CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 021068 and 18044/S025

MEDICAL REVIEW(S)

Weber

NOV - 6 1998

N18044/SO25Rocaltrol

NDA 18044 SO25
Hoffmann-La Roche
Rocaltrol (calcitriol) solution
1,25$(OH)_2$ cholecalciferol
Vitamin D metabolite
For hyperPTH in ESRD
Application received 11/20/97
Review completed 11/6/98

Team Leader's Comments

Rocaltrol is marketed for management of hypocalcemia in patients with end stage renal disease (ESRD). This application is to extend the indication to pre-dialysis patients.
Ten studies are reported to support the safety and efficacy of calcitriol in **predialysis** patients for the treatment of secondary hyperparathyroidism and resultant **metabolic bone disease of ESRD**. Roche sponsored one study. Four studies in children and 5 other adult **studies were selected from the literature** reports "...because they are well-controlled trials that evaluated calcitriol or alfacalcidol treatment using a dosage regimen consistent with the proposed recommended adult dosage (0.25 mcg to 0.50 mcg daily)..." Actually the Roche study and the proposed dose included doses to 1.0 µg/d. In the five studies, there were 123 subjects on drug for 8 months or longer, 109 for 12 months, and 89 for 24 months. The six adult studies (one Roche and 5 literature) based efficacy evaluation on **histomorphometry**.

The studies provide evidence of **improved bone histomorphometry**, and a tendency to reduced PTH. The evidence in support of a drug effect is convincing but does not indicate that major benefit is likely. This is offset by a consistent and also convincing **tendency to hypercalcemia**. The hypercalcemia is usually managed successfully and without sequelae. It will be necessary for patients and health-care providers to consider carefully whether, **in the pre-dialysis patient**, the benefits to bone will outweigh the risks of hypercalcemia.

Recommendation: Approve. /S/ AP

/S/

Gloria Troendle Cc: NDA 18044 Div File/HFD-510GTroendle/EColman

The Roche study (N2086) is the only one included in the review by the FDA statistical reviewer, Dr. Pian.

1. **Objective:** to demonstrate efficacy and safety in predialysis patients with hyperparathyroidism associated with chronic renal failure.
2. **Design**: double-blind, randomized, placebo controlled, 1-year. Diet supplemented with 400 IU vit D. Measurements made: Ca, P, Cr, alk phos, PTH, serum calcitriol and 25(OH)D. Tetracycline was given prior to biopsy at entry and after 1 yr.
3. **Population**: 18-70 years of age, creatinine clearance (CrCl) 15-55 or 20-60 mL/min. Exclusions: serum Ca >10.5 mg/dL, P >5.5 mg/dL, Ca x P >60, or used vit D suppl within 6 mo.
4. **Endpoints.** Primary efficacy outcome is bone histomorphometry.

bone resorption:

Osteoclast Index, OCI, count/mm^2;
Surface Density of Interface, S-VOCL;
Percent Fibrosis, FIB, %;

bone formation:

Osteoblast Index, OBI, count/mm^2;
Surface Density of Osteoid Seam S-VOS, mm^2/cm^3;
Volume Density of Osteoid, V-VOS, mm^2/cm3;

mineralization:

Mineralization Lag, MLT, days).

Secondary efficacy outcomes are measures of bone resorption, formation, and mineralization. Serum iPTH, alk phos, Ca, P, calcitriol, calcifediol (25OHD).

5. **Treatment**: initial dose 0.25 to 1 µg/d. If, at any time, hypercalcemia, hypercalciuria, or Ca x P product >70, discontinue calcitriol until value returns to normal limits.
6. **Analyses**: ITT and completers.
7. **Results**: 54 subjects, 51 randomized, 25 to Rocaltrol (Roc), 26 to placebo (Plbo), 20 and 21 completed; ________ were male and African-American. Mean CrCl 30.5 mL/min.

Efficacy. Mean change from baseline (reductions) in Rocaltrol-treated subjects for **S-VOS, V-VOS, OCI, and S-VOCL** were significantly different from the corresponding reductions in placebo patients by sponsor's covariance analysis, but **not by the analysis of FDA statistician, Lee-Ping Pian.**
OBI, FIB, and MLT were **not significantly different even by sponsor's analysis.** Mean changes in **PTH and alk phos** levels and AUCs in Rocaltrol patients were **not statistically different** from changes in placebo patients. Trends consistently favor Rocaltrol.
Safety. There were 3 deaths, and 3 serious AEs, all in the placebo group. 64% of Rocaltrol and 12% of placebo patients had at least one episode of **hypercalcemia**, and 44 vs 3 instances in Rocaltrol vs placebo patients. **Hyperphosphatemia** was seen in 56

vs 39% of Rocaltrol vs placebo patients, and 8 vs 2 patients had at least one episode of **elevated Ca x P product**. No signs of deteriorating renal function were seen.

The **literature studies** were double blind and placebo controlled, using 0.25 mg/d calcitriol unless noted differently below. None of them showed an effect of treatment on renal insufficiency.

Hamdy 1995, 89 drug (alphacalcidol up to 1 μg/d) and 87 placebo subjects (72 and 62 completed 2 years). 55 drug and 45 placebo patients had **histological abnormalities of bone** at baseline, 39 and 51 at endpoint. Of the 55, 45 who had abnormalities at baseline, 23, 2 were normal at endpoint. Endosteal fibrosis decreased. Alkaline phosphatase and PTH increased in placebo and decreased in drug patients during treatment, but by the end of the study had increased almost to baseline. Serum calcium and episodes of **hypercalcemia** increased.

Przedlacki 1995, 13 and 13 subjects (13 and 12 subjects completed 1 year). **BMD of the femoral neck and of the lumbar spine increased significantly** in treated and decreased in the placebo group by one year. **PTH and osteocalcin decreased** significantly in treated and increased in placebo subjects. **Hypercalcemia** occurred in 2 drug and no placebo patients.

Baker 1989, 8 and 8 subjects (7 and 6 completed 12 months). Following 0.25 μg for 4 weeks patients were titrated to 0.5 μg/d. **Normalization** of some bone biopsy parameters is seen: Lamellar Osteoid Volume, Lamellar Osteoid Surface, and Osteoid Seam Thickness differ more (lower) from the normal value after treatment, but high placebo level was not greatly changed. Other parameters (Woven Osteoid Volume and Surface, Bone-Osteoblast Interface, Osteoblastic Index, Bone-Osteoclast Interface, and Osteoclastic Index) appear to be improved. **PTH levels did not decrease**, and **hypercalcemia** occurred in 4 patients who increased the dose to 0.5 μg/d.

Nordahl & Dahl 1988, 15 and 15 subjects (14 and 14 completed 8 months). An extension continued this study in 13 subjects 5-60 months until transplant. Rocaltrol 0.25 μg/d was taken for 14 days and then 0.5 μg/d. Serum calcium increased and PTH and alkaline phosphatase decreased during treatment. **Histomorphometry improved** in drug, but not in placebo patients. Endosteal fibrosis improved. **Hypercalcemia** resulting in reduced dose occurred at least once in 8/15 patients. Serum **PTH decreased.**

Bianchi 1994, 17 subjects for 24 months, open without concomitant cont~~rols~~. Also received $CaCO_3$ 1 g/d. Endpoints: alkaline phosphatase, parathormone, 25(OH)D, 1,25(OH)D, osteocalcin, urinary hydroxyproline, bone mass of forearm and spine, and bone biopsy. Markers of bone turnover and **bone loss** by dual photon absorptiometry were reduced during treatment. There seems to have been an adverse shift between baseline and 6 months, but **improvement between 6 and 18 months** (still improved at 30 months). There was a decrease in PTH, hydroxyproline, alkaline phosphatase. Plasma Ca decreased slightly by 6 months, 8.9 to 8.5, then increased to 9.3 at 18 months and 9.9 at 30 months. Episodes of **hypercalcemia** occurred with a frequency of 9.6% during the treatment period. All of the **histomorphometry parameters** (osteoblastic surface, osteoclastic surface, bone trabecular volume, mean lacunar surface, osteoid index, mineral apposition rate, double-labeled osteoid seams and mineralization lag time) are closer to the normal range at 30 months than at 6 months, and some are normalized.

