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Real-World Assessment: Clinical Effectiveness and Safety of Extended-Release Calcifediol

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Keywords
Extended-release calcifediol · Real-world · Secondary hyperparathyroidism · Vitamin D insufficiency · Vitamin D therapy

Abstract

Introduction: The safety and efficacy of extended-release calcifediol (ERC) as a treatment for secondary hyperparathyroidism (SHPT) in adults with stage 3 or 4 chronic kidney disease (CKD) and vitamin D insufficiency (VDI) has been demonstrated in prospective randomized clinical trials (RCTs). ERC (Rayaldee®) was approved by the Food and Drug Administration in 2016 on the basis of these prospective RCTs. The current retrospective study assessed the postlaunch data available with respect to ERC's efficacy and safety in increasing serum 25-hydroxyvitamin D (25D) and reducing parathyroid hormone (PTH) in the indicated population. ***Materials and Methods:*** Medical records of 174 patients who met study criteria from 15 geographically representative United States nephrology clinics were reviewed for 1 year before and after initiation of ERC treatment. Enrolled subjects had ages ≥18 years, stage 3 or 4 CKD, and a history of SHPT and VDI. Key study variables included patient demographics, medication usage, and laboratory results, including serial 25D and PTH determinations. ***Results:*** The enrolled subjects had a mean age of 69.0 years, gender and racial distributions representative of the indicated population, and were balanced for CKD stage. Most (98%) received 30 mcg of ERC/day during the course of treatment (mean follow-up: 24 weeks). Baseline 25D and PTH levels averaged 20.3 ± 0.7 (standard error) ng/mL and 181 ± 7.4 pg/mL, respectively. ERC treatment raised 25D by 23.7 ± 1.6 ng/mL ($p < 0.001$) and decreased PTH by 34.1 ± 6.6 pg/mL ($p < 0.001$) with nominal changes of 0.1 mg/dL ($p > 0.05$) in serum calcium (Ca) and phosphorus (P) levels. ***Discussion/Conclusion:*** Analysis of postlaunch data confirmed ERC's effectiveness in increasing serum 25D and reducing PTH levels without statistically significant or notable impact on serum Ca and P levels. A significant percentage of these subjects achieved 25D levels

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≥30 mg/mL and PTH levels which decreased by at least 30% from baseline. Dose titration to 60 mcgs was rarely prescribed. Closer patient monitoring and appropriate dose titration may have led to a higher percentage of subjects achieving an increase in 25D levels to at least 50 ng/mL and a reduction in PTH levels of at least 30%.

Introduction

Chronic kidney disease (CKD) is a major and growing global health burden and is projected to be one of the top 4 leading causes of lost potential years of life by 2040 [1]. In the United States (US), CKD prevalence and mortality rates have been rising in recent years. According to the US Renal Data System, nearly 50 million people (14.9% of the US population) have CKD [2], and kidney disease ranks as the ninth highest cause of death [2]. The prevalence of stage 3 and 4 CKD in US adults is expected to rise from 6.9% in the period of 2015–2018 to 10.6% by 2030 [3].

CKD is a progressive condition in which kidney function declines gradually. It is classified into stages 1 through 5 based on a patient's estimated glomerular filtration rate (eGFR) [4]. Complications associated with CKD include secondary hyperparathyroidism (SHPT), vitamin D insufficiency (VDI), pervasive soft tissue calcification, cardiovascular disease, and microbial infections [5]. As kidney function deteriorates, there are significant alterations in the metabolism of phosphorus (P), calcium (Ca), and vitamin D, which may cause the production and secretion of parathyroid hormone (PTH) to increase over time. This combination of decreased kidney function, mineral abnormalities, and high rates of comorbidities results in reduced health-related quality of life for many individuals with stage 3–4 CKD [6, 7].

