Secondary Hyperparathyroidism: Where are we now?

Dylan M. Barth, Pharm.D.
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Objectives

• Identify risk factors for the development of complications caused by secondary hyperparathyroidism (SHPT)

• Discuss treatment strategies for secondary hyperparathyroidism

• Recognize changes to recommendations for drug therapy in secondary hyperparathyroidism
Hyperparathyroidism

- Primary
- Secondary
- Chronic Kidney Disease
Parathyroid Hormone

- Secreted by chief cells in parathyroid gland
- Important regulator of calcium metabolism
- Short half-life
  - 2 to 4 minutes
- Works primarily on two organs
  - Kidney
  - Bone
- Starts to increase at the beginning of CKD stage III

Pathophysiology

**Calcium** → **Intestines**
- 1. Increase Ca
- 2. Increase Phos

**Vitamin D** → **Intestines**

**Parathyroid Gland** → **Kidney** → **Bone**
- 1. Increase Ca
- 2. Decrease Phos
- 3. Increase Vitamin D
- 1. Increase Osteoclastic activity

**Phosphorus** → **Kidney** → **Bone**

Increase serum calcium and phosphorus

Fibroblast Growth Factor-23 (FGF23)

- Stimulated by hyperphosphatemia
- Secreted by osteocytes
- Acts mainly on kidney to increase phosphorus clearance
- Inhibits 1-α hydroxylase activity to decrease vitamin D
- Causally linked to left ventricular hypertrophy and heart failure
- Effects diminish as patients’ CKD progresses

Block et al. JAMA. 2017; 317(2):156-164
Cardiovascular Issues

- Arterial calcifications
- Increased rates of MI and death with CKD 3/4
- 64% of patients with CrCl 15-90 mL/min had coronary calcifications
  - Up to a quarter were severe

Mineral Bone Disorder

- Rapid remodeling of bone
- Formation of bone, but not calcified
- Low rate of remodeling
- Calcifications in soft tissue and vasculature

Osteitis Fibrosa Cystica
Osteomalacia
Adynamic Bone Disorder
Calciphylaxis

Which of the following would lead to increased parathyroid hormone release?

A. Hypercalcemia
B. Decreased Vitamin D
C. Hypophosphatemia
D. Increased FGF-23
What has changed?
## KDIGO Guidelines

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>KDIGO 2009</th>
<th>KDIGO 2016</th>
</tr>
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<tbody>
<tr>
<td>CKD Stage 3-5D with hyperphosphatemia</td>
<td>Use phosphate binder</td>
<td>Use if “progressively or persistently” elevated</td>
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<tr>
<td>CKD Stage 3-5 (not on dialysis) with PTH persistently &gt; ULN</td>
<td>Use calcitriol or vitamin D analogs</td>
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**KDIGO Guidelines**

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**Phosphate Binders**

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<tr>
<td>Aluminum Hydroxide</td>
<td>Calcium Acetate</td>
</tr>
<tr>
<td>Sevelamer carbonate</td>
<td>Lanthanum carbonate</td>
</tr>
</tbody>
</table>
**Study Design**

- Randomized, placebo-controlled pilot trial

**Population**

- Non-dialysis requiring CKD patients

**Inclusion Criteria**

- eGFR (MDRD) between 20-45
- Serum phosphorus between 3.5-5.9 mg/dL

**Exclusion Criteria**

- Use of phosphate binder, active Vit. D, cinacalcet
- Intact PTH >499 pg/mL or uncontrolled HLD

*Modification of Diet in Renal Disease
Block et al.