One pediatric study was intended to compare growth velocity effects of calcitriol with those of dihydrotachysterol. Children 18 months to ten years with predialysis renal insufficiency were randomized to 20 ng/kg/d calcitriol (40 completed 1 year) or 15 μg/kg/d dihydrotachysterol (42 completed). Neither treatment had a greater effect on linear height than the other. There was an **increased decline in renal function** with both treatments, and a significantly steeper decline in those treated with calcitriol. Placebo control would be very helpful, because neither treatment has reliable data on its effect. We do not now know whether both drugs have the same effects or both have no effect.

In another study, using oral drug, 11 children 3 months to 16 years were treated 4-32 months with calcitriol. This study was open - no comparator group. **PTH levels fell** from 1060 to 201 μlEq/ml. Rickets are reported to have healed in 10 children. All 5 children who had dual photon absorptiometry before and after treatment, saw **BMC return toward normal**. Only 4 patients could be evaluated for height velocity, and they showed increase from 2.6 to 8.0 cm/year. 5 patients developed **hypercalcemia**.

A third study in 7 children compared calcitriol 10-15 ng/d after 21 months with the same dose at less than 12 months and with vitamin D 10-15 ng/kg/d. Serum **alkaline phosphatase fell** in all 3 groups and **PTH fell** only in calcitriol-treated patients.

A fourth study in 4 adolescents used 1-2 μg/d calcitriol. **PTH did not fall** but there was **radiographic evidence of improved bone** metabolism.

The **Pediatric studies** are adequate to establish dose and guide therapy with respect to toxicity (hypercalcemia). Label should include the indication based on similarity of children's ESRD to adult ESRDs and on these supporting data.

MEDICAL/CLINICAL REVIEW
SUPPLEMENTAL NDA

CALCITRIOL
NDA 18-044

Sponsor: Hoffman-La Roche Inc.
Drug: Calcitriol (Rocaltrol®) Oral Solution
Category: Vitamin D
Indication: Secondary Hyperparathyroidism in Predialysis Patients
Submission: November 18, 1997

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/S/ 8/31/98
Eric Colman, M.D.

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cc: NDA Arch
HFD-510
JWeber/GTroendle/

Introduction

Roche has submitted this supplemental application after receiving a letter dated April 27, 1993, from Stuart Nightingale, M.D., Associate Commissioner of Health Affairs, in which he requested assistance in the identification of approved drugs currently being used off label and for which unpublished data and/or data derived from the literature is available to support the established off label use.

The sponsor replied to the above letter by stating that Rocaltrol or Calcitriol ($1,25(OH)_2D_3$) is widely used to treat secondary hyperparathyroidism (Hpth) and the resultant bone disease in predialysis patients with chronic renal failure (CRF); this represents off label use.

Rocaltrol is currently approved for the management of hypocalcemia in patients undergoing dialysis (original approval 1978), management of hypocalcemia and its clinical manifestations in patients with postsurgical hypoparathyroidism, idiopathic hypoparathyroidism, pseudohypoparathyroidism (approved 1982), and the treatment of osteotis fibrosa cystica and defective mineralization in dialysis patients with end-stage renal disease (approved 1986).

Clinical Background

Proposed Indication

"Predialysis Patients: Rocaltrol is indicated for the treatment of predialysis patients, i.e., for the treatment of secondary hyperparathyroidism and resultant metabolic bone disease in patients with moderate to severe chronic renal failure (Ccr 15 to 55 mL/min); in children, the creatinine clearance value must be corrected for surface area of 1.73 square meters. A serum iPTH level of ≥ 100 pg/ml is strongly suggestive of secondary hyperparathyroidism."

Overview of Secondary Hyperparathyroidism and Metabolic Bone Disease of Chronic Renal Failure

In the early 70s it was discovered that the kidney is responsible for the formation, through α hydroxylation, of the active form of vitamin D ($1,25(OH)_2D_3$). One eventual effect, therefore, of renal failure is a relative or absolute deficiency of active vitamin D.

Another inevitable consequence of renal failure, often early in the disease, is secondary hyperparathyroidism. Elevated levels of PTH are due to hypocalcemia and/or to a deficiency of $1,25(OH)_2D$, as mention above. The hypocalcemia associated with CRF is caused by one or more of the following: 1) phosphate retention; 2) skeletal resistance to the calcemic action of PTH, and; 3) altered vitamin D metabolism.

While a discussion of phosphate retention and skeletal resistance to PTH is beyond the scope of this review, a more detailed discussion of altered vitamin D metabolism is pertinent to this application. A phenomena associated with early renal failure is altered responsiveness of target organs to vitamin D. This includes impaired intestinal absorption of calcium and defective mineralization of osteoid. That blood levels of the active form of vitamin D are often normal in patients with early renal failure, despite altered end-organ function, suggests the presence of a relative deficiency of, and/or resistance to, active vitamin D.

Because active vitamin D may directly suppress the parathyroid glands, may render the parathyroid glands more susceptible to the suppressive effects of calcium, and decreases prepro-PTH messenger RNA in a dose-dependent manner, it□s possible that vitamin D deficiency may initiate secondary Hpth in the absence of overt hypocalcemia. Blood levels of active vitamin D decrease when GFR falls below 50 ml/min in children and below 30 ml/min in adults.

Since hypocalcemia and an absolute or relative deficiency of active vitamin D may develop early in the course of renal failure, hyperactivity of the parathyroid glands is also encountered in the early stages of renal insufficiency. In fact, elevated blood levels of PTH may be noted when GFR falls below 70 ml/min. This finding forms the basis for the idea of providing patients with moderate to severe chronic renal failure (Ccr 15 to 55 mL/min) who are not yet on dialysis with supplemental active vitamin D.

One of the outcomes of hypocalcemia, hypovitaminosis D, and Hpth is metabolic bone disease. There are two principal types of bone disease in chronic renal failure patients: osteitis fibrosa or high bone turnover disease resulting from elevated levels of PTH, and defective mineralization of osteoid, which is referred to as osteomalacia in adults and rickets in children. This condition has been associated with aluminum toxicity. Recently, aplastic renal osteodystrophy has been found in patients with no evidence of excess aluminum accumulation. These patients, in contrast to those with osteitis fibrosa, have extremely low levels of PTH and resultant low turnover bone disease.

Osteitis fibrosa or high turnover bone disease is associated with enhanced osteoclastic activity and increased bone resorption. The end result of Hpth and uremia include increased numbers of osteoclasts and osteoblasts (which may be suppressed in uremic patient), osteoclastic bone resorption, most evident in cortical bone, enlarged haversian lacunae, endosteal fibrosis, and accumulation of woven osteoid and woven bone.

Osteomalacia (rickets in children) is defined as the accumulation of excess unmineralized osteoid. Osteomalacia is characterized by minimal osteoid-osteoclast interface, reduced tetracycline uptake, no evidence of enhanced bone resorption, and no evidence of endosteal fibrosis. In addition to aluminum toxicity, which is less common now that non-aluminum containing phosphate binders are used, reduced levels of vitamin D have been implicated in the pathogenesis of osteomalacia. Some data do suggest that active vitamin D therapy improves osteomalacia in patients with advanced renal failure.

It should be mentioned that many patients with renal disease manifest osteosclerosis — which histologically is an accumulation of unmineralized trabecular bone with an increase in total bone mass. Hyperparathyroidism has been implicated in the development of osteosclerosis, a condition that appears as increased bone density of the trabecular bone.

The common laboratory abnormalities that accompany metabolic bone disease include hypocalcemia, Hpth, and elevated levels of alkaline phosphatase (alk phos) and hydroxyproline from bone. Although alk phos levels are usually elevated in patients with renal bone disease, in some patients with advanced bone lesions, the level of bone-derived alk phos may be normal. Alk phos levels, however, are useful for following patients during treatment which agents like active vitamin D. Similarly, levels of hydroxyproline usually fall in association with healing of osteitis fibrosa.