SHPT is characterized by parathyroid hyperplasia and overproduction of PTH which cause imbalances in mineral and bone metabolism [8–10]. Normal levels of PTH range between approximately 10 and 70 pg/mL, and abnormally high levels often develop in patients who have stage 3–5 CKD. Concurrent diagnosis of CKD and SHPT has been linked to increased risk of disease progression, cardiovascular disease, and death [11–15]. Individuals with SHPT have also been found to have higher risk of bone disease, which can lead to loss of bone mineral density and increased risk of bone fractures [10]. Due to these associated complications, individuals with CKD and SHPT report significantly higher medical costs and increased health-care resource utilization than those who have CKD only [11, 12, 16]. Early and sustained control of SHPT is necessary in order to manage the course of CKD and bring PTH, other metabolic parameters and vitamin D back in balance [17].

Over the last several decades, earlier diagnosis of CKD and more accurate staging through use of eGFR have widely improved the understanding of treatment options for SHPT and VDI. Excision of parathyroid glands was previously considered a viable option, but surgery is now reserved for patients whose disease is refractory to pharmacologic treatment [4]. Traditionally, nutritional vitamin D (NVD), more specifically ergocalciferol and cholecalciferol, has been used as initial therapy for SHPT in adults with concurrent stages 3–4 CKD and VDI. As the kidney disease progressively worsens, active vitamin D (AVDs) analogs are added or replace NVDs for treatment. In June 2016, a new therapy, extended-release calcifediol (ERC) (Rayaldee®), was approved by the Food and Drug Administration for treatment of SHPT in stage 3–4 CKD patients having serum 25-hydroxyvitamin D (25D) levels below 30 ng/mL. Clinical trial data to this point in time have drawn inconsistent conclusions regarding the safest and most effective therapy option for most patients with CKD who develop SHPT [18, 19].

Head-to-head randomized clinical trials (RCTs) have shown NVD supplementation is inferior to AVDs in controlling PTH levels [19] and that use of NVD as first-line therapy may only delay the introduction of treatment that may provide more effective PTH reduction [18, 20]. However, in terms of safety, AVDs are associated with increased Ca and P levels [21, 22] and require frequent monitoring for potential development of hypercalcemia [23] and hyperphosphatemia. Due to these associated complications, the current Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline recommends avoiding routine use of AVDs in patients with stage 3–4 CKD [24]. In addition, chronic use of or bolus doses of current SHPT therapies such as AVDs may lead to therapy resistance [25]. Therapy with AVDs can also lead to or worsen VDI via upregulation of the vitamin D catabolic enzyme, CYP24A1. ERC has been evaluated for safety and efficacy through several phase 1 [26] and phase 2 [27] studies, 2 large randomized controlled phase 3 studies [28, 29], and 1 open-label extension of the phase 3 study populations [30]. These clinical trials have demonstrated the efficacy of ERC for increasing 25D levels and reducing PTH, while maintaining acceptable serum Ca or P levels in adult patients with stage 3–4 CKD [27].

