FR-PO319 Extended-Release Calcifediol Overcomes Impact of Low eGFR on Vitamin D Metabolism.

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Introduction

Serum 25-hydroxyvitamin D (25D) falls below 30 ng/mL and serum 1,25-dihydroxyvitamin D (1,25D) becomes undetectable as chronic kidney disease (CKD) progresses. Cholecalciferol or ergocalciferol are widely prescribed but cannot reliably raise 25D and 1,25D and lower elevated parathyroid hormone (PTH). They are replaced/combined with calcitriol (or 1α-OH analog) when PTH inevitably rises, contrary to the current KDIGO guideline. The justification for calcitriol use is that too much renal CYP27B1 has been lost, limiting hormone production. Randomized clinical trials (RCTs) have demonstrated that extended-release calcifediol (ERC) safely and sufficiently raises serum 25D and 1,25D, and effectively treats elevated PTH despite declining estimated glomerular filtration rate (eGFR), but the mechanism is not fully elucidated and requires further investigation.

Objective

To examine the effect of declining eGFR on vitamin D metabolism in three different clinical populations treated with ERC: patients with normal kidney function, patients with stage 3 - 4 CKD, and patients with end-stage renal disease (ESRD).

Methods

Changes in serum total 25D and 1,25D, calcifediol ($25D_3$), 24,25-dihydroxyvitamin D_3 ($24,25D_3$) and calcitriol ($1,25D_3$) during ERC treatment in four RCTs were assessed compared as a function of eGFR. In one study, 80 non-CKD patients with COVID-19 were treated for 4 weeks (wks) with 300 mcg/day (d) for the first 3 days and 60 mcg/d thereafter (Bishop 2023). In two other studies (pooled), 285 non-dialysis patients with eGFR of 30.6±0.6 (mean±SE) mL/min/1.73m^2 were treated with 210 mcg/wk for 12 weeks, at which time 74% were increased to 420 mcg/wk (Sprague 2016). In another, 33 hemodialysis (HD) patients were treated for 26 wks with 900 mcg/wk (Strugnell 2021).

Subjects

Baseline eGFR and serum total 25D levels of subjects included in the present analysis are listed in Table 1, along with subject numbers, ERC doses, and treatment durations for each population.

Table 1. Characteristics of Patients Included in this Analysis

Patients	Baseline eGFR (mL/min/1.73m^2) Mean (SE)	Baseline Serum 25D (ng/mL) Mean (SE)	ERC Dose	Treatment Duration
Non-CKD n = 80	98.0 (2.1)	37.7±12.1	300 mcg for 3 d, then 60 mcg/d	4 wks
CKD 3-4 N = 285	30.6 (0.6)	19.9±0.3	210 mcg/wk increasing as needed to 420 mcg/wk	26 wks
ESRD N = 30	6.2 (0.5)	23.6±2.2	900 mcg/wk	26 wks

Figure 1. Changes in Serum $1,25D_3$ or Total 1,25D as a Function of Serum $25D_3$ or Total 25D

