with a progressive slowing of the rate of loss of appendicular bone density, decrease in osteoblastic and osteoclastic hyperfunction, and an improvement of bone mineralization. Renal function was stable throughout the study, and episodes of hypercalcemia and hyperphosphatemia were infrequent.

The patients in this study had relatively stable renal function with a slow progression of renal failure, primarily due to tubulointerstitial diseases. During the treatment phase of the study, patients received low-dose Calcitriol (0.25 µg/day) plus calcium carbonate (1 g/day) for 24 months. All patients were on a moderately restricted phosphate and protein diet which permitted the use of only mild doses of calcium carbonate, thus reducing the risk of hypercalcemia. Dietary calcium was also low (500 mg/day) as a consequence of protein and phosphate restriction.

In these patients, the rate of progression of chronic renal failure did not change during treatment, suggesting that the low doses of Calcitriol used had a minimal effect on renal function. Plasma and urinary calcium were strictly monitored to avoid pathological increases for prolonged periods, and this protected residual renal function. Episodes of hypercalcemia, hyperphosphatemia, or increased urinary excretion of these ions were infrequent throughout the study (incidence rate = 7.9% during the observation period and 9.6% during the treatment period).

An increase in plasma calcium levels was observed during the treatment phase. At the low daily dose of Calcitriol used, the expected calcium increase is about _____ mg/dL. The observed increase was _____ mg/dL, indicating that both Calcitriol and calcium carbonate contributed to elevated plasma calcium levels.

All biochemical markers of bone turnover (plasma alkaline phosphatase, plasma osteocalcin, and urinary hydroxyproline) decreased significantly after Calcitriol therapy. Osteoclastic and osteoblastic activity was also reduced during treatment. The observed changes in both biochemical and histomorphometric parameters correlated with the decrease in intact PTH levels. The bone histology findings are in accordance with previously published data showing that a state of mild histological hyperparathyroidism with moderately increased bone resorption corresponded to slightly increased levels of PTH. In the predialysis patients in this study, histomorphometric analysis showed signs of secondary hyperparathyroidism at intact PTH levels just above normal, and this supports the hypothesis that skeletal responsiveness to PTH is altered only in advanced uremia.

A consistent decrease of unmineralized bone was observed in all patients with osteomalacia or hyperparathyroidism plus osteomalacia. The reduction of osteoid volume, reflecting better calcification of new bone collagen, and the improvement of dynamic parameters were the manifestations of enhanced mineralization. In patients with hyperparathyroidism alone or with mixed skeletal lesions, osteoclastic bone resorption decreased. All these improvements were probably the skeletal response to the decrease of PTH levels.

In this study, improvement of skeletal status was also reflected by the slowing of bone loss in the appendicular skeleton. Continuous cortical bone loss in the extremities is considered a PTH-induced catabolic action. The progressively decreasing rate of bone loss observed in these patients correlated with reduced parathyroid activity.

Investigator's Conclusions

Our data support the efficacy and safety of low doses of Calcitriol plus calcium carbonate in the improvement of biochemical and skeletal features in ECRF, especially in patients with a slowly progressive renal failure due to tubulointerstitial disease on conservative treatment. After 2 years of treatment no patients showed signs of adynamic bone disease.

Medical Officer's Conclusions

Within the confines of a non-placebo controlled study, the results of this trial provide suggestive evidence that rocaltrol is beneficial in the management of secondary hyperparathyroidism and the resultant bone disease.

Study #4

Effect of alfacalcidol on natural course of renal bone disease in mild to moderate renal failure

Publication *Br Med J.* 1995; 310:358-363

Objective: To evaluate the safety and efficacy of moderate doses of alfacalcidol (1α-hydroxycholecalciferol) for prevention of renal osteodystrophy in patients with early renal failure.

Design: This was a prospective, double-blind, randomized, placebo-controlled, multicenter study of patients with predialysis mild to moderate chronic renal failure (creatinine clearance = 15-50 mL/min). Patients were randomly allocated to receive alfacalcidol or placebo. The starting dose of alfacalcidol was 0.25 μg per day as a single morning dose. Doses were adjusted between 0.25 μg every other day to 1μg per day, titrated to maintain serum calcium concentration at the upper limit of the normal laboratory reference range. Treatment was continued for two years or until the patient required dialysis. Calcium supplements, when previously taken, were continued up to a maximum daily dose of 500 mg of elemental calcium. The use of phosphate binding drugs other than calcium was permitted when dietary restriction of phosphate failed to maintain serum phosphate concentrations below 2.2 mmol/L; doses were documented. All other drugs required for the daily management of patients were also allowed and the doses documented.

Population: This study included 176 men (107) and women (69) aged 18-81 years. Inclusion criteria included creatinine clearance of 15-50 ml/min and no evidence of renal bone disease by clinical, biochemical, and radiographic criteria. Exclusion criteria included increased serum calcium or alkaline phosphatase.

Endpoints: Bone Histology

- A tetracycline double-labeled transiliac bone biopsy sample was obtained from all patients at the start and, when possible, at the end of the study. A second bone biopsy sample from the opposite ilium was obtained for 134 patients (76%). The biopsy was taken under local anesthesia with a modified Meunier bone biopsy trephine with a 4-8 mm internal diameter. Bone samples were processed for light and ultraviolet light microscopy. The presence of aluminum at the mineral-osteoid interface was assessed with aurintricarboxylic stain (Aluminon).
- Qualitative, semiquantitative, and quantitative analyses of bone biopsies were performed blind by one observer at the end of the study.
- Hyperparathyroidism was diagnosed by an increase in the number of active bone cells (osteoblasts and osteoclasts).
- Osteomalacia was diagnosed by the presence of five or more osteoid lamellae as identified by birefringence under polarized light.
- Important aluminum retention was diagnosed when stainable aluminum was identified on >25% of the mineral-osteoid interface.
- Adynamic bone lesions were diagnosed by the paucity of active bone cells, a normal or decreased osteoid seam width, and a pronounced decrease in the rate of bone formation (<0.001 $mm^2/mm^3/day$).
- Quantitative Histomorphometry was performed with a semiautomated digitizing system (Osteo-Measure, OsteoMetrics, Atlanta) and a dedicated microcomputer. The standard recommended nomenclature for bone Histomorphometry was used. The mineralization surface was calculated as the double-labeled surface plus one half of the single-labeled surface.

Biochemical Parameters

Serum concentrations:	Creatinine (μmol/L), corrected calcium (mmol/L), phosphate (mmol/L), alkaline phosphatase (IU/L), intact parathyroid hormone (pmol/L)
24-Hr urine excretion:	Creatinine (mmol/day), calcium (mmol/day), phosphate (mmol/day), hydroxyproline (μmol/day)
Glomerular filtration rate:	Creatinine clearance (mL/min)

Radiographs

Plain posterioanterior radiographs of the hands.

Statistical Analyses

Quantitative histology of bone, the primary criterion of efficacy, was analyzed in all patients with adequately paired bone biopsies, and histological abnormalities were compared between the treatment groups at the start of the study and at its end (2 years or on withdrawal from the study). For sequential biochemical assessments, all values were used to show changes with time.