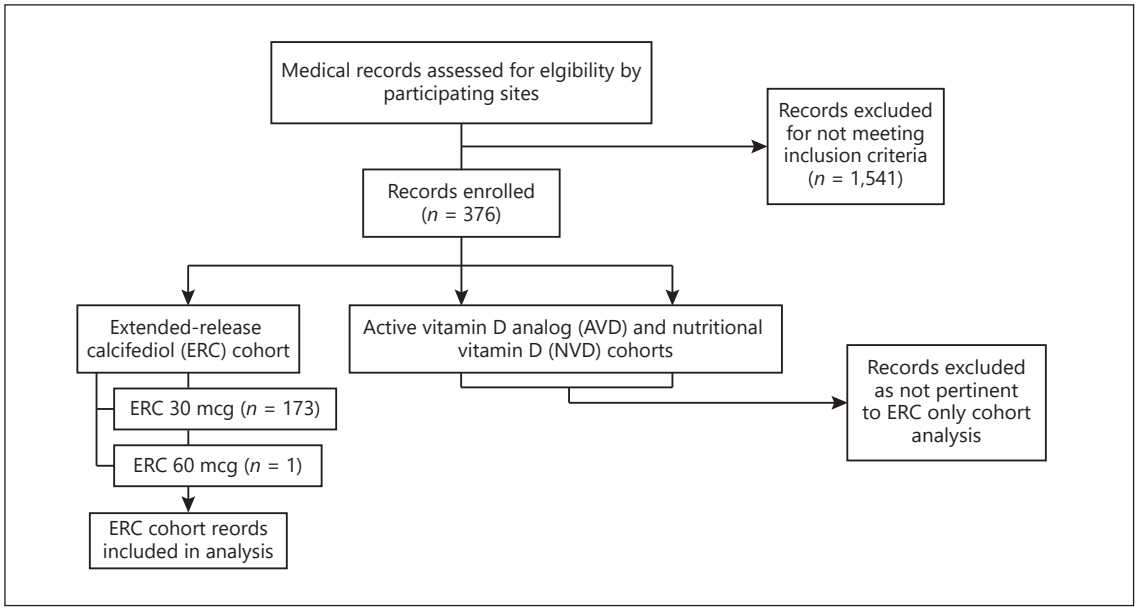

Fig. 1. Study CONSORT diagram specific to ERC cohort analysis. ERC, extended-release calcifediol; AVD, active vitamin D.

Though phase 3 clinical trial data are available to support the positive clinical benefit of ERC treatment and inform treatment guidelines [31, 32], there is a lack of published data describing whether the safety and efficacy of ERC in general clinical practice reflect phase 3 clinical trial results. The main purpose of the current study was to generate real-world evidence to estimate the effectiveness and safety of ERC during a 12-month follow-up period. Effectiveness was determined by evaluating changes in serum 25D and PTH levels, achievement of normal 25D levels, and achievement of ≥30% PTH reduction. Safety measures of interest included changes in serum Ca and P levels from initiation of therapy to follow-up. Additionally, this study aimed to advance the understanding of the demographics and characteristics of patients receiving ERC treatment and the patterns of treatment with ERC in the real-world among the indicated population.

Materials and Methods

Twenty nephrology clinics located throughout the US were contracted to participate in the study, of which 15 were able to provide medical records of patients meeting the inclusion criteria for retrospective analysis. Sites were consecutively screened for eligible patients through application of inclusion criteria to identified records with the treatments of interest in reverse chronological order until target enrollment numbers were met. A total of 1,917 patients were screened for eligibility. Of these, 376 patients were determined to be eligible for the ERC, AVD, and NVD index therapy cohorts and entered into the larger retrospective medical record review via a data collection entry tool pilot-tested by 5 site investigators or research staff. For the ERC cohort analysis reported in this manuscript, only the 174 patients identified who met study criteria and received ERC treatment were included.

Key inclusion criteria for the study were a diagnosis of CKD stage 3 or 4 as determined by an eGFR ≥15 and <60 mL/min/1.73 m^2 prior to the index date and history of VDI and SHPT. Additional inclusion criteria were availability of medical records for 6 months before and after the index date, patient treatment with the index therapy for at least 1 month after initiation, no switching of the index therapy during the follow-up period (exception made for AVD), no past treatment with ERC and AVD within the 3 months prior to initiation of the index therapy, and at least 1 determination of 25D or PTH available within 1 year of the index therapy initiation. The index date was defined as the date when the index therapy was initiated. In this retrospective analysis of the ERC cohort, the index therapy was the most recent ERC treatment with at least 6 months of medical history following treatment initiation. To capture ERC treatment in the medical records, the index date was required to be on or after the ERC utilization date of November 30, 2016. Data captured included eligible patient records from November 30, 2016, up through October 11, 2019. No exclusion criteria were established for this study. The study CONSORT diagram is shown in Figure 1.

Data for this retrospective analysis were captured from electronic and paper medical records and laboratory databases. Beyond collecting patient demographics and characteristics, data capture included information regarding diagnosis, past medical history, treatments, and any clinical laboratory data of interest for up to 6 months prior to the index date and for at least 6 months