Relevant Literature

In addition to one Hoffman-La Roche sponsored double-blind, placebo-controlled trial, this application includes 33 published studies in adult patients and 16 clinical studies in pediatric patients. Four of the adult studies were double-blind and placebo-controlled. None of the pediatric studies were placebo-controlled.

Human Pharmacology and Pharmacokinetics

see pharmacology and biopharm reviews.

Description of Clinical Data Sources

Aside from one double-blind, placebo-controlled study sponsored by Roche, the data in this submission come from published literature. Specifically, in adult patients, five controlled trials (four of which are double-blind, placebo-controlled) and 28 additional clinical studies, many of which are comparative or open-label, have been submitted to support the new indication. In the pediatric population, the sponsor has collected published data from 16 clinical studies, none of which are placebo-controlled.

A total of 217 adult patients were studied in those trials designated as "major, controlled clinical trials," and an additional 300 patients were examined in the 28 supporting clinical studies. Regarding the pediatric population, a total of 200 patients were examined in 16 trials submitted by the company.

It should be recognized that some of the published literature refers to treatment with alfacalcidol. This compound undergoes 25-hydroxylation in the liver to form the biologically more active metabolite $1,25(OH)_2D_3$ or Calcitriol. This form of vitamin D is widely used in Europe, Canada, and Japan.

Clinical Studies

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Adult Population

Study #1

A double-blind, randomized, placebo-controlled study of Rocaltrol in the treatment of moderate to severe renal failure (predialysis renal insufficiency) Roche Report N-139375

This study, which was sponsored by Roche, was conducted at three medical institutions from December 1979 to January, 1985.

Objective: To examine the efficacy and safety of oral Calcitriol for the prevention or correction of renal osteodystrophy in predialysis patients with secondary Hpth associated with chronic renal failure.

Design: This was a three-center, double-blind, randomized, placebo-controlled, one-year study. Fifty-four subjects were randomized to one of two treatment groups: initial dose of 0.25 ug/day with maximal dose of 1.0 ug/day; or placebo. Subjects in the active-treatment group could have their dose increased after two months if the following conditions were satisfied: 1) serum calcium level did not increase by > 1.0 mg/dl or 2) serum calcium remained within normal limits for each study site. If at any time hypercalcemia or hypercalciuria or serum Ca x P product > 70 occurred, the medication was to be discontinued until these values returned to within normal limits. All patients received a multivitamin containing 400 IU of vitamin D and were instructed to consume at least 800 mg/day of calcium. Magnesium-free phosphate binders were administered to maintain serum phosphorus levels between 2.5 to 6.0 mg/dl.

Population: This study included men and women between the ages of ____________ with creatinine clearance rates of ____________. Patients were excluded if they had a serum Ca level > 10.5 mg/dl, a phosphorus (P) level ≥ 5.5 mg/dl, or a serum Ca x P product > 60 and if they had taken any vitamin D supplements within 6 months of study start.

Endpoints: The primary efficacy parameters included measures of bone resorption, formation, and bone mineralization. Also serum levels of iPTH and alk phos. (The assay used to measure PTH recognized the intact hormone, the mid-region and the carboxy-terminal portion). Secondary endpoints included serum total Ca, P, Calcitriol, and calcifediol (25(OH)D).

Statistical Analyses: Two patient populations were defined : ITT and standard. The ITT utilized a LOCF approach to the data. The standard population was in essence a completers population. For the bone biopsy and serum PTH and alk phos results, a multivariate, nonparametric procedure was applied to the seven primary variables. Treatment-related differences were tested using an ANOVA model, while within group differences were analyzed by paired t-tests. In addition, for the biochemical parameters, the change in area under the curve from baseline to year 1 was computed.

Results

Patient Disposition

A total of 51 patients were randomized to treatment: 25 to rocaltrol and 26 to placebo. Five patients from each group were withdrawn early from the study, although not because of adverse events but mostly lost to follow-up. Two patients in the placebo group and one in the rocaltrol group died during or shortly after the study was completed. Forty-one patients completed the study. One patient was excluded from the ITT analysis because of lack of on-treatment data.

Demographics

The two groups were well matched for baseline characteristics. The mean age was 50 years (range__________),____________ of the patients in each group were male and African-American.

The mean creatinine clearance was 30.5 mL/min ′). The most common primary medical diagnosis (≈ 60%) was urinary system disorder. Sixty-five to 75% of patients were taking more than 3 medications at baseline.

Primary Efficacy Outcomes (ITT)

Bone Histomorphometry: Baseline and 1 year bone biopsied were obtained in 16 rocaltrol and 15 placebo patients. The table below shows the changes from baseline to 1 year in the primary endpoint parameters. For the majority of parameters, there were statistically significant within group decreases in the rocaltrol, but not the placebo group. Two of the three bone resorption and formation indices decreased by a significant degree in the rocaltrol group compared with the response in the placebo group. The decrease in mineralization lag time in the active-treatment group vs. the placebo-treated patients was of borderline statistical significance (0.06).

Variable	Placebo	Rocaltrol
Osteoblast Index (count/mm^2)		
baseline	5.8	4.9
change from baseline	0.37	-3.83a
Surface Density of Osteoid Seam (mm^2/cm^3)		
baseline	1521	1674
change from baseline	371	-678ab
Volume Density of Osteoid (mm^3/cm^3)		
baseline	12.6	14.1
change from baseline	2.59	-9.40ab
Osteoclast Index (count/mm^2)		
baseline	1.5	1.0
change from baseline	0.32	-0.62ab
Surface Density of Interface (mm^2/cm^3)		
baseline	59.9	43.2
change from baseline	1.98	-18.9b

Variable	Placebo	Rocaltrol
Percent Fibrosis (%)		
baseline	1.57	1.28
change from baseline	1.03	-1.04a
Mineralization Lag Time (days)		
baseline	18.1	23.8
change from baseline	-0.92	-11.6a

a within group difference p<0.05, b between group difference p<0.05

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Serum Biochemical Parameters: Levels of PTH and alk phos were measured at baseline and throughout the study. The table below provides the results for the changes in these two parameters.

Variable	Placebo	Rocaltrol
PTH (uLeq/ml)	n=19	n=24
baseline	35.9	34.4
change from baseline	-3.3	-8.6
Alk Phos (IU/L)	n=25	n=25
baseline	148	126
change from baseline	-5.7	-33.6a

a within group difference p<0.05

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Although PTH levels decreased by a greater amount in the rocaltrol vs. placebo group the difference did not reach statistical significance (p=0.3). Similarly, the decrease in alk phos in the rocaltrol subjects was of borderline statistical significance when compared to the decrease in the placebo subjects (p=0.08). The analysis of the changes in AUC for PTH and alk phos were very similar to the results shown in the above table.

In an analysis of completers, the within group decrease in PTH was statistically significant for the rocaltrol group but not the placebo group. Moreover, the differences between the two groups, -21uLeq/ml, was of borderline significance (0.09). The results for alk phos were similar in the completers and ITT analyses.

When the mean percent changes from baseline were analyzed for PTH and alk phos the results were more favorable from ~~a~~ statistical standpoint.

Secondary Efficacy Outcomes

Serum Biochemical Parameters: There were no significant within or between group changes in the mean or AUC levels of total serum calcium, phosphorus, calcifediol, or Calcitriol. In general, results were similar for the ITT and completers analyses.

Supplemental Efficacy Analyses (ITT)

Three parameters — osteoclast index, percent fibrosis, and volume density of osteoid — improved by a statistically significant amount ($p<0.05$) in the rocaltrol vs. placebo treatment. Specifically, 50% vs. 7%, 63% vs. 20%, and 94% vs. 47% of patients in the rocaltrol vs. placebo groups had values within the normal range after one year of treatment for osteoclast index, percent fibrosis, and volume density of osteoid, respectively. There were no significant differences in the proportion of patients in each group that had normal values in the other bone parameters after one year treatment.