Statistical significance of the histological changes was evaluated by analysis of variance for treatment and center effects and any interaction. Biochemical changes were assessed by analysis of variance to determine the significance of the treatment effect, the effect of time and any interaction. Measurements made on nominal scales (such as histological assessments and radiographic responses) were compared with chi-square tests.

Results

Patient Disposition

Eighty-nine (89) patients were randomized to receive alfacalcidol and 87 were randomized to received placebo. At the end of the study, 134 pairs of biopsy specimens were available for analysis of the primary efficacy outcome measure (quantitative histology of bone): 124 after two years of treatment and 10 on withdrawal from the study after 5-17 months of treatment to start dialysis. Sixteen (16; 18%) patients in the alfacalcidol group and 22 (25%) patients in the placebo group withdrew prematurely from the study. The most common reason for withdrawal was the need to start dialysis. Default and death (mainly due to cardiovascular disease) were other common causes. No patient withdrew from the study because of adverse events.

Demographics and Baseline Characteristics

There were no differences in age (52 yrs), sex distribution (61% male), distribution of primary renal disease (60% glomerulovascular), or degree of renal impairment (Crcl 32 ml/min) between study groups. There were also no differences in mean height, weight, and systolic and diastolic blood pressure, and the two groups had similar biochemical, radiological and semiquantitative histological features at the start of the study.

Most patients had normal serum biochemistry, except for impaired renal function. Serum phosphate and parathyroid hormone concentrations were elevated in 50 (28%) and 72 (40.9%) patients, respectively, and 132 (75%) patients were retrospectively found to have one or more histological abnormality of bone at the start of the study. Of these patients, 98 had important osteitis fibrosa, 25 had osteomalacia, usually in combination with osteitis fibrosa, and one patient had osteomalacia alone. Aluminum was present at the mineral-osteoid interface in five (2%) of the biopsy specimens; in none of these did it cover more than 25% of this surface. Nine (9, 5.1%) patients had ~~adyna~~mic bone lesions at the start of the study. The 44 patients with no important histological abnormalities had a significantly higher mean rate of creatinine clearance compared with patients with significant bone pathology (35.9 ± 1.7 mL/min vs. 30.8 ± 1.2

mL/min, respectively, p<0.03).

At the start of the study, 9 (5.1%) patients had mild bone pain, 4 (2.3%) had borderline elevation of serum alkaline phosphatase activity, and 7 (4.0%) had important subperiosteal erosions (retrospectively assessed). Three (3, 3.4%) patients treated with alfacalcidol and 1 (1.1%) given placebo had a creatinine clearance slightly in excess of 50 mL/min; 13 (14.6%) patients treated with alfacalcidol and 9 (10.3%) given placebo were receiving more than 500 mg of calcium supplements a day. None of these patients was excluded from the analysis.

When semiquantitative and quantitative histomorphometric data were examined before treatment for patients from whom a second biopsy was taken for paired analysis (alfacalcidol, 72; placebo, 62), there were also no differences in any variable before treatment between study groups. There were no differences in histomorphometric findings between the 124 patients who completed the study and the 10 patients who were withdrawn early to begin dialysis.

The two groups had similar concomitant drug treatment, which consisted mostly of antihypertensive drugs and diuretics. Similar numbers of patients were receiving glucocorticoids in both groups.

Primary Efficacy Outcomes

The dose of alfacalcidol administered increased progressively over the first six months of the study and then remained reasonably constant. At the end of the study, 34 (46%) of the 73 patients still taking alfacalcidol were receiving 0.25 μg daily, 22 (30%) were taking 0.5 μg daily, and 9 (12%) were taking 1μg daily. The remaining 8 patients received alfacalcidol every other day or once a week.

Bone Histomorphometry

Of the 72 alfacalcidol patients and 62 placebo patients who had paired biopsy specimens available for analysis, 55 (76%) and 45 (73%), respectively, had bone abnormalities at the start of treatment. At the end of treatment, a total of 39/72 (54%) alfacalcidol patients and 51/62 (82%) placebo patients had bone abnormalities. Among patients with histological abnormalities at the start of the study, 23/55 (42%) treated with alfacalcidol showed normal histological appearances at the end of the study, compared to only 2/45 (4%) patients given placebo (p<0.001). For those patients with apparent normal bone histology at the start of the study, there was no significant between-treatment difference in bone histology at the end of the study (p=0.73).

By the end of the study, patients with pre-existing histological abnormalities who were treated with alfacalcidol showed improvements in hyperparathyroid bone disease, as evidenced by a decrease in the severity of marrow fibrosis and a decrease in bone turnover (indicated by a significant decrease in histological indices of bone resorption, including the eroded surface and active eroded surface), and a decrease in indices of bone formation (including the number of osteoblasts, osteoblast surface, and osteoid surface and volume). Osteomalacia, though uncommon, also improved as indicated by a decrease in the maximum number of osteoid lamellae and in the osteoid thickness. In the placebo group, these histological indices tended to

worsen. No significant differences were seen between centers in the histological responses recorded.

Biochemical Parameters

After treatment, mean serum alkaline phosphatase activity and intact parathyroid hormone concentration had increased by 20 IU/l and 8 pmol/l, respectively, in the placebo group, whereas alk phos and PTH decreased by 5.7 IU/l and 0.6 pmol/l, respectively in the alfacalcidol group ($p<0.001$). The changes in serum alkaline phosphatase activity were similar to the changes observed in serum parathyroid hormone; i.e., in patients taking alfacalcidol, alkaline phosphatase activity decreased by 15% in the first 6 months of treatment, remained reduced for most of the duration of the study, but increased to near pretreatment values by the end of the study. In the placebo group, there was a significant, progressive increase in serum parathyroid hormone concentrations and alkaline phosphatase activity during the study.

There was a small but significant increase in mean corrected serum calcium concentration (0.07mmol/L) in patients treated with alfacalcidol; this was observed at the first assessment (4 weeks after the start of therapy) and persisted during the 2-year treatment period. There was no significant change in mean corrected serum calcium concentration in the placebo group ($p<0.001$). Mean 24-hour urinary calcium excretion increased in patients taking alfacalcidol but not in those taking placebo. Mean serum phosphate concentration increased in both groups, with no significant difference between groups at any time during the study. There was no significant difference between groups in urinary phosphate excretion. Hydroxyproline excretion decreased at the end of the study in patients taking alfacalcidol compared with those taking placebo (-73 umol/day; $p=0.09$).

Radiological Response

There was no significant change in subperiosteal erosions during the study and no significant difference between groups. Measurements of combined cortical width decreased equally and non-significantly in both study groups.

Safety Assessments

Adverse Events

Reported adverse events were mild in intensity and included gastrointestinal disturbances and pseudogout. No patient was withdrawn from the study prematurely because of adverse events, persistent hypercalcemia, or unexpected progression of renal failure.

Biochemical Analyses

During the study, 3 patients given placebo and 10 patients given alfacalcidol developed mild hypercalcemia ($p=0.09$). In patients taking alfacalcidol, hypercalcemia readily resolved when the daily dose was decreased. Severe hypercalcemia (corrected serum calcium concentration >3.00 mmol/L) occurred in 4 patients (one occasion in each case) taking alfacalcidol. Of the patients taking calcium supplements, one patient in each group required phosphate binding

drugs that contained aluminum to control serum phosphate concentration. Two other patients (one in each group) were taking aluminum-based compounds as antacids.

