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Review Article

A Review of Extended-Release Calcifediol in Patients with Chronic Kidney Disease Stage 3 and 4 and in Healthy Patients

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Abstract

Purpose: The objective of this review is to evaluate the role of calcifediol among the currently available vitamin D products in treating secondary hyperparathyroidism in chronic kidney disease. Calcifediol studies in healthy patients will also be reviewed.

Methods: A literature search was performed in the PubMed database using the search terms calcifediol, 25-hydroxyvitamin D3, and 25D3. Limits were set to include clinical trials phases I-IV, controlled clinical trials, randomized controlled trials, or comparative studies in human subjects in the English language within the past 5 years. Studies were included if calcifediol was compared to cholecalciferol in terms of their ability to increase vitamin D serum concentrations.

Findings: Four studies met the inclusion criteria above and were included in this review. Calcifediol has been shown to replete vitamin D stores more rapidly than cholecalciferol. Calcifediol has also been found to decrease serum concentrations of intact parathyroid hormones in patients with secondary hyperparathyroidism in chronic kidney disease.

Implications: Calcifediol is a new vitamin D receptor activator that can be used in chronic kidney disease patients not on dialysis for rapid correction of serum vitamin D concentrations. Further studies are necessary to examine its effectiveness and role in therapy compared to other agents in this class.

Introduction

Vitamin D plays an important role in the management of Secondary Hyperparathyroidism (SHPT) for Chronic Kidney Disease Patients with Mineral and Bone Disorder (CKD-MBD). The National Kidney Foundation's (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) and Kidney Disease Improving Global Outcomes (KDIGO) have published clinical practice guidelines and commentaries in 2010 and 2017, respectively, that provide some guidance on how vitamin D and vitamin D receptor activators (VDRAs) should be used in practice [1-3]. There are currently two vitamin D products (cholecalciferol and ergocalciferol) and three VDRAs (calcitriol, paricalcitol, and doxercalciferol) used in clinical practice in the United States for treating SHPT in CKD patients. Another vitamin D product, calcifediol (Rayaldee), has recently appeared on the market again, as it was approved and marketed from 1980 to 2001. The clear reason for the product withdraw is unknown; however, it was deemed that the product was not withdrawn for any safety reasons.

In clinical practice, 25(OH)D3 is measured to determine if an individual patient has vitamin D deficiency or insufficiency. The reference range for vitamin D (i.e., 25(OH)D3) is typically > 30 ng/mL, although this is still debated with most studies defining vitamin D deficiency as serum concentrations < 20 ng/mL and insufficiency as >20 ng/mL but less than 30 ng/mL. (KDIGO 2009). Further activation of 25(OH)D3 occurs in the kidney when 1-alpha-hydroxylase converts 25(OH) D3 into the biologically active 1-25 dihydroxyvitamin D or 1,25(OH)2D3 which is also known as calcitriol, a VDRA. Paricalcitol and doxercalciferol are also VDRAs as previously mentioned but they are sometimes called vitamin D analogues because they are synthetic VDRAs, unlike the naturally occurring calcitriol. Figure 1 illustrates how these vitamin D components are metabolized by the body. In patients who develop end stage renal disease and require renal replacement therapy, the kidneys have deteriorated to the point where they are no longer capable of converting 25(OH)D3 into the active 1,25(OH)2D3 in the kidneys. This has a particularly negative effect on the parathyroid gland that relies on activated vitamin D to modulate the release of parathyroid hormone. With insufficient activated vitamin D available, more parathyroid hormone is produced which results in calcium mobilization from the bones into the blood. Over time, this can lead to hypercalcemia, soft tissue calcification, and bone fractures. Generally, current therapies for treating SHPT rely mostly on the VDRAs (calcitriol, paricalcitol, and doxercalciferol) to manage end stage renal disease patients, and cholecalciferol and ergocalciferol to manage CKD patients who still have some kidney function present (CKD 3a-CKD 4). Calcifediol, the newest addition to the treatment

armamentarium, still requires activation by the kidneys in order to affect the vitamin D receptors on the parathyroid gland and so it would seem likely that it would be comparable to cholecalciferol and ergocalciferol in its efficacy and safety. The following review evaluates the current literature and examines calcifediol's effects on vitamin D serum concentrations and Parathyroid Hormone (PTH) suppression as well as its comparative efficacy.