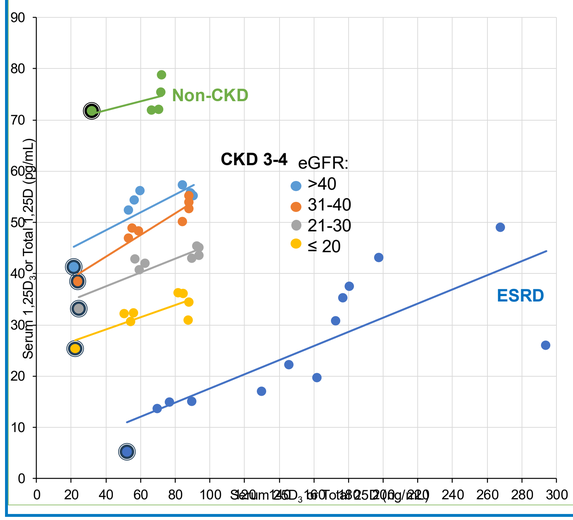


Figure 2. Changes in Mean Serum $24,25D_3$ as a Function of Serum $25D_3$

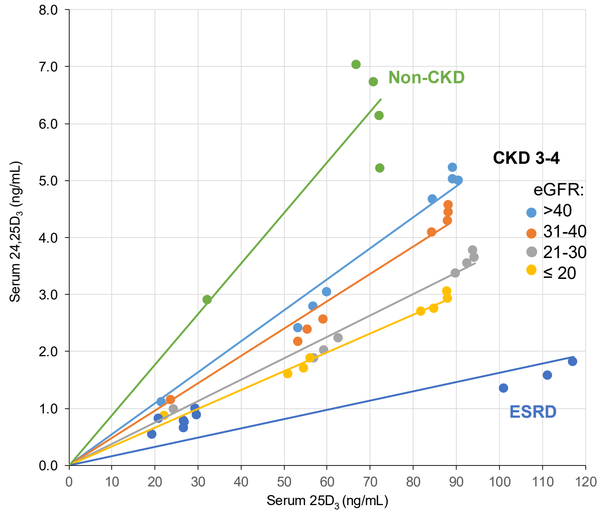
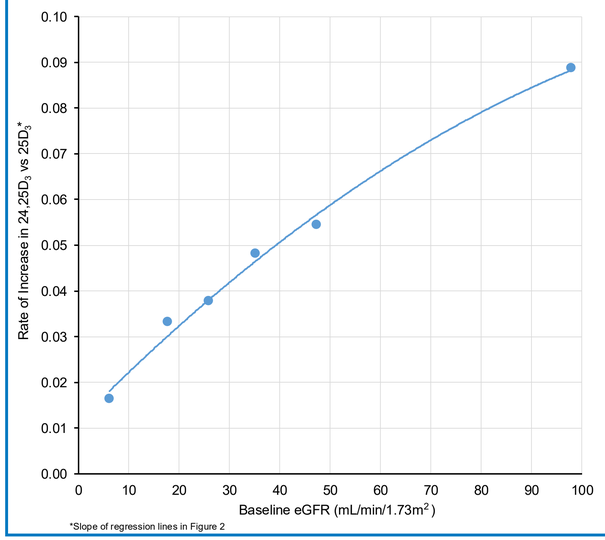


Figure 3. Increase in Serum $24,25D_3$ vs $25D_3$ by Baseline eGFR



*Slope of regression lines in Figure 2

Results

- Mean serum total 25D values at baseline were lower in patients with reduced eGFR (Table 1).
- Mean serum $1,25D_3$ or total 1,25D values at baseline (circled in Figure 1) were proportional to eGFR.
- During ERC treatment, mean serum $25D_3$ or total 25D rose to ≥70 ng/mL with peak levels proportional to the total administered dose (Figure 1).
- Mean serum $1,25D_3$ or total 1,25D rose linearly with serum $25D_3$ or total 25D at similar rates in all eGFR groups (Figure 1).
- However, serum $24,25D_3$ levels rose less quickly with rising serum $25D_3$ as eGFR decreased (Figures 2 and 3).

Conclusions

- ERC reliably raised serum $25D_3$, $1,25D_3$, and total 25D and 1,25D irrespective of eGFR, making it an attractive alternative to calcitriol (or 1α-hydroxylated analogs) for treating persistently rising PTH in CKD 3-4.
- Declining eGFR does not affect rate of conversion of $25D_3$ to $1,25D_3$, indicating the importance of extra-renal conversion in raising serum 1,25D during ERC treatment.
- Increases in serum $24,25D_3$ were dependent on $25D_3$ elevation and limited by declining eGFR, suggesting that this metabolite is not disproportionately increased by ERC and derives primarily from kidney.

References

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Acknowledgements

This study was sponsored by the Renal Division of OPKO Health Inc.

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