Safety Assessment

Drug Exposure

During months 3-12 there was a fairly even distribution of patients receiving 0.25 through 1.0 ug/day of rocaltrol.

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Adverse Events

Deaths and Symptomatic Adverse Events: Three deaths occurred during or shortly after the study was completed; all patients were randomized to placebo.

There were 3 serious adverse events reported, all in placebo patients: one for cerebral ischemia, and two for angina pectoris.

A total of 3 adverse events reported by 2 of the rocaltrol patients (8%), and a total of 11 adverse events were reported by 9 of the 26 placebo patients.
(35%). One rocaltrol patient developed herpes zoster and the other patient complained of increased sweating and lethargy beginning on day 283 and lasting for 59 days. None of the placebo patients were reported under these COSTART terms.

Abnormal Laboratory Values: Sixty-four percent of rocaltrol and 12% of placebo patients experienced at least one or more episodes of hypercalcemia (>10.8 mg/dl). Moreover, there were 44 vs. 3 instances of hypercalcemia in the rocaltrol vs. placebo-treated patients, respectively. With respect to hyperphosphatemia (>5 mg/dl), 56% and 39% of rocaltrol and placebo patients, respectively had one or more episodes of elevated phosphorus levels.

Many of the cases of hypercalcemia occurred at the 0.75 and 1.0 ug/day doses. In contrast, many of the cases of hyperphosphatemia first occurred at low doses of rocaltrol.

Eight rocaltrol and two placebo patients had at least one episode of an elevated Ca x P product

(>70) during the trial.

Renal Function: The creatinine clearance values for the two groups were similar at baseline (≈ 31 ml/min). At year one, the Ccr had decreased by 4 ml/min in the rocaltrol group and increased by 4 ml/min in the placebo group (p=0.2). Likewise, there was no significant difference between the two groups in the change from baseline to year one in serum creatinine.

There were no significant changes in the levels of the other clinical chemistries, or in any of the vital signs in the rocaltrol or placebo groups (data not shown).

Sponsor's Conclusions

In this study, long-term treatment with low doses of rocaltrol safely and effectively improved the histomorphometric and biochemical indices of hyperparathyroid bone disease in predialysis patients with moderate to severe chronic renal failure. Rocaltrol was not associated with an accelerated rate of renal impairment.

Medical Officer's Conclusions

This study primarily examined the effects of rocaltrol vs. placebo treatment on bone Histomorphometry and serum levels of calcium and PTH in adult patients with predialysis renal failure. At baseline most of the bone Histomorphometry values were near the upper limit of the reference range for both groups. After one year of treatment there were statistically significant improvements in surface density of osteoid seam, volume density of osteoid, osteoclast index, and surface density of interface. Because secondary hPTH is mainly characterized by a marked increase in bone turnover and abnormal formation, changes in activation frequency and the amount of woven osteoid and fibrosis are important to assess. In this study there was no significant difference between groups in the reduction in percent fibrosis. And regrettably, woven osteoid volume and activation frequency were not evaluated.

The mean values for serum PTH were above normal in both groups at the start of the study. After one year of treatment, both groups had a reduction in PTH: -3.3 and -8.9 uLeq/ml, respectively (p=0.3); however, the mean values still remained in the abnormally high range after treatment. These findings indicate that, in the population of hyperparathyroid patients studied, treatment with rocaltrol does not translate into normalization of PTH levels.

Regarding safety, the expected increase in the frequency of hypercalcemic episodes was indeed observed in this study. Presumably, this problem can be managed safely with frequent monitoring of serum calcium levels and adjustment of rocaltrol dose as needed. Years ago it was postulated that treatment of chronic renal patients with vitamin D might precipitate worsening renal function. This one-year study did not find a significant difference between groups in the rate of change in renal function, as assessed by creatinine clearance and serum creatinine values.

In sum, this study indicates that rocaltrol at doses of 0.25-1.0 ug/day favorably affects levels of PTH and alkaline phosphatase. These changes in serum biochemistry presumably would lead to improvements in bone histology. Yet, percent fibrosis did not decrease by a significant amount in the rocaltrol compared with the placebo group, and activation frequency was not measured. The increased risk for hypercalcemia associated with rocaltrol use does not, in general, seem to represent a serious adverse event.

Study #2

1,25(OH)$_2$D$_3$ administration in moderate renal failure: a prospective double-blind trial

Publication: *Kidney Int.* 1989; 35:661-669

Objective: The objective of this study was to evaluate the efficacy (effects on bone histologic and serum biochemistry abnormalities) and safety of Calcitriol (1,25(OH)$_2$D$_3$) in patients with mild to moderate renal failure.

Design: This was a prospective, randomized, double-blind, placebo-controlled study of patients with mild to moderate renal failure (creatinine clearance, 20-60 mL/min). Patients were randomized to receive Calcitriol (initial dose, 0.25 μg/day) or matching placebo and were followed for 12 months.

The initial dose of Calcitriol was 0.25 μg daily. The dose was doubled between 4 and 8 weeks after starting treatment if serum calcium remained below 2.6 mmol/L and urinary calcium was less than 7 mmol/24hr.

If hypercalcemia (serum calcium ≥2.6 mmol/L) or hypercalciuria (urinary calcium ≥7.5 mmol/24hr in males; ≥6.25 mmol/24hr in females) occurred, the trial medication was stopped. When levels returned to normal, treatment was recommended at half the previous dose.

All patients received 400 IU of Vitamin D$_3$ to rule out substrate deficiencies.

Population: *Inclusion Criteria*

- Creatinine clearance =

Exclusion Criteria

- Pregnancy
- Hypercalcemia
- Renal stones
- Poorly controlled hypertension
- Gastrointestinal or liver disease
- Urinary protein output >3g/day
- Psychosis
- Known tetracycline allergy
- Treatment with medications known to affect bone (anticonvulsants, heparin, corticosteroids) or vitamin D metabolites in pharmacological doses within the previous 6 months

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Patients continued their usual antihypertensive medication during the study. A renal dietitian assessed all patients before entry to ensure an oral calcium intake of 800 mg daily; oral calcium supplements were taken when necessary in the morning. Patients were instructed to continue their usual diet throughout the study; no specific instructions as to protein or phosphorus intake were given.

Endpoints: Initial assessment included: history and physical examinations, urinalysis, and biochemical measurements (Ca, P, Cr, ALP, PTH, Calcitriol, 25(OH)D) from fasting serum. Twenty-four hour urinary calcium and phosphorus excretions were measured on two occasions before start of study, and baseline creatinine clearance was determined from the mean of two measurements. An initial bone biopsy and radiographs were obtained. Patients were seen at least every 4 weeks. At each visit symptoms were recorded, blood pressure checked, and fasting blood and urine samples were taken for biochemical tests. Radiographs were repeated at 6 and 12 months, and the iliac crest bone biopsy repeated at 12 months.

All bone biopsy slides were read without knowledge of the biochemical results or therapy.

Assessments	Schedule
History and Physical exams	Entry
Fasting Serum Biochemical Measurements (Ca, P, Cr, ALP, PTH, Calcitriol, 25(OH)D	Entry and Four-Weekly
Urinary Ca and P Excretions	Entry and Four-Weekly
Creatinine Clearance	Entry and Four-Weekly
Radiographs	Entry, 6 and 12 Months
Bone biopsy	Entry and 12 months

Biochemical Assessments

- Serum and urinary Ca, P and Cr and serum ALP concentrations were measured
- PTH was estimated using a The coefficient of variation of this method was <10% and normal values <0.9 μg/mL.
- Serum Calcitriol was extracted and purified by and measured in duplicate by competitive binding assay using a semipurified receptor from calf thymus. Intraassay variation was 5%; interassay variation was 9%.
- Serum 25(OH)D was measured with a competitive binding assay using rat serum. Intraassay variation was 5%; interassay variation was 10%.

