonates in spite of a smaller effect on the prevention of bone mass compared with estrogen and bisphosphonates. Active vitamin D forms physiological bones by regulating calcium and bone metabolism. New vitamin D analogs, ED-71, RO-26-9228, and 2-MD will soon appear as more improved drugs for osteoporosis.

REFERENCES

Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, Delmas PD, Meunier JP. 1992. Vitamin D_3 and calcium to prevent hip fractures in the elderly women. New Engl J Med 327:1637–1642.

Ebeling PR, Sandgren ME, DiMano EP, Lane AW, DeLuca HF, Riggs BL. 1992. Evidence of an age-related decrease in intestinal responses to vitamin D: Relationship between serum 1α,25-dihydroxyvitamin D and intestinal vitamin D receptor concentration in normal women. J Clin Endocrinol Metab 75:176–182.

Francis RM. 1997. Is there a differential response to alfacalcidol and vitamin D in the treatment of osteoporosis ? Calcif Tissue Int 60:111–114.

Fukushima M, Suzuki Y, Tohira Y, Matsunaga I, Ochi K, Nagano H, Nishii Y, Suda T. 1974. Metabolism of 1α-hydroxyvitamin D3 to 1α,25-dihydroxyvitamin D_3 in perfused rat liver. Biochem Biophys Res Commun 66:632–638.

Hayashi Y, Fuzita T, Inoue T. 1992. Decrease of vertebral fracture in osteoporotics by administration of 1α-hydroxyvitamin D_3. J Bone and Miner Metab 10:50–54.

Ikeda K, Ogata E. 1999. The effect opf vitamin D on osteoblasts and osteoclasts. Curr Opini Orthop 10:339–343.

Itoi E, Yamada Y, Sakurai M, Sato K, Kasama F. 1992. Long-term treatment with 1α-hydroxyvitamin D_3 with calcium supplement in spinal osteoporotic patients. Orthopedics 15:1409–1414.

Koike N, Ichikawa F, Nishii Y, Stumpf WE. 1998. Sustained osteoblast nuclear receptor binding of converted 1α,25-dihydroxyvitamin D_3 after administration of ^{3}H-1α-hydroxyvitamin D_3: A combined receptor

autoradiography and radioassay time course study with comparison to H^3-1α,25-dihydroxyvitamin D_3. Calcif Tissue Int 63:391–395.

Lips P, Graafmans WC, Ooms ME, Bezemer PD, Bouter LM. 1996. Vitamin D supplementation and fracture incidence in elderly persons. A randomized, placebo-controlled clinical trial. Ann Intern Med 124:400–406.

Meyer HE, Smedshaug GB, Kvaavik E, Falch JA, Tverdal A, Pedersen JI. 2002. Can vitamin D supplementation reduce the risk of fracture in the elderly? Arandomized controlled trial. J Bone Miner Res 17:709–715.

Ott SM, Chesnut CH III. 1989. Calcitriol treatment is not effective in postmenopausal osteoporosis. Am Coll Physicians 110:267–274.

Riggs BL, O'Fallon WM, Muths J, O'Conner MK. 1996. Long-term effects of calcium supplementation on serum PTH, bone turnover, and bone loss in elderly women. J Bone and Miner Res 11:S118.

Sairanen S, Karkkanen M, Tahtela R, Laithmen K, Makela P, Lamberg-Ilardt C, Velmaki MJ. 2000. Bone mass and markers of bone and calcium metabolism in postmenopausal women treated with 1α,25-dihydroxyvitamin D(calcitriol) for 4 years. Calcif Tissue Int 67: 122–127.

Sato K, Nishii Y, Woodiel FN, Raisz LG. 1993. Effects of two new vitamin D_3 derivatives, 22-oxa-1α,25-dihydroxyvitamin D_3 (OCT) and 2β-(3hydroxypropoxy)-1α,25$(OH)_2D_3$, on bone metabolism in organ culture. Bone 14:47–51.

Shiraki M, Ito H, Orimo H. 1993. The ultra long-term treatment of senile osteoporosis with 1α-hydroxyvitamin D_3. Bone Miner 20:223–234.

Slovic DM, Adams JS, Neer RM, Holick MF, Potts JT. 1981. Different production of 1α,25-dihydroxyvitamin D in elderly osteoporotic patients. N Eng J Med 305:372–374.

Tilyard MW, Spears GFS, Thomson J, Doey S. 1992. Treatment of postmenopausal osteoporosis with calcitriol or calcium. New Engl J Med 326:357–362.