Renal Function

Renal function declined progressively in both study groups. At end of the study there was a significant deterioration in renal function but there was no significant difference between treatment groups. There were no significant between-group differences in serum creatinine concentration or endogenous creatinine clearance at the end of therapy, as calculated by the Cockcroft method.

Adynamic Bone Lesions

At the end of the study, adynamic bone lesions had resolved in 4/6 patients taking alfacalcidol who had been affected at the start of the study and in 2/3 patients taking placebo. Adynamic bone lesions developed in 8 patients given alfacalcidol and in 4 patients given placebo (no statistical comparison provided). None of the patients with adynamic bone lesions at the start or end of the study had positive staining for aluminum at the mineral-osteoid interface. Aluminum staining appeared in 1 patient taking alfacalcidol and 2 patients taking placebo by the end of the study.

Sponsor's Conclusions

In this study, patients with mild to moderate chronic renal failure (creatinine clearance 15-50 mL/min) showed significant improvement in bone histology when treated with alfacalcidol (up to 1 µg/day for two years), whereas patients given placebo showed a sustained deterioration in biochemical and histological indices of bone metabolism. Most of the patients (132/176, 75%) in this study had renal bone disease at baseline, despite normal serum activity of alkaline phosphatase and normal radiographic findings. The authors point out that this is consistent with previous findings demonstrating that biochemical and radiographic indices are less sensitive indicators of bone disease than bone histology in patients with renal failure. Among patients with abnormal bone histology before treatment, bone disease resolved in 42% of those treated with alfacalcidol and 4% of those given placebo ($p<0.001$). In the control group, mean serum alkaline phosphatase activity and intact parathyroid hormone concentration increased by 13% and 126%, respectively, after treatment but showed no net change in the alfacalcidol group ($p<0.001$). In the treated group, serum parathyroid hormone concentration and alkaline phosphatase activity decreased after six months of treatment, but later increased to pretreatment levels. The authors point out that this "escape" pattern is similar to that seen in the treatment of renal bone disease with vitamin D derivatives in patients receiving hemodialysis.

There was no difference in rate of progression of renal failure between the two groups in this study, suggesting that long-term use of vitamin D derivatives in patients with impaired renal function does not accelerate the progression of renal failure. Incidences of hypercalcemia were infrequent (16% in the alfacalcidol group and 3% in the placebo group) and resolved in alfacalcidol patients when the daily dose was decreased. One of the potential hazards of long-term treatment with alfacalcidol could be inappropriate suppression of bone turnover, resulting in adynamic bone lesions characterized histologically by a paucity of bone cells and a decrease in bone formation. In this study, adynamic bone lesions developed in 12 patients during treatment,

but they also resolved in 6 of the 9 patients in whom they had been present before treatment, suggesting that long-term use of alfacalcidol does not increase the risk for adynamic bone lesions.

Investigator's Conclusions

The authors conclude that renal bone disease is common in patients with mild to moderate chronic renal failure (creatinine clearance of 15-50 mL/min) and that the use of alfacalcidol to a maximum of 1 µg/day can safely improve subclinical bone histology and favorably alter the natural course of the disease. The high prevalence of bone disease in patients with early renal failure and the safety and efficacy of alfacalcidol suggest that this regimen might be more widely used in the management of predialysis patients with asymptomatic bone disease.

Medical Officer's Conclusions

This was a fairly large, placebo-controlled study. As such, the results of this trial carry sufficient weight with respect to the approvability of this supplemental NDA. Importantly, severity of marrow fibrosis decreased as did bone turnover in the active-treatment group. Both serum PTH and alk phos levels decreased by a significant amount in the active vs. placebo-controlled subjects. Not surprisingly, active treatment was associated with more episodes of hypercalcemia. And consistent with other studies, there was no obvious decrease in renal function following treatment with alfacalcidol compared with placebo treatment.

The data presented in this study support the claim that calcitriol (alfacalidol) treatment is beneficial to patients with predialysis renal failure.

Study #5

Low dose Calcitriol *versus* placebo in patients with predialysis chronic renal failure

J Clin Endocrinol Metab. 1988; 67(5):929-936

Objective: The objective of this study was to evaluate the effects of a small dose of Calcitriol (≤0.50 µg/day) on parathyroid and renal function, bone histomorphology, and aluminum metabolism in patients with predialysis chronic renal failure.

Design: This was an 8-month, randomized, double-blind, placebo-controlled study of patients with predialysis chronic renal failure. Consecutive patients were allocated to receive Calcitriol (initial dose 0.25 µg/day for 14 days; then 0.50 µg/day for the duration of the study) or matching placebo. Patients received one tablet of Calcitriol (0.25 µg/day) or identical placebo for the first 14 days and then two tablets (Calcitriol, 0.50 µg) per day for the duration of the study. Treatment was suspended for 3 days if serum calcium levels were ≥2.7 mmol/L. The dosage then was reduced by half until serum calcium levels declined to ≤2.4 mmol/L, and thereafter dosage was adjusted to maintain the serum calcium level between 2.4 - 2.7 mmol/L. Serum phosphate levels were maintained below 1.7 mmol/L with the lowest possible dose of aluminum (Al)-containing phosphate binder. Patients maintained their regular diets and medications throughout the study.

Population: This study included both men and women with serum creatinine values greater than 180 umol/L and stable renal function within the 4 months prior to enrollment.

Endpoints: The following parameters were evaluated:

- Serum creatinine (µmol/L), calcium (Ca; mmol/L), ionized Ca (mmol/L), phosphate (P; mmol/L), alkaline phosphatase (ALP; U/L), parathyroid hormone (PTH; µg/L), aluminum (Al; µg/L)
- Urinary Ca (UCa; mmol/day), P (mmol/day), cyclic adenosine monophosphate (cAMP; nmol/100 mL glomerular filtrate); creatinine clearance (Ccr; mL/min)
- Bone biopsy:
  - Eroded surface (ES/BS; %), osteoid surface (OS/BS; %), osteoclast surface (Oc.S/BS; %), bone formation rate (BFR/BS; %), tetracycline-labeled surfaces (LS/BS; %) expressed as a function of bone surface (BS)
  - Bone volume, mineralized plus nonmineralized cancellous bone, expressed as a function of tissue volume (BV/TV; %); osteoid volume expressed as a function of BV (OV/BV; %); osteoid thickness (O.Th; µm)
  - Mineralizing surface, double-labeled plus single-labeled surface, expressed as a function of BS (MS/BS; %); mineral apposition rate = interlabel distance per day (MAR, µm/day), adjusted apposition rate = MAR×MS/OS (Aj.AR; µm/day); mineralization lag time = O.Th/Aj.AR (Mlt; days)

- Hyperosteoidosis; osteomalacia; endosteal fibrosis

Statistical Analyses: Nonparametric statistical methods were used; i.e., Wilcoxon tests for paired differences and for two samples. The results were considered statistically significant when $p<0.05$.