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Bone Biopsy, Histology, and Histomorphometry

- Patients received tetracycline hydrochloride (Acromycin) 250 mg 4 times daily for 2 days. Ten days thereafter, they received demeclotetracycline (Declomycin) 150 mg, 4 times daily for 4 days. After a further interval of 4 days, a transiliac crest bone biopsy was performed.
- Bone samples were fixed with ethanol, dehydrated, and embedded in methylmethacrylate for mineralized bone histology. Serial undecalcified sections of 3- and 7-μm thickness were cut. Three-μm sections were stained with the modified Masson-Goldner trichrome stain, which permits discrimination between mineralized and nonmineralized bone. Seven-μm unstained sections were prepared for phase contrast and fluorescent light microscopy. In addition, 7-

μm sections were stained with the aurin tricarboxylic acid stain for detection of aluminum.

Statistical Analyses: Serum Ca, P, ALP, Cr, PTH, Calcitriol, 25(OH)D; creatinine clearance; and, urinary Ca, P and Cr data were analyzed by analysis of covariance with the initial value being used as the covariate.

Analysis was performed using multiple regression analysis (Minitab statistical package). Logarithmic values of Cr were used for analysis of covariance, because serum Cr concentration was not normally distributed.

Comparison between initial and final values of histomorphometric parameters of bone was made using the Wilcoxon Signed Rank Test for non-parametric data. Comparison between experimental and normal histomorphometric data was done using the Kruskall-Wallis analysis of variance.

Results

Patient Disposition

Patient disposition is shown in **Table 1** below.

Table 1. Patient Disposition and Reasons for Premature Withdrawal from Study

	Calcitriol	Placebo
Enrolled	8	8
Evaluated	7 (88%)	6 (75%)
Prematurely Withdrawn	1 (12%)	2 (25%)
Reasons for Premature Withdrawal		
Hypersensitivity to tetracycline	1	0
Myocardial infarction	0	1
No satisfactory bone biopsy at 12 months	0	1

Demographics

Baseline demographic characteristics and diagnoses of study patients are summarized in **Table 2**. Patients (7 male, 6 female) ranged in age from ______________ None of the patients were symptomatic or had radiological evidence of bone disease. Initial serum Calcitriol levels were low in 7/13 (54%) patients and PTH levels were elevated in 7/13 (54%) patients at baseline. Bone histology was abnormal in all patients. One Calcitriol patient with hypertensive nephropathy received thyroxine replacement and was clinically and biochemically euthyroid throughout the study. 1 patient (Calcitriol group) required oral aluminum containing phosphate binders. Four (4) patients (3 Calcitriol, 1 placebo) required oral calcium supplements. There was no evidence that any patient substantially restricted protein intake after starting the study.

Table 2. Baseline Demographic Characteristics and Diagnoses

Parameter	Calcitriol (n=7)	Placebo (n=6)
Male	3 (43%)	4 (67%)
Female	4 (57%)	2 (33%)
Age Range, years		
Diagnoses	______	______
Glomerulonephritis	4	1
Urinephrectomy, glomerulonephritis	1	0
Membranoproliferative/membranous glomerulonephritis	1	1
Uretero-pelvic junction obstruction	0	1
Tubulointerstitial disease	0	1
Cortical necrosis	0	1
Hypertensive nephrosclerosis/nephropathy	1	1

Efficacy Outcomes

Biochemical Parameters: Biochemical parameters in serum and urine before and after the study (12 months) are summarized in **Table 3**.

Serum calcium increased (between 8 and 16 weeks) in the treatment group and remained relatively constant in the control group. This was preceded by or coincided with a rise in urinary calcium excretion, a rise in serum creatinine concentration, and a fall in creatinine clearance in the Calcitriol group. Although serum calcium concentration was higher in the treatment group compared to the control group throughout the study, the difference did not reach statistical significance when analyzed by analysis of covariance. Urinary calcium excretion did not change significantly throughout the study.

Mean serum phosphorus increased in the placebo group and decreased slightly in the Calcitriol group. The difference between study groups was statistically significant ($p<0.001$), and remained statistically significant when the Calcitriol patient who received an oral phosphate binder was excluded from the analysis. Urinary phosphorus was in the normal range in both study groups at baseline and throughout the study.

Serum alkaline phosphatase decreased significantly, albeit within the normal range, during treatment in the Calcitriol group ($p<0.01$) and did not change in the placebo group. At baseline serum alkaline phosphatase levels correlated, respectively, with creatinine clearance ________ $p<0.01$), and parameters of osteoid and osteoblasts (________ After treatment with Calcitriol, alkaline phosphatase levels did not correlate with serum creatinine or creatinine clearance; however, the correlations with parameters of osteoid and osteoblasts were still observed (________ $p\leq0.05$).

At baseline, 7/13 (54%) patients had elevated concentrations of C-terminal PTH. During treatment with Calcitriol, the PTH concentration decreased but the change from baseline was not statistically significant. No change in mean PTH concentration occurred in the placebo group.

Mean Calcitriol concentrations were low before starting the study and had not increased significantly by the end of the study in either group (trough values; blood samples taken immediately before the next morning dose). There was a positive correlation between serum Calcitriol levels at baseline and at the end of the study in the placebo group ($r = 0.98$; $p<0.001$) but not in the treatment group ($r = 0.29$). Mean 25(OH)D concentrations were in the lower normal range at baseline and had increased similarly at the end of the study in both study groups ($p<0.05$).

During the study serum creatinine concentration increased and creatinine clearance decreased in both study groups, but there was no significant difference between treatment groups. Creatinine clearance at baseline was lower in the Calcitriol group than in the placebo group, but the difference was not statistically significant. There was a significant correlation at baseline between: 1) creatinine clearance and both serum phosphorus ($r = -0.70$; $p<0.01$) and PTH ($r = -0.78$; $p<0.001$), and 2) PTH and both creatinine clearance ($r = -0.78$; $p<0.001$) and serum phosphorus ($r = 0.76$; $p<0.001$).

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Table 3. Serum and Urine Biochemical Parameters Before and After 12 Months of Therapy

Parameter	Calcitriol (n=7)	Placebo (n=6)	Normal Values
Serum Calcium (mmol/L)			<2.62
Before the study	2.47 ± 0.06	2.48 ± 0.07	
After the study	2.53 ± 0.05	2.45 ± 0.08	
Urinary Calcium (mmol/24hr)			<7.5 M; <6.25 F
Before the study	1.23 ± 1.00	1.65 ± 1.24	
After the study	2.54 ± 1.32	2.17 ± 2.19	
Serum Phosphorus (mmol/L)			<1.65
Before the study	1.40 ± 0.27	1.12 ± 0.14	
After the study	1.37 ± 0.22	1.24 ± 0.3	
Urinary Phosphorus (mmol/24hr)			13 - 42
Before the study	19.8 ± 6.0	22.2 ± 5.7	
After the study	21.2 ± 7.7	25.3 ± 6.6	
Serum Alkaline Phosphatase (IU/mL)			110
Before the study	73.7 ± 27.1	72.3 ± 22.0	
After the study	56.6 ± 18.3	75.5 ± 18.8	
Serum PTH (µg/mL)			<0.9
Before the study	0.87 ± 0.43	0.67 ± 0.23	
After the study	0.63 ± 0.24	0.60 ± 0.23	
Serum 25(OH)D (ng/mL)			18 - 35
Before the study	23.0 ± 11.5	18.5 ± 16.2	
After the study	34.2 ± 7.8	31.5 ± 10.4	
Serum Calcitriol (pg/mL)			17 - 54
Before the study	16.0 ± 2.5	16.0 ± 9.5	
After the study	17.6 ± 3.0	22.2 ± 14.6	
Serum Creatinine (mmol/L)			0.06 - 0.12
Before the study	0.240 ± 0.071	0.220 ± 0.103	
After the study	0.286 ± 0.108	0.242 ± 0.166	
Creatinine Clearance (mL/min)			120
Before the study	34.7 ± 14	44.7 ± 13.1	
After the study	31.4 ± 16.3	40.2 ± 14.3	

Values are means ± SD.
Statistical analysis using multiple regression analysis.
PTH = parathyroid hormone (C-terminal); M = male; F = female.