Materials and Methods

A literature searched was performed using the search engine PubMed with the search terms "calcifediol", "25-hydroxyvitamin D3" and "25D3". The search was limited to studies in human subjects in clinical trials phases I-IV, controlled clinical trials, randomized controlled trials, or comparative studies and published in the English language within the past 5 years. Studies that were included in this review were specifically looking to compare calcifediol to cholecalciferol in terms of its effects on increasing vitamin D serum concentrations. Results were further narrowed to include studies that specifically measured the efficacy and safety of calcifediol compared to placebo or cholecalciferol.

Results

Using the search methods described above, four studies were selected to include in this review.

Pharmacokinetics (PK) of Cholecalciferol and Calcifediol in Healthy Patients.

The first is a prospective, randomized, double-blind, seven-arm, parallel group study investigated the long-term pharmacokinetics after supplementation with vitamin D3 or calcifediol [4]. The main objective of the study was to compare the plasma pharmacokinetics of 25(OH)D3 during daily and weekly intakes of vitamin D and calcifediol, as well as the pharmacokinetics of a single oral bolus of calcifediol, cholecalciferol, or the combination over 15 weeks. The study population included a total of 25 non-smoking, Caucasian, postmenopausal women (no vaginal bleeding for at least a year) between ages 50 to 70 with a body mass index between 18 and 29 kg/m^2 in overall good health. Baseline characteristics were similar between the treatment groups and had no statistically significant differences.

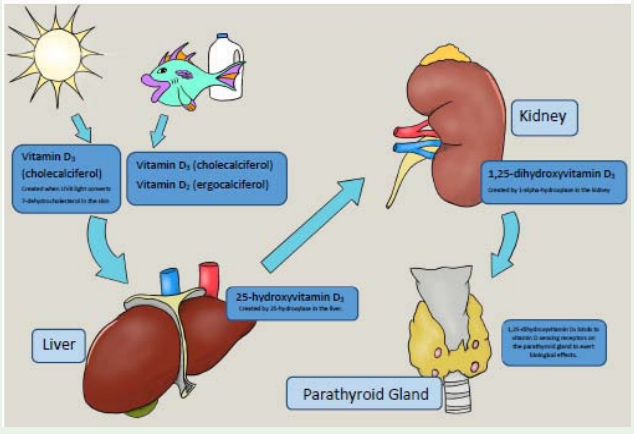

Figure 1: Vitamin D Synthesis Diagram.

Study participants received daily administration of cholecalciferol 20 mcg or calcifediol 20 mcg; weekly administration of cholecalciferol 140 mcg or calcifediol 140 mcg; or a single oral bolus of calcifediol, cholecalciferol or their combination. Study subjects receiving calcifediol achieved a higher AUC after the first dose and achieved an increase in serum 25(OH)D3 faster than in the cholecalciferol treatment group. The calcifediol treatment group had higher AUC and Cmax values four months after the last dose. In study participants that received weekly administration of either cholecalciferol 140 mcg or calcifediol 140 mcg, the AUC was 67% larger after the first weekly dose of calcifediol. After the last weekly dose, the AUC was 2.8-fold higher with calcifediol intake compared to cholecalciferol. Overall, the plasma concentration of 25(OH)D3 was higher with calcifediol treatment compared to cholecalciferol treatment. Between the daily and weekly dose, there were no statistically significant differences between AUC and maximum concentrations. For those that received a single oral bolus of calcifediol, cholecalciferol, or their combination; a single dose of calcifediol led to higher exposures and maximum plasma concentrations compared to cholecalciferol. Calcifediol achieved AUC and Cmax values that were not significantly higher than the values achieved with both agents combined. All subjects achieved >20 ng/mL of plasma 25(OH)D3 by the end of the treatment. However, the daily or weekly cholecalciferol treatment groups took an average of 20.6 days to achieve serum concentrations above 20 ng/mL, while daily or weekly calcifediol treatment groups took an average of 3 days to achieve serum concentrations above 20 ng/mL. In comparison, not all participants in the cholecalciferol group achieved above 30 ng/mL of plasma 25(OH)D3 by the end of the treatment, while all participants in the calcifediol group achieved serum concentrations above 30 ng/mL. Daily or weekly calcifediol achieved >30 ng/ml of plasma 25(OH)D3 in about 16.8 days, while daily or weekly cholecalciferol took an average of 68.4 days to reach target serum concentrations of 25(OH)D3. No adverse events were reported during this study.