Table 1. Patient demographics and characteristics

Variable	Study ERC cohort (*n* = 174)	Clinical trial ERC cohort [32] (*n* = 285)
Age, mean (SD)	69.0 (13.2)	66.0 (10.6)
Male, *n* (%)	84 (48.3)	142 (50.2)
Hispanic, *n* (%)	27 (15.5)	57 (20.0)
Race, *n* (%)		
Caucasian	113 (64.9)	183 (64.2)
African American	34 (19.5)	93 (32.6)
Asian American	0 (0)	NR
Native American	0 (0)	NR
Other	19 (10.9)	8 (2.8)
Not available	8 (4.6)	NR
BMI, mean (SD)	34.2 (20.7)	34.4 (8.1)
Primary insurance status, *n* (%)		
Commercial	47 (27.0)	NR
Medicare	103 (59.2)	NR
Medicaid	11 (6.3)	NR
Tricare/Other military or VA	2 (1.1)	NR
Uninsured	1 (0.6)	NR
Other	7 (4.0)	NR
Unknown	3 (1.7)	NR
Primary cause of CKD, *n* (%)		
Unknown/not documented cause	*n* = 105	
Known cause	*n* = 69	
Hypertension	36 (52.2)	103 (36.1)
Diabetes	30 (43.5)	129 (45.3)
Other	3 (4.3)	NR
CKD stage, *n* (%)		
CKD stage 3	81 (46.6)	222 (51.7)
CKD stage 4	93 (53.4)	202 (48.3)
Comorbidities, *n* (%)		
Hypertension	128 (73.6)	NR
Diabetes	90 (51.7)	NR
Anemia	67 (38.5)	NR
Hyperlipidemia	48 (27.6)	NR
Coronary artery disease	17 (9.8)	NR
Heart failure	14 (8.0)	NR
Angina	1 (0.6)	NR
Peripheral vascular disease	3 (1.7)	NR
Cerebral vascular disease	3 (1.7)	NR
Cancer	3 (1.7)	NR
None	39 (22.4)	NR
Concomitant medications, *n* (%)		
Phosphate binders	6 (3.4)	NR
Anemia medications	25 (14.4)	NR

BMI, body mass index; CKD, chronic kidney disease; ERC, extended-release calcifediol; SD, standard deviation.

after the index date. Specific laboratory data collected included 25D, PTH, Ca, and P levels. The 25D and PTH levels were collected for up to 1 year prior to and following the index date.

All data collected from individual sites were aggregated into a single analytical dataset. Descriptive analyses were conducted on all continuous and categorical variables. For continuous variables, the mean value, standard deviation, and standard error were calculated. For categorical variables, counts and percentages were computed. In order to determine whether statistically significant changes occurred to outcome measures, significance testing was conducted between pre-treatment and post-treatment values. Primary analysis of the enrolled population included changes in 25D and PTH levels from baseline to follow-up as key clinical effectiveness endpoints. Safety-related endpoints included changes in serum Ca and P among all enrolled patients before and after index therapy treatment initiation. In the clinical trial analysis, primary endpoints included the proportion of patients who achieved 25D levels ≥30 ng/mL and ≥30% reduc-

Table 2. Primary analysis – key lab values supporting clinical effectiveness and safety

Lab value	Study ERC cohort (n = 174)					Clinical trial ERC (n = 234) [25]				
	pre	post	Δ	$mean_{FU}$	med_{FU}	pre	post	Δ	$mean_{FU}$	med_{FU}
25D, ng/mL* mean (SE)	20.3 (0.7)	44.0 (1.7)	23.7[a] (1.6)	24.6	19.9	19.7 (0.3)**	67.1 (1.4)**	47.4[a] (1.4)**	26.0	NR
PTH, pg/mL* mean (SE)	181.4 (7.4)	147.4 (7.1)	−34.1[a] (6.6)	23.4	18.8	143.7 (3.6)**	111.8 (4.2)**	−31.9[a] (3.0)**	26.0	NR
Ca, mg/dL mean (SE)	9.2 (0.1)	9.3 (0.1)	0.1[b] (0.1)	27.8	22.2	9.2 (0.02)**	9.4 (0.03)**	0.2[a] (0.02)**	26.0	NR
P, mg/dL mean (SE)	3.8 (0.1)	3.9 (0.1)	0.1[b] (0.1)	28.8	22.1	3.8 (0.03)**	3.9 (0.04)**	0.1[b] (0.03)**	26.0	NR
eGFR mean (SE)	31.1 (1.1)	28.0 (0.9)	−3.1[b] (0.7)	28.1	22.2	30.6 (0.6)**	29.6 (0.7)**	−1.0[b] (0.4)**	26.0	NR