Bone Histology: Histomorphometric parameters of bone structure are summarized in **Table 4**. In all patients, cancellous bone mass, mean trabecular diameter, mean trabecular plate density and mean wall thickness were within the normal range at the beginning of the study and after 12 months of therapy. No significant changes were observed in these parameters. None of the patients exhibited stainable aluminum at the bone osteoid interface or within bone at the beginning or the end of the study.

Table 4. Histomorphometric Parameters of Bone Structure Before and After the Study

Parameter	Calcitriol (n=7)	Placebo (n=6)	Normal Values*
Cancellous Bone Mass (%)			18.3 ± 0.7
Before the study	18.5 ± 0.9	18.6 ± 1.9	
After the study	17.1 ± 0.6	21.8 ± 2.0	
Mean Trabecular Diameter (μm)			254 ± 4
Before the study	262 ± 10	253 ± 9	
After the study	270 ± 12	280 ± 3	
Mean Trabecular Plate Density (#/mm)			1.83 ± 0.05
Before the study	1.83 ± 0.13	1.86 ± 0.15	
After the study	1.64 ± 0.09	1.74 ± 0.14	
Mean Wall Thickness (μm)			55.5 ± 1.2
Before the study	50.4 ± 1.7	55.9 ± 2.7	
After the study	51.2 ± 2.2	60.7 ± 4.6	
Stainable Aluminum at the Bone-Osteoid Interface (%)	0	0	0

*Age and sex-matched normal controls.
Values are means ± SD.

Parameters of bone formation and resorption are presented in **Table 5**. Volume of lamellar osteoid was above the normal range at baseline in 2/7 (29%) patients who received Calcitriol and in 2/6 (33%) patients who received placebo. Abnormal bone formation as evidenced by the presence of woven osteoid was found at baseline in all biopsies. Mean thickness of lamellar osteoid seams was not increased. The number of osteoblasts per unit of trabecular boundary length and the bone-osteoblast interface were elevated at baseline in 8 (62%) and 9 (69%) patients, respectively; therefore, the mean values for both parameters were significantly higher in patients than age- and sex-matched controls. Also, the number of osteoclasts per unit trabecular boundary length and the bone-osteoclast interface were elevated in 9 (69%) and 11 (85%) patients, respectively, resulting in a significant increase in mean values of these parameters at baseline in both placebo and Calcitriol patients. Four (4, 31%) patients had trabecular fibrosis at baseline; they were the patients with the lowest creatinine clearances.

Administration of Calcitriol for 12 months resulted in a significant decrease in lamellar osteoid volume and thickness. Woven osteoid volume and surface were significantly reduced and parameters of bone cells showed a decrease in the number of osteoblasts and osteoclasts (osteoblastic index and osteoclastic index). At the end of the study, the number of osteoblasts and the bone-osteoblast interface were normal or below normal in all Calcitriol patients. The number of osteoclasts and bone-osteoclast interface were still above normal in 3 (43%) patients. Five (5) of 7 (71%) patients still exhibited some woven osteoid.

Administration of placebo for 12 months did not change lamellar osteoid volume, the number of osteoblasts or osteoclasts, bone-osteoblast interface or bone-osteoclast interface. All parameters remained above normal. Volume and surface of woven osteoid had increased at the end of the study period.

Table 5. Histomorphometric Parameters of Bone Formation and Resorption Before and After the Study

Parameter	Calcitriol (n=7)	Placebo (n=6)	Normal Values[d]
Lamellar Osteoid Volume (mm^3/cm^3)			4.05 ± 0.09
Before the study	4.66 ± 1.07	6.27 ± 2.51	
After the study	2.21 ± 0.67[b,c]	6.49 ± 1.66	
Lamellar Osteoid Surface (%)			15.4 ± 0.58
Before the study	15.6 ± 2.59	19.6 ± 7.34	
After the study	11.3 ± 3.10	19.3 ± 4.72	
Mean Osteoid Seam Thickness (μm)			9.51 ± 0.18
Before the study	9.47 ± 0.85	9.76 ± 0.90	
After the study	6.98 ± 0.44[b,c]	10.70 ± 1.24	
Woven Osteoid Volume (mm^3/cm^3)			0
Before the study	1.95 ± 0.70[a,b]	0.58 ± 0.16[a]	
After the study	0.76 ± 0.60[a,c]	2.27 ± 0.65[a,c]	
Woven Osteoid Surface (%)			0
Before the study	4.20 ± 1.24[a]	1.56 ± 0.39[a]	
After the study	2.06 ± 1.27[a,c]	5.04 ± 1.34[a,c]	
Bone-Osteoblast Interface (%)			2.70 ± 0.20
Before the study	6.18 ± 0.82[a]	7.18 ± 2.45[a]	
After the study	1.81 ± 0.28[b,c]	8.28 ± 1.84[a]	
Osteoblastic Index			174 ± 11
(#/100 mm boundary length)	429 ± 58[a]	444 ± 144[a]	
Before the study	127 ± 17[b,c]	492 ± 118[a]	
After the study			
Bone-Osteoclast Interface (%)			0.73 ± 0.05
Before the study	1.16 ± 0.16[a]	1.64 ± 0.35	
After the study	0.72 ± 0.26	1.47 ± 0.35	
Osteoclastic Index			17 ± 0.91
(#/100 mm boundary length)	42 ± 7.3[a]	54 ± 13[a]	
Before the study	24 ± 7.2	43 ± 10.6[a]	
After the study			

[a]Difference between experimental group and normal controls ($p<0.05$)
[b]Difference between Calcitriol and placebo ($p<0.05$)
[c]Difference between baseline and 12 months of Calcitriol or placebo within the same group ($p<0.05$)
[d]Age and sex-matched normal controls.
Values are means ± SD.

As shown in **Table 6**, mineral apposition rate was not significantly different from normal controls at baseline or after therapy in all patients. Fraction of trabecular surfaces exhibiting double or single tetracycline labels was not different from normals at baseline. There was a trend toward a decrease in labeling after 12 months of treatment with Calcitriol, and a trend toward an increase in labeling in the placebo group, but the change was not statistically significant in either group.

Table 6. Dynamic Histomorphometric Parameters Before and After the Study

Parameter	Calcitriol (n=7)	Placebo (n=6)	Normal Values*
Mineralization Rate (μm/day)			0.51 ± 0.02
Before the study	0.59 ± 0.05	0.47 ± 0.07	
After the study	0.48 ± 0.08	0.64 ± 0.07	
Doubly labeled trabecular surfaces (%)			3.76 ± 0.68
Before the study	3.01 ± 0.81	2.6 ± 1.07	
After the study	1.72 ± 0.41	5.8 ± 1.26	
Mineralization lag time (days)			18.9 ± 0.78
Before the study	17.7 ± 3.70	21.8 ± 2.18	
After the study	16.4 ± 2.43	17.5 ± 2.49	
Osteon Remodeling time (days)			169 ± 2.2
Before the study	148 ± 34	221 ± 45	
After the study	187 ± 42	158 ± 31	

*Age and sex-matched normal controls.
Values are means ± SD.

Radiographs: The x-rays taken at baseline and 6-monthly intervals were not different and did not show definitive pathologic findings.

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Safety Assessment

No patient reported any clinical adverse events attributable to treatment during the study. One patient in the Calcitriol group withdrew from the study because of hypersensitivity to tetracycline (see **Table 1**). There was no significant deterioration of renal function attributable to Calcitriol during treatment, as evidenced by similar changes in serum creatinine concentration and creatinine clearance for both study groups (see **Table 3**).

Compliance, as judged by repeated direct questioning of patients, was excellent throughout the study. In 1 patient, serum calcium reached the upper limit of normal at the initial starting dose (0.25 μg daily) and no increase in dosage was made. Two patients tolerated Calcitriol at a dose of 0.5 μg daily. In 4 patients, hypercalcemia occurred when the dose of Calcitriol was increased to 0.5 μg daily. Hypercalcemia resolved within 1 week of stopping treatment, and all patients subsequently tolerated 0.25 μg daily with no further hypercalcemia. There was 1 episode of hypercalcemia in the placebo group. Extent of exposure and incidence of hypercalcemia is summarized in **Table 7**.