Modified-Release (MR) Calcifediol versus Placebo in Chronic Kidney Disease Patients

A randomized, double-blind, placebo-controlled trial evaluated the efficacy and safety of a MR formulation of calcifediol in controlling secondary hyperparathyroidism in chronic kidney disease [5]. The main objective of the study was to evaluate the increase in serum concentrations of 25(OH)D3 to ≥ 30 ng/mL and the decrease in elevated plasma intact PTH in predialysis CKD patients. The 78 subjects enrolled in this study were divided up into two cohorts. Between the two cohorts, there were 47 subjects in treatment groups and 31 subjects in placebo groups. The study population included more females (55%) that were mostly white with a mean age of 63 years. Eligible subjects had to have CKD (not requiring regular dialysis) with an eGFR between 25 and 70 mL/min/1.73 m^2. Other inclusion criteria included total serum concentrations of 25(OH)D3 between 10 and 29 ng/mL, plasma intact PTH (iPTH) above 70 pg/mL, serum calcium between 8.4 and 10 mg/dL, and serum phosphorus between 2 and 5 mg/dL. Baseline characteristics were overall similar between the treatment groups and placebo groups.

Patients were randomized to six weeks of daily treatment with either MR Calcifediol or placebo, followed by six weeks of post-treatment monitoring. Subjects that were receiving supplementation with ergocalciferol or cholecalciferol had to remain at a dose below

threshold as to not skew results. Threshold was defined as doses below 1,600 IU/day of ergocalciferol or cholecalciferol. Patients on bone metabolism therapy had to be discontinued, while patients on bisphosphonates were allowed to continue if they met certain criteria. Bone metabolism therapy refers to drugs that can cause or minimize bone loss. For example, heparin, warfarin, cyclosporine, glucocorticoids, cancer drugs, medroxyprogesterone acetate and thyroid hormones can cause bone loss while thiazide diuretics can minimize bone loss. If subjects were on stable doses of bisphosphonates for more than 6 months prior to enrollment, they had to maintain the dose for the study duration. With a total of 51 subjects in Cohort 1, 17 subjects were assigned to receive calcifediol 60 mcg; 17 subjects were assigned to receive calcifediol 90 mcg; and 17 subjects were assigned to receive placebo. Cohort 2 had a total of 27 subjects with 13 subjects assigned to receive calcifediol 30 mcg and 14 subjects receiving placebo.

At the end of the treatment, 90% of subjects in the calcifediol treatment arm achieved serum 25(OH)D3 concentrations ≥ 30 ng/mL, compared to only 3% of subjects in the placebo group. The mean serum 25(OH)D3 concentration increased statistically significantly ($p<0.0001$) from baseline and were 37.3 ± 6.95, 66.9 ± 17.72, and 84.8 ± 20.49 for the 30, 60, and 90 mcg calcifediol treatment groups, respectively. Based on per protocol subjects, the mean serum 25(OH)D3 of the treatment groups was 64.4 ± 24.9 ($p<0.0001$), compared to placebo which was 18.5 ± 5.35. The mean iPTH also decreased statistically significantly ($p<0.001$) from baseline and were 123.6 ± 57.39, 78.8 ± 31.33, and 93.4 ± 41.10 for the 30, 60 and 90 mcg calcifediol treatment groups, respectively. Based on per protocol subjects, the average iPTH for the treatment groups was 96.5 ± 46.03 ($p<0.0001$), compared to 165.7 ± 82.54 in the placebo group. The gradual increases in serum 25(OH)D3 were proportional to the doses of calcifediol given throughout the six weeks. The average serum calcium concentration rose from 9.3 ± 0.37 to 9.4 ± 0.35 in the MR calcifediol treatment group, which deemed to be statistically significant ($p<0.05$). No significant changes were evident during the 6-week treatment period for eGFR and serum FGF23. Overall, the drug was well tolerated and most patients (68.1%) experienced at least one drug related Treatment-Emergent Adverse Event (TEAE). The TEAEs were mostly GI-related and mild adverse events that did not require any further follow up. No specific adverse event was thought to be statistically significant compared to others, but the most common adverse events were gastrointestinal related. Only two patients experienced adverse events requiring study termination: one in the treatment group and the other in the placebo group.