25D, 25-hydroxyvitamin D; PTH, parathyroid hormone; Ca, calcium; P, phosphorus; eGFR, estimated glomerular filtration rate; RCT, randomized clinical trial; ERC, extend-release calcifediol; $mean_{FU}$, mean follow-up (weeks); med_{FU}, median follow-up (weeks); SE, standard error. * Sites had varying truncation points for 25D levels and differing reference ranges for PTH. ** Standard error values were calculated from data on the file. [a] $p < 0.001$. [b] $p > 0.05$.

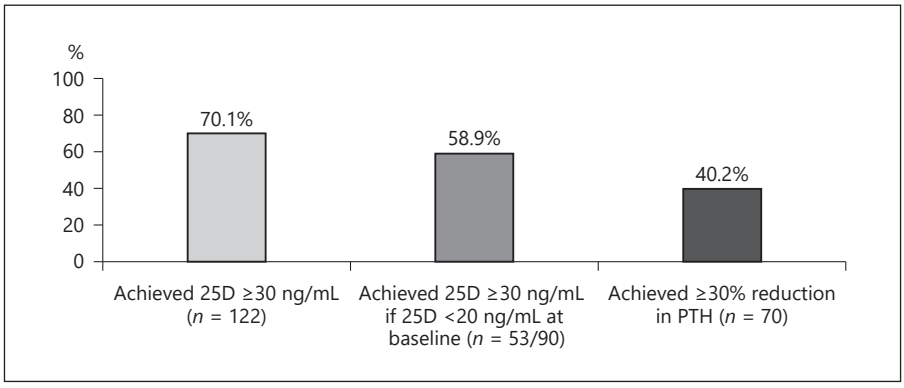

Fig. 2. Primary analysis – key endpoints. 25D, 25-hydroxyvitamin D; PTH, parathyroid hormone.

tion in PTH. This retrospective study included these primary endpoints captured in the clinical trial as well as the proportion of patients who achieved 25D levels ≥30 ng/mL if their baseline 25D levels were <20 ng/mL.

Results

Of the 376 patients enrolled in the larger study, 174 (46.3%) initiated treatment with ERC. Within the ERC cohort, 173 (99.4%) of patients initiated treatment with 30 mcg ERC daily, and 1 patient (0.6%) began treatment with 60 mcg ERC daily. Overwhelmingly, patients received 30 ERC daily during the course of therapy (n = 170, 97.7%). Few patients received any dose titration, either up or down. Only 2 patients (1.1%) were titrated up to 60 mcg/day within 6 months, and a single patient (0.6%) was titrated down to 30 mcg every other day. Follow-up monitoring of 25D and PTH levels was recorded among 42.0% of patients in the first 16 weeks and 59.8% of patients within the first 24 weeks.

Baseline patient demographics and characteristics collected as close to the index date as possible and no more than 6 months prior were analyzed in the study population and compared to published data from phase 3 RCTs conducted with ERC, shown in Table 1. Clinical trial data reported demographic information for 285 patients and included 234 patients in the primary analysis [25, 32]. In both ERC cohort and clinical trial populations, approximately half of the population was male (48.3% and 50.2%, respectively), and the majority were Caucasian (64.9% and 64.2%, respectively). The mean age, height, weight, and body mass index of the ERC cohort and clinical trial population were comparable. In both groups, diabetes and hypertension were the most common primary causes of CKD. The majority of patients in the ERC cohort had a baseline CKD stage of 4 (53.4%) versus 48.3% of patients enrolled in the clinical trials [32].