Table 7. Extent of Exposure and Incidence of Hypercalcemia

Calcitriol Maximum Dose	Calcitriol (n=7)	Placebo (n=6)
0.25 µg daily ___ tolerated*	1	
0.50 µg daily ___ tolerated	2	
0.50 µg daily ___ reversible hypercalcemia**	4	
Incidence of Hypercalcemia	4 (57%)	1 (17%)

*Patient's serum calcium reached the upper limit of normal at the initial starting dose (0.25 µg daily) and no increase in dosage was made.
**Hypercalcemia resolved within 1 week, and all patients subsequently tolerated 0.25 µg daily with no further hypercalcemia.

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Sponsor's Conclusions

In this study, patients with mild to moderate renal failure (creatinine clearance ______ mL/min) showed improvement in bone histology when treated with Calcitriol (0.25 or 0.5 µg/day for 12 months), whereas patients given placebo showed no change or deterioration. No deterioration of renal function attributable to Calcitriol occurred and episodes of hypercalcemia were readily reversible when treatment was stopped.

Although the patients in this study were asymptomatic with normal serum alkaline phosphatase concentrations and normal bone x-rays, histologic data at baseline showed an increased number of bone resorbing and forming cells in all patients, presence of woven osteoid in all patients, and fibrosis in some patients. Patients treated with Calcitriol for 12 months in this study showed histomorphometric improvement in bone turnover, as evidenced by significant decreases in lamellar osteoid volume and thickness, reduced woven osteoid volume and surface, and decreases in the number of osteoblasts and osteoclasts. In the placebo group, there were either no changes in these parameters or increases were observed. Calcitriol treatment was associated with a significant fall in serum phosphorus and alkaline phosphatase concentration, which correlated with changes in osteoid and osteoblast parameters.

Failure to find a statistically significant decrease in serum PTH levels after Calcitriol therapy might be related to the assay used. The ______ used in this study measures ______ fragments (as well as intact ______ which may experience a delay in clearance due to renal impairment.

Serum Calcitriol concentrations were low or in the lower end of normal at the start of the study and 24-hour trough serum Calcitriol concentrations did not increase significantly on treatment. This is not unexpected as Levine et al showed that in normal humans serum levels of Calcitriol are increased 4 hours, but not 24 hours, after oral administration of 0.5 µg Calcitriol.(Levine, 1985)

Serum calcium levels were higher in the Calcitriol group than in the placebo group. In 4 patients, hypercalcemia occurred when the dose of Calcitriol was increased to 0.5 µg daily. Hypercalcemia resolved ~~with~~in 1 week of stopping treatment and all patients subsequently tolerated 0.25 µg daily with no further episodes. There was no deterioration of renal function related to treatment with Calcitriol.

Investigator's Conclusions

We recommend that long-term 1,25(OH)2D3 administration in patients such as those we described should be carried out only if frequent and meticulous follow-up can be ensured, and lower doses than those used in end-stage renal failure are employed.

Medical Officer's Conclusions

The findings from this study are not conclusive, but suggest that rocaltrol is beneficial in the management of hyperparathyroidism and the resultant metabolic bone disease associated with predialysis chronic renal failure. Patients need close monitoring of serum Ca, and episodes of hypercalcemia must be followed by drug dosage adjustment or discontinuation.

Study #3

Calcitriol and calcium carbonate therapy in early chronic renal failure

Publication *Nephrol Dial Transplant* 1994; 9:1595-1599

Objective: The objective of this study was to evaluate the effects of combined therapy, consisting of low-dose Calcitriol (0.25 μg/day) and calcium carbonate (1 g/day), on mineral and bone metabolism in early chronic renal failure.

Design: This was an 30-month, open-label study of patients in the early phases of chronic renal failure (ECRF). The study consisted of a 6-month observation period, followed by a 24-month treatment period with low-dose Calcitriol (0.25 μg/day) supplemented with calcium carbonate (1 g/day). 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.

Population: • Seventeen patients (9 women and 8 men) ages ______ years participated in this study. Some of the inclusion and exclusion criteria were as follows:

- Moderate degree chronic renal failure in early phase
- No concurrent disease
- No vitamin D or metabolites, or any drug affecting calcium metabolism or inducing liver enzymes
- None of the patients had a history of previous fractures or suffered from fractures during the study

Endpoints: The following parameters were evaluated, with bone parameters representing the primary endpoints:

- Plasma and urinary calcium (Ca; mg/dL), phosphate (PO_4; mg/dL), creatinine (Cr; mg/dL)
- Plasma alkaline phosphatase (ALP; U/L), parathormone (PTH; pg/mL), 25(OH)D (ng/mL), $1,25(OH)_2D$ (pg/mL), osteocalcin (BGP; ng/mL) and urinary hydroxyproline (OHPr/Cr; mg/mg)
- Bone mass at forearm and spine: bone mineral density (BMD; mg/cm^2)
- Bone biopsy: mean lacunar surface (MLS; μ^2), bone trabecular volume (BTV; %), osteoblastic surface (OB; %), osteoclastic surface (OC; %), osteoid volume (OV; %), osteoid index (OI; %), mineral apposition rate (MAR; μ/day), double-labeled osteoid seams (LAB-OS-d; %), mineralization lag time (MIN LAG t; days)

Patients were monitored during a 6-month observation period followed by a 24-month treatment period. Blood samples were taken in the morning after a 12-hour fast; urine specimens were collected over 24 hours.

Assessments	Schedule
Plasma and urine calcium, phosphate, creatinine	Monthly
Plasma alkaline phosphatase, PTH, 25(OH)D, 1,25$(OH)_2$D, osteocalcin and urinary hydroxyproline	Every 6 months
Bone mass at forearm and spine	Every 12 months
Bone biopsy	At 6 and 30 months

The procedures for measuring bone mass and obtaining bone biopsies are as follows:

Bone Mass

- Forearm mineral density was evaluated by __________ using a __________ (^{125}I source) at the distal third of the dominant forearm: variation coefficient of 1.5% *in vivo*. Forearm bone mass was expressed as the average of radius and ulna BMD in mg/cm^2.
- Lumbar spine bone mineral density was evaluated by __________ using a __________ densitometer: variation coefficient of 3% *in vivo*. Lumbar bone mass was expressed as the sum of the average area densities (AAD, mg/cm^2) of three vertebrae (L_2-L_4), and calculated as the sum of the ratios of the bone mineral content of each vertebra to its anteroposterior projection area.

Bone Biopsy

- Transiliac bone biopsy was performed with a __________ drill.
- MLS (the mean surface of 500 osteocytic lacunae) and BTV (the percentage of cancellous bone space occupied by bone) were measured by an automatic analyzer on microradiographs of a non-decalcified section.
- OB (the percentage of total trabecular surface covered by osteoblasts) and OC (the percentage of total trabecular surface covered by resorption lacunae filled with osteoclasts) surfaces and OV (the percentage of trabecular surface covered by osteoid) were evaluated from stained sections.
- OI was calculated by dividing OB by OV.
- Aluminum deposition in bone was evaluated by a colorimetric method __________
- Double tetracycline labeling was performed in order to evaluate the dynamic parameters of bone remodeling. The following parameters were considered: MAR (mean distance/labeling interval in μ/day), percent of LAB-OS-d (mean double label length/mean osteoid length) and MIN LAG t (mean osteoid seams width/apposition rate per day).

Statistical Analyses: Data are presented as mean ± SEM, with the exception of PTH where the median and the range were used due to the non-Gaussian data distribution. Student's t test for paired data, Wilcoxon test (for the PTH data), and ANOVA were used to analyze the results. Linear regression analysis was also performed.

Results

Patient Disposition

The published paper does not indicate how the 17 patients were chosen for study. This reviewer assumes from the report, although it is not explicitly stated, that all 17 patients completed the study.