Effects of Cholecalciferol and Calcifediol on Total *vs* Free 25D in Healthy Patients

A 16-week, randomized, controlled trial investigated the effects of cholecalciferol and calcifediol on total and free 25D as well as the change in iPTH [6]. Of the 35 subjects to be randomly assigned, 16 were assigned to cholecalciferol and 19 were assigned to calcifediol. Within each treatment group, study subjects were further divided into blocks of four, stratified by race/ethnicity. The study population included mostly African Americans (31.4%) and Asian Americans (34%) with a mean age of 35 years. Eligible subjects had to have a baseline 25D concentration <20 ng/mL. Subjects also agreed to not change their dietary calcium intake drastically and agreed to refrain from taking additional calcium or vitamin D supplements during study. Baseline characteristics were overall similar between the two treatment groups. Patients were randomized to 16 weeks of daily treatment with either 60 mcg of cholecalciferol or 20 mcg of calcifediol. With a total of 16 subjects in the cholecalciferol treatment group, two were White, six were African American, six were Asian American, and two were Hispanic/Latino. Of the 19 subjects in the calcifediol treatment group, three were White, five were African American, six were Asian American, and five were Hispanic/Latino.

At the end of the treatment, both the total and free 25D were elevated significantly with calcifediol compared to cholecalciferol. The total 25D was 17.0 ± 2.5 ng/mL at baseline and increased to 42.4 ± 15.9 ng/mL after treatment with calcifediol, whereas the total 25D was 16.2 ± 3.7 ng/mL at baseline and increased to 29.6 ± 4.1 ng/mL with cholecalciferol. The free 25D was 4.7 ± 1.0 pg/mL at baseline with calcifediol treatment and increased to 11.6 ± 5.6 pg/mL. With cholecalciferol treatment, the free 25D was 4.2 ± 0.8 pg/mL at baseline and increased to 7.8 ± 1.9 pg/mL. By week four, majority of the participants (14 out of 16) in the calcifediol group had already achieved total 25D concentrations of ≥ 30 ng/mL, while only 3 out of 19 in the cholecalciferol group had achieved the target vitamin D concentrations. Plasma iPTH was proportionally decreased from baseline with the 60 mcg calcifediol dose having the greatest effect on iPTH concentrations. Higher total and free 25D concentrations correlated with further decreases in PTH. The results were similar across all race/ethnic groups. Adverse events were not collected in this study.

Extended-Release (ER) Calcifediol *vs* Placebo in Chronic Kidney Disease Patients

A multicenter (two identical), randomized, double-blind, placebo-controlled study evaluated ER calcifediol to increase total serum 25(OH)D3 concentrations to improve SHPT control in patients with stage 3 or 4 CKD [7]. The study also looked at minimizing CYP24A1 and FGF23 induction with ER calcifediol use. Study A had a total of 213 subjects (72 placebo and 141 ER calcifediol) and Study B had a total of 216 subjects (72 placebo and 144 ER calcifediol) that were randomized to receive either placebo or ER calcifediol. The study population is mostly white with an average age of 66 years. Eligible subjects had to have CKD not requiring dialysis, eGFR between 15 and <60 mL/min/1.73 m^2, total serum 25(OH)D3 between 10 and 30 ng/mL, iPTH between 85 and 500 pg/mL, serum calcium between 8.4 and 9.8 mg/dL, and serum phosphorus between 2 and 5 mg/dL. Baseline characteristics were overall similar between the treatment group and placebo.

Patients were randomized to two different study groups: A and B. The total study duration was 52 weeks long. Each study group was randomized in a 2:1 ratio to receive either 30 mcg ER calcifediol or placebo for 12 weeks. Additional 14 weeks of treatment followed with study subjects receiving either 30 mcg or 60 mcg of ER calcifediol or placebo. Participants remained at 30 mcg unless their iPTH remained >70 pg/mL, total 25(OH)D3<65 ng/mL, and serum calcium <9.8 mg/dL. In the latter case, the dose was increased to 60 mcg nightly. At the end of the 26-week treatment period, subjects entered an open-label extension study in which the placebo group was started on 30 mcg of ER calcifediol and subjects who met the above cut offs for iPTH and serum calcium concentrations could increase to 60 mcg at week 38.

At the end of 26 weeks, 80% of Study A had achieved serum 25(OH)D3 concentrations of at least 30 ng/mL, while only 3% of the placebo group had achieved the target serum concentrations. About 83% of Study B had achieved the target 25(OH)D3 serum concentrations compared to only 7% in the placebo group. The changes were statistically significant ($p<0.001$). Subjects that went on to the extension study (week 26-52) achieved goal 25(OH)D3 concentrations of >30 ng/mL within four weeks of initiation. At the end of 26 weeks, more subjects (72%) treated with ER calcifediol achieved reductions in iPTH compared to 27% in the placebo group. Overall, the drug was well-tolerated and an equal number of patients in both the treatment group and placebo group experienced at least one TEAE. The most common side effects that the treatment group experienced more frequently than placebo subjects were anemia (4.9 *vs* 3.5 %), nasopharyngitis (4.9 *vs* 2.8%), increased serum creatinine (4.9 *vs.* 1.4%), and dyspnea (4.2 *vs* 2.8 %), respectively.