**Intervention**
- Calcium acetate
- Lanthanum carbonate
- Sevelamer carbonate
- Placebo (Active:Placebo,3:2)

**Primary Endpoint**
- Change in serum phosphorus
  - Baseline compared to 3, 6, 9 month, and mean levels

**Secondary Endpoints**
- Lab: PTH, urine Phos, fractional excretion of phos, Vitamin D
- Clinical: Change in coronary artery, thoracic and abdominal aorta calcium volume scores; BMD

# Results

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Active (88)</th>
<th>Placebo (57)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in serum phos</td>
<td>-0.3 mg/dL</td>
<td>Unchanged</td>
<td>0.03</td>
</tr>
<tr>
<td>Urine Phos</td>
<td>-22%</td>
<td>unchanged</td>
<td>0.002</td>
</tr>
<tr>
<td>Mean FEPhos</td>
<td>-6%</td>
<td>+1%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PTH</td>
<td>Unchanged</td>
<td>+21%</td>
<td>0.002</td>
</tr>
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</table>

Vascular calcification and bone mineral density changes on study by treatment arm.

Mean annualized percent change

Geoffrey A. Block et al. JASN 2012;23:1407-1415
Interpretations

• In patients with moderate to advanced CKD:
  • Lower serum and urinary phosphorus
  • Slow down progression of SHPT
  • Increase progression of coronary artery and abdominal aortic calcification

• Safety and efficacy in CKD patients with normal phosphorus levels remain uncertain

• Limitations: Single-center, calcium and non-calcium phosphate binders analyzed together

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<tr>
<th>Vitamin D Analog</th>
<th>Calcium</th>
<th>Phosphorus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcitriol</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Paricalcitol</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Doxercalciferol</td>
<td>+</td>
<td>+</td>
</tr>
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</table>
Wang et al.

**Study Design**
- Prospective, double blind, randomized, placebo-controlled

**Population**
- Stages 3-5 CKD with LV hypertrophy

**Inclusion Criteria**
- CKD Stage 3-5
- PTH > 55 pg/mL

**Exclusion Criteria**
- Hx renal stones
- Malignancy
- ARF in last 3 months

Wang et al.

**Intervention**
- Paricalcitol or placebo for 52 weeks

**Primary Endpoint**
- Change in LV mass index by plain cardiac MRI over 52 weeks

**Secondary Endpoints**
- Change in LV end systolic volume index, EDV index and EF
- Change in PTH, calcium, phosphorus

## Results

<table>
<thead>
<tr>
<th>Change in Parameter</th>
<th>Paricalcitol (30)</th>
<th>Placebo (30)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV Mass Index (g/m²)</td>
<td>-2.59</td>
<td>-4.85</td>
<td>0.40</td>
</tr>
<tr>
<td>LV EDV (mL/m²)</td>
<td>+5.43</td>
<td>+2.79</td>
<td>0.30</td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>+0.45</td>
<td>-0.80</td>
<td>0.80</td>
</tr>
<tr>
<td>PTH</td>
<td>-86</td>
<td>+21</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

- Hypercalcemia >10.2 mg/dL
  - Paricalcitol: 43.3%
  - Placebo: 3.3%
- 70% on concomitant calcium-based phosphate binders

Interpretations

• 52 weeks of paricalcitol that effectively controls secondary hyperparathyroidism
  • Did not regress LV hypertrophy or improve LV systolic and diastolic dysfunction

• Limitations:
  • Sample size
  • Duration

Summary

Block et al.

• Phosphate binders show no benefit even when phosphorus is controlled

Wang et al.

• Vitamin D analogs show no effects on patient-level outcomes

Every patient with CKD Stage 3 or worse should be on a vitamin D analog and phosphate binder.

A. True

B. False
What’s Next?
Cinacalcet

- First generation oral calcimimetic
- Dialysis patients with hyperparathyroidism
- Adverse Effects
  - Nausea and vomiting
  - Hypocalcemia
- Limitations: Adherence

EVOLVE Trial

• Daily cinacalcet vs. standard therapy in hemodialysis patients

• Failed to show significant reduction in death or major cardiovascular events

• Limitations: Failure of randomization, high rate of off-protocol use of cinacalcet in standard care use, high rate of drop-out in cinacalcet group

Etelcalcetide

- Second generation intravenous calcimimetic
- Dosed three times a week
- Compared to placebo (2 identical phase 3 trials)
  - Primary Outcome: 30% reduction in PTH
    - 74 vs 8.3 % (p< 0.001)
    - 75.3 vs. 9.6 % (p<0.001)

Block et al.