Demographics

Seventeen (17) patients with moderate chronic renal failure in early phase were enrolled in this study. Basal histomorphometric measurements showed some degree of pathological bone alterations in all of the patients, even in cases of very mild renal failure. The most frequent condition was mixed secondary hyperparathyroidism plus osteomalacia (9 patients). Five (5) and 3 patients, respectively, exhibited hyperparathyroidism and osteomalacia alone. Aluminum deposition was not present in any study patient.

Demographic and baseline characteristics of study patients are summarized in **Table 1**. All patients were on a moderately restricted diet of phosphate (600-800 mg/day) and protein (0.8 g/kg/day). Five patients were regularly receiving calcium carbonate at study entry (mean daily dose: 1.0 ± 0.2 g). Diet, living habits, and drug prescriptions remained unchanged during the study.

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Table 1. Demographic and Baseline Characteristics

Parameter	Study Patients (n=17)
Male	8 (47%)
Female	9 (53%)
Age, years	
Mean ± SEM	47.5 ± 3
Range	28 - 55
Baseline Histomorphometric Evaluation, n (%)	
Secondary hyperparathyroidism	5 (29%)
Osteomalacia	3 (18%)
Mixed secondary hyperparathyroidism plus osteomalacia	9 (53%)
Duration of CRF, months	
Mean ± SEM	29.6 ± 9.8
Range	13 - 48
Plasma Creatinine, mg/dL	
Mean ± SEM	2.3 ± 0.9
Range	
Creatinine Clearance, mL/min	
Mean ± SEM	48.2 ± 12.3
Range	
Plasma albumin, g/dL	
Mean ± SEM	4.6 ± 0.7
Range	
BMD, mg/cm² (mean ± SEM)	
Forearm	638 ± 32
Lumbar spine	958 ± 48

Abbreviations: CRF = chronic renal failure; BMD = bone mineral density.

Efficacy Outcomes

Histomorphometric Parameters

During treatment with Calcitriol and $CaCO_3$, there was a progressive slowing of the rate of appendicular bone loss; i.e., the percent change in forearm BMD after 12 and 24 months of therapy was approximately -1.2% *vs.* -0.25%, respectively ($p<0.01$). Vertebral BMD remained stable during Calcitriol treatment (i.e., percent change in lumbar spine BMD was essentially the same after 12 and 24 months of treatment at about 0.5%).

As shown in **Table 2**, all histomorphometric parameters (mean values) were outside the normal range when measured after the 6-month observation period. After 24 months of Calcitriol therapy there was improvement in all measurements, although normal values were not reached for all parameters. There was a significant reduction in osteoblastic and osteoclastic activity ($p<0.01$), a decrease in non-mineralized bone, and an improvement of dynamic parameters of bone remodeling following treatment.

Table 2. Histomorphometric Results

Parameter	Normal Range	Months of Study	
		6	30
OB (%)	3 ± 1.2	6.9 ± 1.2	4.2 ± 0.9[a]
OC (%)	4 ± 1	19.3 ± 4.2	11.5 ± 3.1[a]
BTV (%)	25 ± 5	28.4 ± 7.1	26.3 ± 5.9
MLS (μ^2)	20 ± 2	26.3 ± 5.8	20.1 ± 4.8[b]
OI (%)	8 ± 1	20.2 ± 6.3	14.1 ± 5.2[b]
MAR (μ/day)	0.51 ± 0.03	0.79 ± 0.09	0.59 ± 0.1
LAB-OS-d (%)	50.8 ± 5	25.2 ± 9.3	40.1 ± 13[b]
MLT (days)	19 ± 1.5	29 ± 13	19 ± 6[b]

Abbreviations: OB = osteoblastic surface; OC = osteoclastic surface; BTV = bone trabecular volume; MLS = mean lacunar surface; OI = osteoid index; MAR = mineral apposition rate; LAB-OS-d = double-labeled osteoid seams; MLT = mineralization lag time.
6 months = start of Calcitriol treatment; 30 months = after 2 years of treatment.
[a]$p<0.01$; [b]$p<0.05$.

Biochemical Parameters

During the 6-month observation period (no treatment) plasma calcium progressively decreased, while alkaline phosphatase and urinary hydroxyproline increased. During Calcitriol treatment, plasma calcium significantly increased, while calcium excretion was unchanged; plasma and urinary phosphate levels were unchanged; and plasma alkaline phosphatase, plasma osteocalcin, and urinary hydroxyproline decreased significantly **(Table 3)**.

During the observation period, PTH increased. During Calcitriol treatment, plasma PTH levels progressively decreased, reaching significance after two years; plasma 25(OH)D levels were unchanged over the study period, while serum $1,25(OH)_2D$ increased as expected.

Table 3. Biochemical Evaluation

Parameter*	Months of Study			
	0	6	18	30
Plasma Ca (mg/dL)	8.9 ± 0.2	8.5 ± 0.3	9.3 ± 0.2[a]	9.9 ± 0.2[b]
Plasma PO_4 (mg/dL)	4.2 ± 0.3	4.1 ± 0.3	4.2 ± 0.3	4.1 ± 0.2
Plasma ALP (U/L)	129 ± 23	168 ± 29	119 ± 25[a]	88 ± 21[b]
Plasma BGP (ng/mL)	12.6 ± 2.1	15.3 ± 3	9.2 ±1.9[c]	6.1 ± 1.4[b]
Urine Ca/Cr (mg/mg)	0.18 ± 0.05	0.16 ± 0.05	0.22 ± 0.06	0.21 ± 0.05
$TmPO_4$ (mg/min)	2.9 ± 0.9	2.9 ± 0.9	3.0 ± 0.8	2.8 ± 0.9
Urine OHPr/Cr (mg/mg)	49 ± 14	61 ± 14	41 ± 13[c]	32 ± 9.6[b]
PTH (pg/mL)	109	142	92.4	81.6
Median (range)	(35 - 158)	(39 - 220)	(32 - 121)	(30 - 99)[c]
25(OH)D (ng/mL)	38.6 ± 7.2	38.9 ± 7.8	37.8 ± 8.3	39.9 ± 9.2
$1,25(OH)_2D$ (pg/mL)	21.8 ± 4	20.1 ± 4.3	25.8 ± 4	29.5 ± 4.7[d]

Abbreviations: Ca = calcium; PO_4 = phosphate; ALP = alkaline phosphate; BGP = osteocalcin; Cr = creatinine; $TmPO_4$ = maximum tubular excretory capacity for phosphate ; *OHPr = hydroxyproline; PTH = parathormone.*

0 months = start of observation period (no treatment); 6 months = start of Calcitriol treatment; 18 months = after 1 year of treatment; 30 months = after 2 years of treatment.

[a]$p<0.05$ *vs.* 0 and 6 months; [b]$p<0.01$ *vs.* 0 and 6 months; [c]$p<0.05$ *vs.* 6 months; [d]$p<0.02$ *vs.* 6 months.

*All parameters are presented as mean ± SEM, except PTH which, as indicated, is presented as median and (range).

Safety Outcomes

Episodes of hypercalcemia (>10.8 mg/dL), hyperphosphatemia (>5 mg/dL), and increased urinary excretion of these ions (Ca, >400 mg/day, PO_4, >1500 mg/day) were relatively infrequent in all patients throughout the study. During the 6-month observation period (no treatment), there were 38/476 (7.9%) instances of pathologic increase in calcemia, phosphatemia, calciuria and phosphaturia. During Calcitriol treatment, there were 163/1700 (9.6%) instances of pathologic increase in the same parameters.

Renal function indices were stable during the study period. Although the creatinine level increased, the CRF progression rate, assessed from the slope of 1/plasma creatinine (1/Cr) over time, did not differ during Calcitriol treatment from the theoretically calculated slope based on previous years experience.

Sponsor's Conclusions

The results of this study suggest that combined low-dose Calcitriol plus calcium carbonate therapy is well-tolerated and improves biochemical and skeletal markers of bone deterioration in patients in the early phases of chronic renal failure. A decrease in plasma alkaline phosphatase, plasma osteocalcin, plasma PTH, and urinary hydroxyproline was observed which correlated