Results

Patient Disposition

Thirty (30) patients with predialysis chronic renal failure were consecutively entered into the study. Fifteen (15) patients were randomized to the Calcitriol group and 15 to the placebo group. Fourteen (14) of the 15 patients in each group completed the One patient in the placebo group received a cadaveric kidney transplant after 6 months, and 1 patient in the Calcitriol group had an emergency unilateral nephrectomy after 6 months due to bleeding from a polycystic kidney. In both patients, a second bone biopsy was obtained during the operation.

Demographics

The two groups were well matched at baseline. Patients ranged in age from _____ years. Twenty (20) men and 10 women were entered into the study. Serum creatinine values ranged from _____ μmol/L. At the start of the study there was no significant difference between study groups in serum concentrations of creatinine, Ca, ionized Ca, P, ALP, or PTH; urinary cAMP, Ca or P excretion; Ccr; or histomorphometric bone values

Primary Efficacy Outcomes

Biochemical Parameters: In the Calcitriol group, median serum Ca increased significantly ($p<0.01$) from start to end of treatment, but remained within the normal range. There were corresponding increases in ionized Ca and urinary Ca excretion. The effect on serum Ca and ionized Ca was significant after 4 weeks of treatment and the differences between treatment groups by the end of the study were significant ($p<0.01$). Serum PTH and urinary cAMP decreased significantly in the Calcitriol group during the study ($p<0.01$). In the placebo group, serum Ca and ionized Ca decreased and serum PTH increased from start to end of treatment. Urinary Ca and cAMP excretion did not change significantly.

Serum P was kept below 1.7 mmol/L by individually adjusted doses of Al-containing phosphate binder. There was no difference in urinary P excretion between the two study groups at any time during the study. Serum ALP values decreased in the Calcitriol group ($p<0.05$ for difference between start and end of the study), to a level significantly lower than that in the placebo group ($p<0.05$ for difference between treatment groups).

Histomorphometry: Median values of most measured bone indices were within the normal range in both study groups both at the start and end of the study. During treatment with Calcitriol, median values of all bone indices decreased significantly with the exception of cancellous bone volume, double-labeled surface (data not shown), and mineralization lag time. In the placebo group, there were no significant changes in any of the median histomorphometric bone indices during the study. Differences between study groups were significant for osteoid volume ($p<0.01$) and mineralizing surface ($p<0.01$). The decrease in mineralizing surface during Calcitriol treatment was due to reduction of the single-labeled surface.

Also during treatment with Calcitriol, significant decreases were reported in eroded surface (ES/BS; $p<0.05$), osteoid surface (OS/BS; $p<0.05$), osteoclast surface (Oc.S/BS; $p<0.01$), and bone formation rate (BFR/BS; $p<0.01$), whereas no significant changes occurred in the placebo group. The difference between study groups was significant for all four parameters.

Endosteal fibrosis disappeared in all but 4 Calcitriol patients by the end of the study, while it was still present in all placebo patients.

Safety Assessment

The Calcitriol dose was reduced at least once in 8/15 (53%) patients due to hypercalcemia. In 6 of the 8 patients, all of whom had ALP values within the normal range initially, the dose was temporarily reduced. Their first hypercalcemic episodes occurred 5-12 weeks after initiation of treatment. Serum PTH levels decreased and bone resorption indices were normal in all 6 patients at the end of the study. The mean daily dose was 0.36 μg. In the other 2 patients, both of whom had high serum PTH (32.5 and 15.5 μg/L) and ALP (303 and 393 U/L) values initially, the Calcitriol dose was permanently reduced (mean daily dose = 0.28 μg). The first hypercalcemic episodes occurred after 3 months when the serum PTH values had decreased to 11.2 and 3.8 μg/L and ALP had reached the normal range. During the study, their serum ALP values remained within the normal range, but serum PTH values increased to 19.7 and 8.0 μg/L, respectively. Bone histology improved slightly in both patients, but the resorption indices remained increased, and endosteal fibrosis was still present at the end of the study. All of the hypercalcemic episodes in the Calcitriol group were of short duration, and serum calcium exceeded 2.8 mmol/L on only one occasion (2.9 mmol/L) in one patient.

Serum Al concentrations were higher in those patients taking Al-containing phosphate binders. There was no significant change in serum Al during the study in either study group. Four patients (two in each study group) developed stainable Al in bone during the study; 3 of the 4 patients were close to end stage renal failure. One additional patient (placebo group) with diabetic nephropathy had stainable Al in his first biopsy; however, the second bone biopsy showed less Al-covered surface.

The mean serum creatinine concentrations increased and creatinine clearance decreased significantly ($p<0.01$) during the study period in both groups. There was no significant difference between the two groups at any time.

Sponsor's Conclusions

The results of this study suggest that low dose Calcitriol treatment can have a beneficial effect on bone metabolism in patients with predialysis chronic renal failure (serum creatinine >180 μmol/L). Patients treated with Calcitriol showed significant improvement in parathyroid hyperfunction, as evidenced by decreased serum PTH values, disappearance of endosteal fibrosis, and decreased bone resorption and bone formation indices. In the placebo group, serum PTH concentrations increased during treatment, no significant change occurred in any of the histomorphometric bone indices and endosteal fibrosis was still present in all patients at the end of the study. In the Calcitriol group, 11/15 (73%) patients had normal bone resorption at the end of the study. Two patients may have needed more than 0.5 μg/day Calcitriol as their serum calcium remained in the lower range, and serum PTH and bone histology did not change. In the other 2 patients, with initially high serum PTH and ALP levels, hypercalcemia occurred when ALP reached the normal range. Both patients later developed overt hyperparathyroidism and underwent ~~hyper~~parathyroidectomy 1 year after successful kidney transplantation

Calcitriol also had a beneficial effect on osteomalacia as evidenced by an improvement in mineralization after 8 months of treatment. Osteoid volume decreased while cancellous bone volume remained constant following treatment with Calcitriol, and there was a significant shift from single to double fluorescent band at the end of the study in the treatment group. Both occurrences indicate improved mineralization.

Serum calcium and ionized calcium concentrations increased in the treatment group, and the Calcitriol dosage had to be reduced at least once in 8 (53%) patients because of hypercalcemia. However, serum calcium concentrations were closely monitored and exceeded 2.8 mmol/L on only one occasion in one patient. Throughout the study, renal function decreased at a similar rate in both study groups, suggesting that low-dose Calcitriol treatment with close control of serum calcium, did not have a deleterious effect on renal function during the 8-month study period. Calcitriol treatment did not significantly influence either serum Al levels or the presence of stainable Al in bone. In this study patients taking Al-containing phosphate binders had higher serum Al levels that those who did not; however, Calcitriol treatment did not significantly increase serum Al concentrations when compared to placebo treatment. Definite conclusions regarding the effect of Calcitriol on stainable Al in bone cannot be made as only 4 patients developed stainable Al during the study; however, the 4 patients were equally distributed in the two study groups.

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Investigator's Conclusions

Low dose Calcitriol treatment can prevent or even restore bone metabolism in patients with predialysis chronic renal failure. The improvement occurs without any significant increase in either serum Al concentrations or incidence of stainable bone Al. The daily dose should be individualized on the basis of serum Cal measurements, which should be monitored closely.