For patients enrolled in the retrospective study who received ERC treatment (n = 174), serum 25D levels raised by an average (standard error) of 23.7 ± 1.6 ng/mL ($p < 0.001$), whereas data from the RCTs showed a 47.4 ±

1.4 ng/mL increase in 25D levels. PTH levels decreased by 34.1 ± 6.6 pg/mL ($p < 0.001$) in the study population and by 31.9 ± 3.0 pg/mL in the clinical trials [25]. Almost two-thirds of subjects (74%) were up titrated per protocol guidelines to 60 mcg at week 13 in the RCTs, while patients were rarely titrated up in the retrospective study (2.2%). Primary analysis of the other study key laboratory values showed a mean change in Ca of 0.1 mg/dL and a mean change in P levels of 0.1 mg/dL, which were similar to those observed in the clinical trial data [25]. Primary analysis of key laboratory values supporting clinical effectiveness and safety is shown in Table 2.

Additional analysis of the data was conducted to determine effectiveness of ERC therapy based on primary endpoints (shown in Fig. 2). Within the ERC cohort, 70.1% ($n = 122$) of patients achieved 25D levels of ≥30 ng/mL at follow-up. Among patients that started at a baseline 25D level of <20 ng/mL, 58.9% ($n = 53$) of patients achieved a 25D level of ≥30 ng/mL by follow-up. In regard to the achievement of *a* ≥30% reduction in PTH over the duration of the study, 40.2% ($n = 70$) of enrolled patients achieved this endpoint.

Discussion

Comparison to Clinical Trial and a CKD Population

In comparison to the phase 3 ERC clinical trials [32], the enrolled chart review population had gender, body mass index, and racial distributions that were similar and representative of the indicated population. In addition, the primary cause of CKD and pooled rates of CKD stage were comparable between groups. However, the ERC cohort of this retrospective study had a slightly higher mean age and a lower percentage of the population was African American. In addition, slightly more patients in the clinical trials had stage 3 CKD at baseline, whereas the majority of patients in the review were CKD stage 4.

Comorbidities were not reported in the clinical trials. However, in comparison to reported comorbidities for the weighted average of a CKD stage 3–4 population from the electronic medical record data of a managed care organization [25], the current study population presented with a much higher proportion of comorbidities, such as hypertension (73.6% vs. 48.1%), diabetes (51.7% vs. 21.3%), anemia (38.5% vs. 15.9%), and hyperlipidemia (27.6% vs. 11.3%). Exceptions were found for the comorbidities of coronary artery disease, heart failure, and peripheral vascular disease, where they occurred more in a CKD stage 3–4 population than in the study population. Beyond the higher proportion of patients in the retrospective analysis having CKD stage 4, these data on comorbidities suggest that the real-world population may have more severe disease burden at baseline than those in clinical trials. Additionally, it is possible that physicians may have a preference to treat sicker patients with a more advanced stage of CKD and comorbidities with ERC.

Dosing protocols of clinical trials also varied significantly from the ERC dosing regimen used in real-world treatment. Clinical trial protocols and prescribing information specified a dose titration from 30 mcg/day of ERC to 60 mcg/day in the absence of sufficient PTH lowering response [33]. While 74% of patients treated with ERC in the clinical trials were titrated per protocol up to 60 mcg/day after 12 weeks of treatment, only 3 (1.7%) patients in the retrospective study were dose titrated from 30 mcg to 60 mcg. The real-world practice of not uptitrating the ERC dose to 60 mcg/day per the label may have negatively impacted some patient outcomes. Based on the clinical trial results, uptitrating to 60 mcg/day in the real-world would have increased the number of patients with higher 25D levels, as well as the percentage of patients that attained 30% or more reductions in PTH levels. While a potential exists for cost savings related to reduced monitoring in the absence of dose titrations, it is unknown if this outweighs possible clinical or economic cost benefits resulting from better efficacy outcomes achieved with ERC dose uptitration.

In this retrospective study, follow-up times after initiation of treatment in clinical practice deviated from recommended follow-up time frames per guidelines in phase 3 clinical trial protocols. While the most common laboratory follow-up period was 13–16 weeks (25.3%), the majority of patients did not have 25D or PTH monitoring until after this period (58.0%), with over a third (33.3%) not having a follow-up within the first 6 months (26 weeks) and some (14.9%) not experiencing a follow-up until ≥41 weeks. These results suggest that many physicians waited longer to test for key clinical and safety markers than is recommended.