Discussion

Calcifediol has been reported to produce a rapid correction of vitamin D and a moderate decrease in iPTH serum concentrations. Calcifediol has been studied in some chronic kidney disease patients, although not extensively. Two of the studies presented in this review were conducted in patients without chronic kidney disease which can present its own limitations as discussed below. Also of note, a clarification in the two formulations (modified-release and extended-release) needs to be made. The MR formulation was used in Sprague's 2014 study, and the ER formulation was used in Sprague's 2016 study. Based on the "Drug Products and Dosing" section in both studies, there was no difference in how the two formulations were prepared and the release mechanism during in vitro dissolution testing. Therefore, MR is synonymous to ER with respect to calcifediol. Jetter's and Shieh's studies did not specify the release mechanism of calcifediol so it will be treated as immediate release throughout the discussion. The commercially available calcifediol product (Rayaldee®) is an ER formulation available in 30 mcg capsules; however, there are notable dosing discrepancies throughout the studies evaluated. The initial dose of 30 mcg can be titrated up to 60 mcg to achieve goal serum concentrations of iPTH [8].

Sprague's 2016 study closely mimicked the dosing regimen as outlined in the package insert; however, Sprague's 2014 study reached calcifediol doses up to 90 mcg, which exceeds the maximum daily dose of calcifediol. The results from the latter study may not be as applicable in the clinical setting for this reason. Additionally, not all studies took bioequivalent doses into consideration. Jetter's study focused on the exact micrograms of both the calcifediol and cholecalciferol, while Shieh's study matched cholecalciferol with a bioequivalent dose of calcifediol. It was found that 60 mcg of cholecalciferol is bioequivalent to 20 mcg of calcifediol. Therefore, a study with matching micrograms of both calcifediol and cholecalciferol may give the calcifediol study arm an unfair advantage, seeing that the calcifediol dose is three times the bioequivalent dose of cholecalciferol.

The route of administration for calcifediol is important to consider, and the intravenous (IV) and MR formulations have also been evaluated previously [9]. IV bolus calcifediol and MR oral calcifediol were both able to increase serum 25(OH)D3 concentrations, with the IV bolus formulation increasing the concentrations rapidly, while the MR oral dosage form increased the concentrations gradually. Additionally, it was found in this study that the IV bolus calcifediol significantly induces CYP24A1 and FGF-23 in both the kidneys and the parathyroid gland. The CYP24A1 enzyme attenuates the breakdown of calcitriol, so less calcitriol is available to affect the parathyroid gland. The IV bolus formulation increases FGF-23, which limits 1,25(OH)2D3 production and in turn increases iPTH (MR Study). Induction of FGF-23 has also been shown to increase cardiovascular risk. MR oral calcifediol, on the other hand, induced neither FGF-23 nor CYP24A1 and was considered to be the superior dosage form in this study (Table 1).

Vitamin D correction is quicker with calcifediol when compared to cholecalciferol. The clinical significance of rapid correction of vitamin D concentrations is that it delays the patient progression to bone disease. Theoretically, if secondary hyperparathyroidism goes without treatment, it will lead to complications faster than it would with treatment. Most, if not all, patients receiving calcifediol achieved vitamin D serum concentrations of ≥30 ng/mL. Not all patients in the cholecalciferol arm achieved goal vitamin D serum concentrations by the end of the study treatment period. Furthermore, there was no statistically significantly difference between the daily and weekly dose treatment groups. In terms of iPTH suppression, calcifediol was able to reduce the serum concentration by ≥30%. In Sprague's 2014 study, calcifediol 30, 60, and 90 mcg were able to reduce plasma iPTH by 20.9 ± 6.2%, 32.8 ± 5.7%, and 39.3 ± 4.3%, respectively. The changes in iPTH were statistically significant when compared to placebo. By contrast, some subjects in the cholecalciferol group were not able to achieve goal iPTH serum concentrations by the end of treatment.