Medical Officer's Conclusions

This reviewer concurs with the conclusions of the study investigators.

Study #6

Bone mineral density evaluated by dual-energy x-ray absorptiometry after one-year treatment with Calcitriol started in the predialysis phase of chronic renal failure

Nephron 1995; 69:433-437

Objective:The objective of this study was to evaluate the effect of one-year treatment with low-dose Calcitriol started in the predialysis phase of chronic renal failure (CRF) on bone mineral density as measured by

Design: This was a double-blind, randomized, placebo-controlled study of patients with predialysis chronic renal failure. Patients received either low-dose Calcitriol (0.25 µg/day) or placebo and were followed monthly for 12 months. Calcium acetate (0.75 - 1.5 g/day) was prescribed to all patients when serum calcium levels did not exceed 2.6 mmol/L, blood ionized calcium level did not exceed 1.29 mmol/L, or serum phosphate was not below 0.8 mmol/L.

Population: This study included men and women. The inclusion and exclusion criteria were as follows:

Inclusion Criteria

- Glomerular filtration rate (GFR) ≤51.2 mL/min
- Age <70 years

Exclusion Criteria

- Pregnancy
- Hypercalcemia (serum calcium >2.6 mmol/L)
- Renal stones
- Intestinal diseases
- Diabetes
- Treatment with steroids, vitamin D metabolites, anticoagulants, anticonvulsants

Endpoints: The following parameters were evaluated:

- Bone mineral density (BMD; g/cm^3) before and after the study
- Serum creatinine (µmol/L), calcium (Ca; mmol/L), phosphorus (P; mmol/L), alkaline phosphatase (ALP; U/L), aluminum (Al; µmol/L) every month
- Serum intact parathormone (i-PTH; ng/L) and osteocalcin (GLA protein; µmol/L) before and after the study
- Serum 1,25$(OH)_2D_3$ (pmol/L)and 25$(OH)D_3$ before and after the study

- Blood ionized calcium (Ca_i; mmol/L) every 3 months
- Glomerular filtration rate (GFR; mL/min) before and after the study

Bone mineral density was measured before and after the study by DEXA, using _____. DEXA was performed in the proximal femur (femoral neck, Ward's triangle, trochanter region) and in the lumbar spine (L_2-L_4 in anteroposterior projection).

Reference values from _____ were used as references for DEXA. The values for healthy Finnish women for lumbar spine and proximal femoral measurements are equal to those from healthy, white American women.

Statistical Analyses: Results are expressed as means ± SEM. The results were considered significant when $p<0.05$. For statistical analysis, Wilcoxon's signed ranks test (for paired data) and the Mann-Whitney U test were used; when possible the t test was used.

Results

Patient Disposition

Twenty-six (26) patients from the Renal Outpatient Clinic of the University Hospital of Oulu, Finland, were enrolled in the study. Thirteen (13) patients were randomized to receive low-dose Calcitriol (0.25 µg/day) and 13 were randomized to received placebo. All patients in the Calcitriol group and 12/13 (92%) patients in the placebo group completed the one-year study. One patient from the placebo group died of myocardial infarction in the ninth month of the study.

Three patients were being treated with continuous ambulatory peritoneal dialysis (CAPD) at the end of the study; 2 from the placebo group (after 9 and 11 months of study) and 1 from the Calcitriol group (after 10 months of study).

Demographics

Demographic and baseline characteristics of study patients are summarized in the table below. There were significantly more women in the Calcitriol group (11/13) than in the placebo group (4/12) ($p<0.05$). There were no significant study-group differences in clinical and biochemical results at baseline, except serum levels of $1,25(OH)_2D_3$ (mean value higher in the placebo group, $p<0.01$).

Five (5) of the 15 female patients were post-menopausal (5-10 years). Patients, depending on the level of their renal function, were on a low-protein diet (average 0.6 g/kg body weight) and a low-phosphorus diet (average 800 mg/day). Some patients had received calcium carbonate or aluminum-containing phosphorus binders before the study. One patient (Calcitriol group) had a thoracic vertebral fracture a few months before the study, and one patient (placebo group) had a tibial fracture in the first month of the study.

Table Demographic and Baseline Characteristics of Evaluable Patients

Parameter	Calcitriol (n=13)	Placebo (n=12)
Sex, n (%)*		
Male	2 (15%)	8 (67%)
Female	11 (85%)	4 (33%)
Age, yrs		
Mean ± SEM	49.3 ± 3.0	50.3 ± 2.9
Range		
Duration of CRF, years		
Mean ± SEM	8.2 ± 0.7	5.7 ± 1.0
Range		
Primary Diagnosis, n (%)		
Glomerulonephritis	1 (8%)	4 (33%)
Polycystic kidneys	3 (23%)	2 (17%)
Nephritis interstitialis	2 (15%)	3 (25%)
Medullary spongious disease	1 (8%)	0
Pyelonephritis	4 (31%)	2 (17%)
Nephrosclerosis	1 (8%)	1 (8%)
Hypoplasia renis	1 (8%)	0

Abbreviations: CRF = chronic renal failure.
*Difference between study groups is significant; $p<0.05$.

Primary Efficacy Outcomes

There was no statistically significant difference between study groups in DEXA results before the study. Compared to age-matched controls, 12 patients were below 1 SD and 5 patients were below 2 SD with regard to bone density of the femoral neck, and 10 and 2 patients, respectively, were below 1 SD and 2 SD with regard to bone density of the lumbar spine.

After one year of study, there was an increase in bone mineral density of 3.37% in the femoral neck ($p<0.01$) and of 3.93% in the lumbar spine ($p<0.01$) in the Calcitriol group. In the placebo group after one year, there was a decrease in bone mineral density of 2.17% in the femoral neck ($p<0.05$) and 0.62% in the lumbar spine (not significant).

After one year of study, a statistically significant increase in bone mineral density in the Calcitriol group was seen for the femoral neck ($p<0.001$) and for the lumbar spine ($p<0.01$) when compared to the placebo group.

Biochemical Parameters

At baseline, mean serum $1,25(OH)_2D_3$ levels were lower than normal values in the Calcitriol group and at the lower end of the normal range in the placebo group. Two (2) of 6 patients tested in the placebo group and none of the 9 patients tested in the Calcitriol group had lower than normal serum $25(OH)D_3$ levels.

There was a statistically significant decrease in serum i-PTH (150 to 105 ng/L)($p<0.05$) and serum osteocalcin ($p<0.01$) at the end of study in the Calcitriol group when compared to the placebo group(122 to 151ng/L). There was a significant negative correlation between serum ionized calcium and PTH before treatment in all patients ($p<0.02$). There was no correlation between the serum osteocalcin and serum alkaline phosphatase levels in either group before the study.