Inconsistency in follow-up times in the ERC cohort as compared to the uniform follow-up time of 26 weeks in the clinical trial may have impacted assessment of the difference in laboratory value results. Longer follow-up times may have allowed more time to identify treatment efficacy or safety impacts. Since the ERC cohort had less mean time (up to −2.6 weeks) to demonstrate 25D and PTH changes and more mean time (up to +2.8 weeks) to evaluate Ca and P changes, it is possible that the magnitude of real-world laboratory values at follow-up may

have been larger for efficacy and smaller for safety results than if assessed at 26 weeks to match the clinical trial.

Laboratory values for 25D and PTH were comparable between the retrospective analysis and clinical trials, although there were some notable differences. Despite baseline values of 25D being almost identical in both the retrospective analysis and the clinical trials, the clinical trials produced a much larger change in 25D value by follow-up (47.4 ng/mL vs. 23.7 ng/mL). This is most likely attributable to the fact that the clinical trials force-titrated dose up to 60 mcg/day whenever appropriate, whereas, in the real-world, clinicians almost uniformly kept patients at a dose of 30 mcg/day. It is possible that the differences in total change of 25D levels could also be attributed to better adherence or compliance or as previously noted, a longer mean follow-up time in the clinical trials. Another difference was that mean baseline PTH levels were much higher in the ERC cohort of the retrospective study than those in the clinical trial populations. This may be indicative of more severe SHPT in the real-world population than was represented in phase 3 clinical trials.

Additionally, there was some variation in the populations in relation to concomitant medications. Concomitant use of NVD occurred in 14.4% of patients treated with ERC in the open-label extension to phase 3 clinical trials, whereas patients receiving NVD and ERC concurrently were excluded from the retrospective study.

While our study used 25D levels ≥30 ng/mL and a ≥30% reduction in PTH as endpoints in order to compare with clinical trial findings, they may not have represented overall achievement of goals in real-world practice. For instance, the achievement goal for 25D levels should be linked to that which promotes the optimal physiologic reduction in PTH. Some evidence suggests that target levels for 25D repletion therapy should be much higher than ≥30 ng/mL to promote the desired PTH reductions [34].

Key Takeaways

The variation between this retrospective study and the prior clinical trials may help inform improvement in the management and treatment of SHPT in the indicated population. Although some clinicians scheduled follow-up visits with their patients to monitor serum 25D, PTH, and safety markers within at least the first 6 months of initiating ERC therapy, follow-up in a significant portion (33.3%) of patients did not occur until much later. Consistent follow-up with patients within the first 3–6 months may have allowed the clinician to make more knowledgeable decisions in the management and treatment of SHPT patients and ultimately improve patient outcomes in terms of clinical effectiveness and safety.

Potentially related to the issue of longer than recommended follow-up and less monitoring of key laboratory values, real-world ERC dose patterns generally did not deviate from 30 mcg/day. As the clinical trial data have suggested, titrating doses up to 60 mcg/day can significantly improve 25D levels and PTH reduction. Clinicians should be encouraged to monitor patients and titrate the ERC dosage up, whenever appropriate. Further study may also be warranted to identify other reasons clinicians choose to not dose titrate to 60 mcg, which elevated 25D levels >50 ng/mL in the RCTs, a threshold suggested for reducing PTH by at least 30% in patients with stage 3 or 4 CKD.

Both clinical trials and the retrospective study showed that patients treated with ERC experienced clinically significant increases in 25D levels and reductions in PTH levels from initiation to treatment to time of follow-up. On average, ERC raised 25D levels in the retrospective study to 44 ng/mL, well beyond the goal of ≥30 ng/mL. PTH reduction assessed by the level of 25D achievement in the clinical trials showed that a mean reduction of ≥30% was not achieved until 25D was increased to at least 50 ng/mL.

The variations in dosing regimens, baseline characteristics, and use of concomitant medications between the clinical trial and real-life practice may have played a part in the differences in achieving clinical trial endpoints. Closer adherence to follow-up and dose titration recommendations utilized in the phase 3 clinical trial protocols may lead to further increases to 25D levels and reductions to PTH levels in clinical practice.