Several limitations exist amongst the four studies evaluated. Jetter's study as well as Shieh's were not related to CKD. The results from these studies may not be applicable to the CKD patients with SHPT. The two studies that were studied in healthy patients were included in this review to demonstrate the efficacy of calcifediol rapidly increasing vitamin D concentrations regardless of the study population. In Shieh's study, the iPTH serum concentrations were not elevated at baseline (i.e., 30-40 pg/mL). An elevated iPTH serum concentration is defined as >65 pg/mL and, according to KDIGO, the optimal serum concentration of iPTH is not known for patients with CKD stage 3-5 not on dialysis. However, the studies that were evaluated in this review defined significant reductions in serum iPTH as a ≥ 30% decrease. Immediate release calcifediol was not

Table 1: Vitamin D Product Names and Terminology.

Generic Name (Trade Name)	Other Names or Terms
Cholecalciferol (Delta D3)	Vitamin D_3
Ergocalciferol (Drisdol)	Vitamin D_2
Calcifediol (Rayaldee)	Calcidiol 25 hydroxyvitamin D 25(OH)D_3, 25(OH)D
Calcitriol (Rocaltrol, Calcijex)	Vitamin D Receptor Activator (VDRA) 1,25 dihydroxyvitamin D 1,25$(OH)_2D_3$
Paricalcitol (Zemplar)	Vitamin D Receptor Activator (VDRA) Vitamin D analog of calcitriol
Doxercalciferol (Hectorol)	Vitamin D Receptor Activator (VDRA) Vitamin D analog of calcitriol

shown to reduce iPTH effectively because it was not able to reduce serum iPTH by more than 30% from baseline. In Sprague's 2014 study, some patients were allowed to remain on cholecalciferol or ergocalciferol if they were stable on these medications with doses below 1,600 IU/day. This could potentially affect results because patients that are taking either cholecalciferol or ergocalciferol could have higher serum concentrations of 25(OH)D3 than patients that are only on calcifediol. Also, patients that were on cholecalciferol and ergocalciferol could have a higher baseline 25(OH)D3 which would give those patients an advantage in achieving a higher 25(OH)D3 in the end. The study sample sizes were small for each study arm with less than 50 study participants for three of the four studies. The ER calcifediol study was the only study with a relatively large number of patients with more than 100 patients in one study arm. The results from the ER calcifediol study may be more applicable to clinical practice as the results from this study are more realistic of what could be seen in the clinical setting. Cost is also a limitation as one calcifediol capsule has a AWP unit price of $37.12. Cholecalciferol is over the counter and costs less than $10 per bottle. Clinicians should take patients' socioeconomic levels into consideration when prescribing calcifediol over cholecalciferol. Overall, calcifediol is a relatively safe drug as the adverse effect profile is similar compared to placebo although the statistical significance of these comparisons was not reported. Although the serum creatinine did increase, there were no other reported adverse effects on renal function [7].

There are still many unanswered questions regarding calcifediol use in specific patient populations. Recent 2017 KDIGO guideline updates state that vitamin D analogs are not recommended for routine use in adult patients with SHPT and CKD stages 3a-5. The guidelines suggest reserving such agents for the use in patients with CKD stage 4 or 5 with severe and progressive hyperparathyroidism. Patients with CKD stage 5 and especially ESRD patients on hemodialysis may not get the full benefit from calcifediol because further activation of 25(OH)D3 occurs in the kidney to its biologically active form. Because the baseline kidney function was not studied in the evaluated trials, the impact of calcifediol on the kidney function is unknown. However, future studies for calcifediol are currently recruiting patients and are looking specifically at the clearance of 25(OH)D3 in patients with chronic kidney disease [10]. Some studies also suggest restoring 25(OH)D3 serum concentrations before osteoporosis pharmacotherapy initiation because of the critical role that calcifediol plays in vitamin D deficiency and insufficiency [6]. Calcifediol will correct vitamin D serum concentrations reliably and quickly, and possesses some ability to lower iPTH in patients with functioning kidneys. There is certainly room for more research and further studies are necessary to determine the efficacy of calcifediol in treating SHPT in CKD.

Conclusion

Calcifediol is a prohormone of calcitriol approved for treatment of SHPT. It is an effective agent to replete vitamin D stores more rapidly compared to cholecalciferol. Areas for further research include comparative trials with calcimemetics like cinacalcet and the newly FDA approved etelcalcetide. Other outcomes that could be studied include the effect on mortality, cardiovascular disease and bone fractures. Randomized and controlled studies are needed to compare its effect and cost when compared with other vitamin D analogues.

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