Safety Assessments

Hypercalcemia (serum Ca >2.6 mmol/L) occurred in 2 (15%) patients in the Calcitriol group and no (0%) patients in the placebo group during the study. In both cases, serum calcium levels normalized when calcium acetate was stopped for a few days, and both patients resumed taking calcium acetate. Hyperionized calcemia (blood ionized calcium >1.29 mmol/L) occurred in 5 (38%) patients in the Calcitriol group and 3 (25%) patients in the placebo group during the study. In all cases ionized calcium levels normalized when calcium acetate was stopped for a few days. Hyperphosphatemia (serum phosphorus >1.5 mmol/L) occurred in 3 (25%) patients in the placebo group and in 10 (77%) patients from the Calcitriol group ($p<0.05$). Two (2) patients in the Calcitriol group and 1 patient in the placebo group did not tolerate calcium acetate, and the treatment was stopped after 1 month. Calcium and phosphorus products never exceeded 70 mg%, a risk factor for metastatic calcification.

There was a statistically significant increase in serum creatinine levels in both study groups at the end of the study ($p<0.05$). There was a statistically significant decrease in GFR in the placebo and Calcitriol groups ($p<0.05$). The increase in serum creatinine and decrease in GFR were not statistically different between the two study groups. There was a decrease in serum alkaline phosphatase level at the end of the study in the Calcitriol group; the difference between the two study groups was not significant. One patient in the placebo group died of myocardial infarction in the ninth month of the study.

Sponsor's Conclusions

The results of this study showed that continuous treatment with low-dose Calcitriol (0.25 μg/day) beginning in the predialysis phase of CRF effectively increased bone mineral density in the proximal femur and lumbar spine. A low-phosphorus diet with calcium acetate did not seem to protect against bone demineralization. The improvement in bone mineral density was probably due to the effect of Calcitriol on bone mineralization and on the suppressive action of Calcitriol on parathyroid function, expressed by a decreased level of serum i-PTH. The fall in serum osteocalcin in the Calcitriol group, as a marker of decreased bone turnover, may also be an indirect marker of decreased serum PTH.

In the placebo group, serum PTH and osteocalcin increased after one year of study. In the Calcitriol group, serum PTH and osteocalcin levels decreased, and the difference between study groups was significant ($p<0.05$ for PTH and $p<0.01$ for osteocalcin), suggesting that maintaining normal serum phosphorus levels is not sufficient to suppress hyperparathyroidism in the predialysis phase of CRF.

Calcitriol at a dosage of 0.25 μg/day for one year was well-tolerated in this study. Deterioration of renal function in the Calcitriol and placebo groups was similar. Hypercalcemia occurred in 2 (15%) patients treated with Calcitriol, but was easily reversed by discontinuing calcium acetate for a few days. Hyperionized calcemia was also normalized by stopping calcium acetate intake. There was a higher risk of hyperphosphatemia in the Calcitriol group (25%, placebo; 77% Calcitriol), which is probably the result of increased intestinal absorption of phosphorus induced by Calcitriol. The higher risk of hyperphosphatemia found in the Calcitriol group indicates that more efficient diet control and use of phosphate binders are necessary in these patients.

Investigator's Conclusions

We conclude that treatment with Calcitriol in a steady low dose of 0.25 ug/day started in the predialysis phase of CRF is effective in increasing BMD in the proximal femur and lumbar spine.

Medical Officer's Conclusions

The results of this investigation support the findings from the other studies reviewed thus far, indicating that rocaltrol has a meaningful and favorable affect on the course of secondary hyperparathyroidism and metabolic bone disease in predialysis renal failure.

Studies in Pediatric Population

Study #1

A Prospective, Double-Blind Study of Growth Failure in childen with Chronic Renal Insufficiency and the Effectiveness of Treatment with Calcitriol versus Dihydrotachysterol

J Ped, 1994

Objective: To compare the effects of Calcitriol with dihydrotachyterol (DHT) on growth velocity and renal function in children with predialysis chronic renal insufficiency.

Design: This was a multicenter, double-blind, randomized trial comparing treatment with 20ng/kg/day vs. 15 ug/kg/day of DHT. The dosages were adjusted for changes in body weight, alk phos, and calcium levels. Treatment with active drug was not initiated until the following conditions were fulfilled: GFR $\leq$ 60 ml/min per 1.73m^2, elevation of serum PTH more than 1 SD above normal, patient at least 2 years of age, and bone age $\leq$ 9 years. During the control period anthropometric measurements and serum chemistries were evaluated on 3 consecutive occasions one month apart. If hypercalcemia occurred (>2.7 mmol/L, 11mg/dl), the medication was stopped until normal calcium level was obtained. Treatment was reinstituted at 75% of the preceding dose.

Population: Children between the ages of 18 months and 10 years with chronic renal insufficiency, documented by a calculated GFR between _____ ml/min per 1.73m^2. Exclusion criteria included: nephrotic syndrome, lupus, or any other condition in which steroids would be used, vitamin-D dependent rickets, primary renal tubular acidosis, and hypoparathyroidism. Children previously treated with Calcitriol or DHT were also excluded.

Endpoints: Serum Ca and PO4 were measured monthly during the trial. It is unclear how often heights were measured, presumably every month. Standard laboratory measurements were obtained monthly during the first 3 months and then every 6 months thereafter. Again, it is unclear from the published paper often often PTH and serum creatinine were measured.

Statistical Analyses: Changes in height and weight were converted to z scores. The height, weight, and GFRs were analyzed using a repeated measures analysis of variance. The occurrence of hypercalcemia was examined by stratified proportional hazard regression analysis. The appropriateness of these techniques should be explored by the Division statistician.

Results

Patient Disposition

A total of 143 patients entered the control period; 94 were randomly assigned to the two treatment groups. The actual number of patients in each arm is not provided. Eighty-two patients (40 in calcitriol and 42 in DHT) completed one year of study. There were 12 patients who dropped out of the treatment phase of the study. Four because of parent's decision, 3 because of physician decision, 2 for noncompliance. 2 because they moved, and one for dialysis. The report does not provide the groups the patients dropped from, nor is are the reasons that the parents and physicians dropped the patients from the study provided.

Demographics

The groups were well matched for baseline characteristics. The average age was 5.5 years, the majority of patients were male and Caucasian, and most of the children had obstructive uropathies. The mean serum creatinine was about 128 umol/L and the average PTH was about 1255 pg/ml.

Primary Efficacy Outcomes

Linear Growth: Neither treatment had a significant effect on linear height z scores.

Renal Function: There were statistically significant decreases in the slopes for GFR in both groups during the treatment period. More importantly, the calcitriol group had a significantly steeper rate of decline in GFR than the DHT group (p=0.003).

Hypercalcemia: There were a total of 47 episodes of hypercalcemia in the calcitriol group and 41 in the DHT group (p=ns). The time to development of hypercalcemia was 11 and 12 months for the calcitriol and DHT groups, respectively.

Investigator's Conclusions

Administration of both calcitriol and DHT was associated with a significant decline in renal function. There was no advantage of use of calcitriol over DHT in promoting linear growth. We conclude that DHT can be used with equal efficacy, although careful follow-up is mandatory because of the accelerated rate of renal deterioration encountered with use of either calcitriol or DHT.

Medical Officer's Conclusions

The results of this study, which would have been more valuable if more detail regarding patient disposition was provided, indicates that the use of calcitriol, at an average dose of 17 ng/kg/day,does not significantly improve growth rates in children with predialysis CRI. Although both treatments were associated with decreased renal function (calcitriol > DHT), the lack of a placebo group, which may be justified on ethical grounds, precludes one from drawing accurate conclusions about calcitriol's effect on renal function. Like adults, children treated with calcitriol are at risk for hypercalcemia and need to be monitored frequently.