Limitations

Due to the study design as a retrospective chart review, the study may have some limitations. As is common to chart reviews, the data available in the medical records may have not included all information specific to the management of SHPT and VDI, may not have reflected care received outside the study site, or may have differed from site to site depending on data reporting practices. Thus, the understanding gained of the treatment patterns may have been limited or incomplete. Chart reviews always possess the potential for data entry errors. Potential data inconsistencies may also arise due to differing data reporting practices and laboratory value ratios between sites. However, efforts were made to minimize potential errors by training of research staff on determining eligibility and accurately and consistently entering the study

data, as well as careful monitoring of entered data for any values that were outliers or not within recognized ranges or units for certain variables. When possible, any potential errors or data reporting inconsistencies identified were verified with the site and corrections or reporting adjustments were made. Data points that were considered to be extreme outliers were also excluded to reduce potential data entry bias. Additionally, selection bias may have been introduced due to the inclusion criteria requirement of documentation of serum 25D and PTH levels before and after the index date, leading to a more severe population being included within the study. Some real-world variations in follow-up times of ERC efficacy and safety laboratory values also exist, but the mean difference compared to the clinical trials is relatively small at ± 2.6 to 2.8 weeks. Finally, incomplete baseline data may have impacted individual calculations of eGFR and CKD stage.

Conclusions

Overall, real-world experience confirmed the data reported from RCTs that demonstrated ERC's efficacy to increase 25D and reduce PTH levels without significant negative clinical impact on serum Ca and P levels. In general, the past clinical trials and the current retrospective analysis demonstrated similar clinical effectiveness and safety outcomes. However, appropriate changes in management and treatment of SHPT patients with stage 3 or 4 CKD and VDI may improve clinical outcomes. Specifically, more consistent follow-up of patients within recommended time frames and better alignment with guidelines for dose titration up to 60 mcg/day may promote optimal increases of 25D levels and reductions in PTH levels that lead to improved patient outcomes. Future research into factors influencing clinician patient follow-up and dose titration practices, as well as what 25D and PTH levels thresholds are best suited as treatment achievement goals can help optimize SHPT management and treatment and patient health among the indicated population.

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Statement of Ethics

This study was conducted in compliance with the principles of the Declaration of Helsinki. The protocol was reviewed and approved by the Western Institutional Review Board in January 2019. A waiver of informed consent was also granted by the Western Institutional Review Board in February 2019 in recognition that the study is a retrospective medical record review that does not include collection or analysis of protected health information and that the requirement of collection of informed consent would make the study not feasible to conduct.

Conflict of Interest Statement

Akhtar Ashfaq's and Charles Bishop's employment for the last 3 years includes OPKO Health, and they have no other conflicts of interests to disclose. Varshasb Broumand has received honoraria for speaking engagements on behalf of OPKO Health and has no further conflicts of interests to disclose. George Fadda and Michael J. Germain have no conflicts of interests to disclose. Matthew Gitlin is the owner of BluePath Solutions, a company which received funding from OPKO Health to conduct the research study and has no further conflicts of interest to disclose. November McGarvey's employment in the last 3 years includes Pfizer Inc and BluePath Solutions (current). She has no other conflicts of interest to disclose. Andy Nguyen has been employed by BluePath Solutions in the past 3 years and has no further conflicts of interest to disclose.

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Author Contributions

Varshasb Broumand, George Fadda, and Michael J. Germain contributed to review of the study protocol, pilot testing of the data collection instrument, identification of eligible medical records based on inclusion criteria, provision of access to or collection of data from eligible medical records, and review of the article. Akhtar Ashfaq, Charles Bishop, Matthew Gitlin, November McGarvey, and Andy Nguyen contributed to the design of the study and data collection instrument, development of the statistical analysis plan, interpretation of study results, and writing of the article. Additionally, Andy Nguyen was involved in the collection of data from eligible medical records and data cleaning and analysis.

Data Availability Statement

The data in this study were obtained from multiple sites where restrictions may apply. Data may be available from the corresponding author (A.A.) upon reasonable request and with the permissions of all contributing sites.

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