**Study Design**
- Randomized, double-blind, double-dummy active, multinational trial

**Population**
- Dialysis patients with elevated PTH levels

**Inclusion Criteria**
- Thrice weekly hemodialysis
- Moderate-severe SHPT (PTH > 500 pg/mL)
- SCa > 8.3 mg/dL

**Exclusion Criteria**
- Cinacalcet within last three months
- Anticipated or scheduled parathyroidectomy
- Malignancy within last 5 years

Block et al. *JAMA.* 2017; 317(2):156-164
Block et al.

**Intervention**
- 26 weeks of IV etelcalcetide or oral cinacalcet along with standard of care

**Primary Endpoint**
- Proportion of patients with more than 30% reduction from baseline in mean PTH during weeks 20-27 (non-inferiority)

**Secondary Endpoints**
- Proportion of patients with more than 30% reduction from baseline in mean PTH during weeks 20-27 (superiority)
- >50% reduction from baseline

Block et al. JAMA. 2017; 317(2):156-164
Results

<table>
<thead>
<tr>
<th>End Point</th>
<th>Cinacalcet (343)</th>
<th>Etelcalcetide (340)</th>
<th>P- value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 % reduction PTH</td>
<td>57.7%</td>
<td>68.2%</td>
<td>&lt;0.001 (NI)</td>
</tr>
<tr>
<td>30 % reduction PTH</td>
<td>57.7%</td>
<td>68.2%</td>
<td>0.04 (S)</td>
</tr>
<tr>
<td>50 % reduction PTH</td>
<td>40.2%</td>
<td>52.4%</td>
<td>0.01</td>
</tr>
</tbody>
</table>

- Gastrointestinal symptoms were not significantly improved with etelcalcetide
- Etelcalcetide had a higher number of heart failure

Block et al. *JAMA*. 2017; 317(2):156-164
Interpretations

• Etelcalcetide showed superiority and non-inferiority when compared to cinacalcet for a surrogate end point

• Limitations:
  • Short duration of 26 weeks
  • Surrogate end point: PTH

• Long term data and patient-centered outcomes need to be evaluated

Block et al. *JAMA*. 2017; 317(2):156-164
In what settings would etelcalcetide be the best option for a patient?

A. Non-compliant patient
B. Patient complaining of incessant nausea from cinacalcet
C. Patient with stage 3 CKD
D. A and B only
E. All of the above
More on the Horizon

• Effect of Etelcalcetide on Cardiac Hypertrophy in Hemodialysis Patients
  • Vienna, Austria
  • Not yet recruiting

• FGF-23?
Conclusion

• SHPT is a complication of a chronic disease with significant morbidity

• Phosphate binders, vitamin D analogs, and calcimimetics all play a role in slowing down progression of the surrogate markers of disease
  • Lack patient-centered outcomes

• New guidance calls for reevaluation of traditional prescribing of drug therapies
Questions and Discussion

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# Laboratory Parameters

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<th>Stage 4 CKD</th>
<th>Stage 5 CKD</th>
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<tbody>
<tr>
<td>Corrected Calcium</td>
<td>Normal (8.4-10.5)</td>
<td>Normal (8.4-10.5)</td>
<td>8.4-9.5</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>2.7-4.6</td>
<td>2.7-4.6</td>
<td>3.5-5.5</td>
</tr>
<tr>
<td>Ca x P</td>
<td>&lt;55</td>
<td>&lt;55</td>
<td>&lt;55</td>
</tr>
<tr>
<td>PTH</td>
<td>35-70</td>
<td>70-110</td>
<td>150-300</td>
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