Study #2

Influence of Long-Term Oral 1,25-Dihydroxyvitamin D in Childhood Renal Osteodystrophy

Contr. Nephrol, 1980

Objective: To evaluate the effects of calcitriol on calcium levels, radiographic status, and growth in children with uremic osteodystrophy.

Design: This was an open-label trial. There is no description of how the patients were selected for study. Patients received calcitriol in doses ranging from 14-55 ng/kg/day; again there is no description of how the dose was chosen. Each patient received daily supplemental calcium gluconate equal to 1.0 g elemental calcium per m^2.

Population: Eleven patients, aged _____, with chronic renal failure were studied. No inclusion or exclusion criteria are presented.

Endpoints: The following endpoints were analyzed: serum Ca, PO4, alk phos, PTH, and Mg, radiological appearance of long bones, 5 patients had _____, and height and weight velocity.

Statistical Analyses: No description of statistics are mentioned.

Results

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Patient Disposition

The 11 patients received calcitriol from _____ months. Patient 1 died of pneumococcal meningitis at age 14 months, patients 3, 4, and 6 received renal allograft transplants after 16, 22, and 4 months of calcitriol.

Patient Demographics

The patients ranged in age from 3 months to 16 years. Nine of the 11 subjects were male. The initial serum creatinine values were _____ mg/dl. All subjects had been taking some form of vitamin D prior to entering the study and all had some indication of rickets on x-ray examination.

Primary Efficacy Outcomes

Serum Chemistries: Serum calcium level increased from _____ mg/dl ($p<0.001$) after

treatment. Five patients developed hypercalcemia, but levels returned to normal quickly after the calcitriol dose was lowered. There was no significant changes in the mean levels of serum PO4 or Mg. After 4 months of therapy the mean level of alk phos decreased from _____ U/L and after 12 months it fell further to 191 IU/L ($p<0.02$). Levels of PTH were markedly elevated prior to the study. Treatment for 12 months resulted in a decrease from _____ ulEq/ml . Only one patient, however, had a normal PTH level after one year of treatment. Although serum creatinine levels increased from _____ mg/dl over the 30 month treatment period, the rate of increase was not significantly different over the entire 56-month observation period.

Radiographic Examination: At study entry 8 patients had severe rickets and the other 3 had early rickets. The authors note that therapy resulted in radiological healing of rickets in 10 patients. Five patients had _____ / before and after treatment. In all 5 patients BMC returned toward or into the normal range.

Height and Weight Velocity: Each patient was short for chronological age prior to treatment. Only 4 patients could be evaluated for height velocity over a one-year treatment period. In these patients, height velocity increased from _____ cm/year ($p<0.02$).

Safety

Episodes of hypercalcemia are discussed above. The authors report no evidence of metastatic calcification on the radiographic evaluations.

Author's Conclusions

This trial demonstrates that oral calcitriol is absorbed from the gut and can offer considerable benefits in the treatment of childhood renal osteodystrophy, particularly in reversing bone disease and increasing height velocity.

Medical Officer's Conclusions

This small, uncontrolled study is of limited value. The results of this study, do however, provide ancillary support for the role of calcitriol in the treatment of secondary hyperparathyroidism.

Study #3

The Importance of Early Treatment of Renal bone Disease in Children

Kid Intern, 1985

Objectives: To examine the effects of calcitriol and vitamin D2 on the clinical and laboratory features of renal bone disease in seven boys with posterior urethral valves.

Design: This was an open-label study in which seven boys with variably diminished renal function after fulguration of their posterior urethral valves were placed in one of three groups: patients 1 and 2 were placebo in group I and treated with oral vitamin D2 at 400 to 1000IU daily; Group II included patients 3-5, who were treated with oral calcitriol at 10 to 15 ng/kg/day after age 21 months; and Group III consisted of patients 6 and 7, who were treated with the same dose of calcitriol beginning at less than 12 months of age.

Population: Seven boys with variably diminished renal function after fulguration of their posterior urethral valves. No other details about the study population are provided.

Endpoints: The following variables were evaluated: serum Ca, PO4, alk phos, creatinine, and HCO3. Immunoreactive PTH was evaluated every 6 months using antibodies against the intact and C-terminal portion of the hormone. Height and weight were also measured. The interval of measurements is not provided.

Statistical analyses: Comparisons were made with the Student t test.

Results

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Patient Disposition

Very little information about disposition is available from the published paper. The subjects in Group I received vitamin D2 for a total of 50 months, while Group II and III were treated with calcitriol for 78 and 30 months, respectively.

Patient Demographics

The ages of the subjects ranged from _____ months; serum creatinine from _____ mg/dl; and serum calcium from _____ mg/dl.

Efficacy Outcomes

Serum Chemistries: Serum calcium was subnormal in four patients pre-therapy, but was normal post therapy in all patients except patient #2 from Group I. Serum alk phos was elevated in all three groups: 545, 383, and 682 IU/L, respectively, pre-treatment and fell post-treatment to 455, 222, and 298 IU/L, respectively (the extremely small sample sizes make statistical analysis moot). Levels of serum PTH pre-treatment were elevated by more than 500% and fell only in those patients receiving calcitriol, although it did not fall into the normal range in any patient.

Growth Pattern: Four of the five patients treated with calcitriol had improved growth after treatment was initiated. Vitamin D2 treatment had no significant effect on growth.

Author's Conclusions

This preliminary study indicates a potential role for the use of early vitamin D analog therapy in childhood renal osteodystrophy and suggests the value of larger studies to investigate this point.

Medical Officer's Conclusions

This study provides some soft data on the usefulness of calcitriol (10-15ng/kg/day) to treat children with renal osteodystrophy.

Study #4

Renal Osteodystrophy in Nondialyzed Adolescents: Long-term Treatment with 1-alpha-hydroxycholecalciferol

Arch Dis Child, 1977

Objective: This paper describes the effects of 1-2 ug/day of 1-alpha-hydroxycholecalciferol on renal osteodystrophy in four nondialyzed adolescent patients with chronic renal failure.

Design: Case report. Each patient was initially treated with oral 1-alpha-HCC 2 ug daily; thereafter the dose was altered from time to time.

Population: The subjects ranged in age from _____ years. Two were male. Three of the subjects had not taken vitamin D, its metabolites or analogues for at least one year previously. One patient had been treated with 1-alpha-25 DHCC 0.7-1.35 ug daily for the five months before the study.

Endpoints: Endpoints included plasma Ca, PO4, creatinine, hydroxyproline, alk phos, PTH. Iliac bone biopsies were performed in two patients. Calcium and PO4 balance was measured in two patients.

Statistical Analyses: Procedures not reported.

Results

Patient #1

Calcium balance became positive within four days of starting treatment. This was largely due to an increased intestinal absorption. Initial improvement in metabolic homeostasis was eventually lost after five months of treatment. At a dose of 2 ug daily PTH, hydroxyproline, and alk phos activity increased, and subperiosteal bone erosions recurred as well. Bone biopsy after 10 months showed no change in the florid osteitis fibrosa and osteomalacia seen before treatment. The rates of change in height and weight were unaffected by treatment.

Patient #2

After 18 months of treatment this patient□s calcium and phosphate balances became positive. This increase was primarily due to an increase in absorption. The patient had one episode of hypercalcemia which resolved after the drug was discontinued. During treatment skeletal x-rays showed healing of bone ~~reso~~rption though skeletal deformities persisted.

Patient #3

This patient received previous treatment with 1-alpha-25-DHCC for 5 months. After initiation of treatment with 1-alpha-HCC she had a progressive fall in alk phos, PTH, and hydroxyproline levels.

Patient #4

Prior to treatment this patient had evidence of rickets on x-ray; although plasma levels of PTH were not markedly elevated. Treatment with 1-alpha-HCC was associated with increased levels of serum calcium and decreased levels of urinary calcium and no change in plasma creatinine. Although there was no drop in PTH, in fact, there was a rise in this hormone during the first five months of treatment, there was radiographic evidence of improvement in bone metabolism.

Author's Conclusions

We conclude that renal bone disease may be effectively treated with long-term 1-alpha-HCC, but careful supervision of the patient is required. Hypercalcemia is readily controlled but despite prolonged treatment relapse may occur in some cases.

Medical Officer's Conclusions

In and of itself, this study (case report) offers little in the way of efficacy data because of its design and small sample. As is well known with this treatment, vitamin D supplementation in chronic renal patients is associated with an increased risk for hypercalcemia; this study supports this safety finding.

Summary of Efficacy

Adults Patients

Data to support the efficacy of rocaltrol in the treatment of secondary hyperparathyroidism and metabolic bone disease in 217 adult patients with predialysis chronic renal failure comes primarily from five controlled trials. Most of the studies ranged in length from 8 to 30 months and studied doses of rocaltrol/alfacalcidol of 0.25 to 1.0 ug/day. The mean baseline creatinine clearance rates ranged from [redacted] mL/min and serum PTH values at baseline were mildly to moderately elevated.

In general levels of PTH decreased following treatment with rocaltrol/alfacalcidol and increased or did not change following placebo treatment. In some cases these changes were statistically significant between the active and placebo-controlled groups. Similar patterns of change were noted with alkaline phosphatase; again suggesting the utility of active drug treatment compared with placebo on the course of secondary hyperparathyroidism and metabolic bone disease in predialysis chronic renal failure.

The changes in bone histology that were observed in these trials were more heterogeneous than the changes in serum PTH and alkaline phosphatase. On the whole however, treatment with rocaltrol/alfacalcidol was associated with improvements in indices of abnormal bone resorption and formation. Some of the specific responses noted following active treatment were:

- Decrease in endosteal/trabecular fibrosis
- Decrease in osteoid volume and thickness
- Decrease in the active and/or inactive resorbing surfaces
- Decrease in the osteoblastic and osteoclastic hyperfunction
- Increase in bone mineral density

A notable deficiency in the submitted data was the lack of data on changes in activation frequency, a parameter which indicates the dynamic aspect of bone turnover.

Pediatric Patients

There are a large number of studies which report the effects of calcitriol therapy in pediatric patients. However, most of these trials were conducted in patient populations that differed from the target population for this supplemental NDA. That is, most children were receiving dialysis. Yet, 16 studies were conducted in predialysis patients. Most importantly though, none of the trials in children were placebo controlled. This, the sponsor states," is because placebo-controlled studies in this population are considered unethical because of the rapidly progressive nature and debilitating sequela of associated bone disease." The rigor with which we can draw conclusions regarding efficacy, and to some extent safety, is consequently hindered.

The patient population represented in the literature ranged in age from _____ years. Dosage varied between _____ ng/kg/day, and the duration of treatment ranged from a few months to more than 6 years.

With baseline measurements serving as a reference, many of the pediatric studies showed some improvements (usually not normalization) in measures of growth, bone histology (including rickets), and serum levels of calcium, PTH, and alkaline phosphatase.

It's fair to say that an indication for rocaltrol in the treatment of secondary hyperparathyroidism and resultant bone disease in pediatric patients with predialysis chronic renal failure is not supported by the pediatric-patient literature *per se*, but rather, comes from extrapolation from adult studies. For the purposes of this supplemental NDA, the literature in pediatric patients will serve as "supportive, uncontrolled data."

Summary of Safety

Exposure

Safety data are derived from 3 sources: the Roche sponsored trial, the published literature on rocaltrol/alfacalcidol, and post-marketing surveillance.

The exposure to rocaltrol has been extensive owing largely to its approval in over 79 countries. The adult patient exposure from the published studies submitted in support of this NDA total nearly 50. And estimates from post-marketing exposure since 1978 indicate that over 3 million patients have been exposed to this drug.

Regarding exposure in the pediatric population, 226 patients were treated with rocaltrol and the results of treatment published in 16 papers. Although not approved for use in children, rocaltrol is apparently used in children with chronic renal failure and we can assume that a sizable number of pediatric patients have been exposed to this drug.

Adverse Events (AE)

The most common safety parameters reported in the literature were episodes of hypercalcemia and hyperphosphatemia and the effects of treatment on renal function, as measured by changes in creatinine clearance and serum creatinine values.

Serious Adverse Events (SAE)

In the Roche sponsored trial there were 3 SAE reported: all three were deaths in placebo patients. From the published literature there were 14 SAE, all were deaths: 12 in rocaltrol/alfacalcidol and 2 in placebo. From the post-marketing database there were 12 deaths among patients treated with rocaltrol. The breakdown by cause is as follows: 2 MI, 2 carcinoma, 4 unknown, 2 multiple organ failure, 1 osteoporosis, 1 respiratory obstruction.

Hypercalcemia/hyperphosphatemia

Sixty four percent of rocaltrol patients and 12% of placebo patients had at least one episode of hypercalcemia (> 10.8 mg/dl). Statistics are not required to make judgements about drug effect here. Most episodes occurred after 3 months of treatment and incidence was clearly related to dose.

Fifty six percent of rocaltrol and 39% of placebo patients had at least one episode of hyperphosphatemia (> 5mg/dl). Unlike hypercalcemia, the first episode of elevated PO4 occurred during the first 3 months in 71% of treated patients.

In general, the published literature indicates that more rocaltrol-treated compared with placebo-treated patients experience more episodes of hypercalcemia and hyperphosphatemia. Importantly, this adverse event can be managed successfully by dose adjustment or drug discontinuation.

In pediatric patients the risk for hypercalcemia and phosphatemia also appears to be the most common drug-related adverse event.

Renal Function

The effect of rocaltrol (or active vitamin D) on renal function was raised as a safety issue some 20 years ago. While it is true that sustained hypercalcemia can precipitate a decline in renal function, the totality of the data in adults indicates that rocaltrol does not significantly increase the rate of decline in renal function when compared with placebo treatment. The lack of placebo comparative data in children makes it difficult to comment on this concern in the pediatric population. It's reasonable to assume, though, that the lack of effect in the adult population is relevant to the pediatric population.

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DRAFT LABELING

Conclusions

The data in this NDA, which come predominately from published literature, support the safe and effective use of calcitriol as described in the reviewed labeling.

/S/

Eric Colman, MD