In the name of God

The role of calcium sensing receptor agonists in the treatment of secondary hyperparathyroidism

Dr parvin kamkar

Assistant Professor, Hormozgan University of Medical Sciences

CKD is commonly associated with disorders of mineral and bone metabolism

- Abnormalities of calcium, phosphorus, PTH, FGF23, and vitamin D metabolism
- Abnormalities in bone turnover, mineralization, volume linear growth, or strength
- Extraskeletal calcification

Each of these abnormalities is associated with high mortality rates, primarily from cardiovascular complications

renal osteodystrophy: alterations in bone morphology

(bone biopsy)

- pathophysiology : is complex and involves a number of feedback loops between the kidney, the parathyroid glands, bone, intestine, and the vasculature
- The main goal of this system is maintenance of calcium and phosphorus balance, often at the expense of abnormalities in other components of the system.

- While most elements of CKD–MBD are usually present when GFR falls below 40 mL/min
- some components may be observed earlier in the course of CKD and precede the onset of clinically detectable abnormalities in serum phosphorus, calcium, PTH, and vitamin D

include:

loss of klotho

increased FGF23 secretion

decreased bone formation rates

vascular calcification

- With progressive loss of functioning nephrons, phosphate excretion is maintained by reducing the proximal tubular reabsorption of filtered phosphate in the remaining functioning nephrons, an effect mediated by both FGF23 and PTH
- Bone disease develops as early as CKD stage 2
- Vascular calcifications also develop early, and their prevalence increases as the GFR declines
- 80 % dialysis patients have evidence of coronary artery calcification

- Secondary hyperparathyroidism:major feature of CKD-MBD
- , begins early in the course of CKD, and its prevalence increases as kidney function declines particularly at eGFR <60 mL/min/1.73 m2)
- Secondary hyperparathyroidism occurs in response to the following series of abnormalities that initiate and maintain increased PTH secretion

- Phosphate retention
- Decreased free ionized calcium concentration
- Decreased 1,25-dihydroxyvitamin D
- Increased FGF23
- reduced expression of VDRs, CaSRs, fibroblast growth factor receptors, and klotho in the parathyroid glands

TREATMENT GOALS

- ●Serum levels of phosphate should be maintained between 3.5 and 5.5 mg/dL (1.13 to 1.78 mmol/L)
- ●Serum levels of corrected total calcium should be maintained <9.5 mg/dL (<2.37 mmol/L)
- ●Parathyroid hormone (PTH) values should be maintained less than two to nine times the upper limit for the PTH assay

- **Treat hyperphosphatemia:** Persistently high phosphate (ie, >5.5 mg/dL) should be treated before treating high PTH

- **Maintain normocalcemia:** maintain serum calcium <9.5 mg/dL (<2.37 mmol/L

do not treat asymptomatic and mild hypocalcemia (ie, >7.5 mg/dL in the setting of normal albumin)

- **treat vitamin D deficiency**

Treat high parathyroid hormone

Treatment options:

- calcimimetics
- calcitriol, or synthetic vitamin D analogs
- A combination of calcimimetics with calcitriol or synthetic vitamin D analogs
- KDIGO work group was divided as to whether calcimimetics, calcitriol/synthetic vitamin D analogs, or a combination of the two be regarded as first-line therapy

All approaches reduce PTH

Calcimimetics

- CaSR of the parathyroid gland regulates secretion of PTH

- Calcimimetics mimic or potentiate the effects of extracellular Ca2+ on the CaR:

reducing the plasma PTH concentration and, decreasing the serum calcium and phosphate levels

despite the improved control of hyperparathyroidism, their use has not been shown to improve cardiovascular or all-cause mortality among patients on dialysis

calcimimetics :

- cinacalcet (oral)
- etelcalcetide (intravenous)
- evocalcet

Cinacalcet

- The addition of cinacalcet to calcitriol or an active vitamin D analog plus phosphate binder:

** increases the chances of decreasing PTH to target values without causing hypercalcemia or hyperphosphatemia

- decreases the chances of requiring a parathyroidectomy

- However, among patients with advanced secondary hyperparathyroidism (baseline PTH levels above 800 pg/mL), monotherapy with cinacalcet may be inadequate to control PTH

- Such patients might be better treated with combination therapy of an active vitamin D analog and cinacalcet

Cinacalcet:

- no benefit on mortality and cardiovascular outcomes, at least among patients <65 years of age

- In the Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) randomized trial, patients were assigned to receive cinacalcet or placebo in addition to conventional therapy including phosphate binders and/or active vitamin D or synthetic analogs :

At a median follow-up of less than two years, a difference between groups in the composite outcome of time until death or the first nonfatal cardiovascular event was not shown

Etelcalcetide

- Intravenous etelcalcetide was compared with placebo and with oral cinacalcet in three randomized trials

- All trials were of short duration and did not examine patient-important outcomes

JAMA | Original Investigation

Effect of Etelcalcetide vs Cinacalcet on Serum Parathyroid Hormone in Patients Receiving Hemodialysis With Secondary Hyperparathyroidism

A Randomized Clinical Trial

Geoffrey A. Block, MD; David A. Bushinsky, MD; Sunfa Cheng, MD; John Cunningham, MD; Bastian Dehmel, MD; Tilman B. Drueke, MD; Markus Ketteler, MD; Reshma Kewalramani, MD; Kevin J. Martin, MB, BCh; Sharon M. Moe, MD; Uptal D. Patel, MD; Justin Silver, MD; Yan Sun, MS; Hao Wang, PhD; Glenn M. Chertow, MD, MPH

IMPORTANCE Secondary hyperparathyroidism contributes to extraskeletal calcification and is associated with all-cause and cardiovascular mortality. Control is suboptimal in the majority of patients receiving hemodialysis. An intravenously (IV) administered calcimimetic could improve adherence and reduce adverse gastrointestinal effects.

OBJECTIVE To evaluate the relative efficacy and safety of the IV calcimimetic etelcalcetide and the oral calcimimetic cinacalcet.

DESIGN, SETTING, AND PARTICIPANTS A randomized, double-blind, double-dummy active clinical trial was conducted comparing IV etelcalcetide vs oral placebo and oral cinacalcet vs IV placebo in 683 patients receiving hemodialysis with serum parathyroid hormone (PTH) concentrations higher than 500 pg/mL on active therapy at 164 sites in the United States, Canada, Europe, Russia, and New Zealand. Patients were enrolled from August 2013 to May 2014, with end of follow-up in January 2015.

INTERVENTIONS Etelcalcetide intravenously and oral placebo (n = 340) or oral cinacalcet and IV placebo (n = 343) for 26 weeks. The IV study drug was administered 3 times weekly with hemodialysis; the oral study drug was administered daily.

MAIN OUTCOMES AND MEASURES The primary efficacy end point was noninferiority of etelcalcetide at achieving more than a 30% reduction from baseline in mean predialysis PTH concentrations during weeks 20-27 (noninferiority margin, 12.0%). Secondary end points included superiority in achieving biochemical end points (>50% and >30% reduction in PTH) and self-reported nausea or vomiting.

RESULTS The mean (SD) age of the trial participants was 54.7 (14.1) years and 56.2% were men. Etelcalcetide was noninferior to cinacalcet on the primary end point. The estimated difference in proportions of patients achieving reduction in PTH concentrations of more than 30% between the 198 of 343 patients (57.7%) randomized to receive cinacalcet and the 232 of 340 patients (68.2%) randomized to receive etelcalcetide was −10.5% (95% CI, −17.5% to −3.5%, *P* for noninferiority, <.001; *P* for superiority, .004). One hundred seventy-eight patients (52.4%) to randomized etelcalcetide achieved more than 50% reduction in PTH concentrations compared with 138 patients (40.2%) randomized to cinacalcet (*P* = .001; difference in proportions, 12.2%; 95% CI, 4.7% to 19.5%). The most common adverse effect was decreased blood calcium (68.9% vs 59.8%).

CONCLUSIONS AND RELEVANCE Among patients receiving hemodialysis with moderate to severe secondary hyperparathyroidism, the use of etelcalcetide was not inferior to cinacalcet in reducing serum PTH concentrations over 26 weeks; it also met superiority criteria. Further studies are needed to assess clinical outcomes as well as longer-term efficacy and safety.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT1896232

JAMA. 2017;317(2):156-164. doi:10.1001/jama.2016.19468

Editorial page 139

Related article page 146

Supplemental content

Author Affiliations: Denver Nephrology, Denver, Colorado (Block); University of Rochester, Rochester, New York (Bushinsky); Amgen Inc, Thousand Oaks, California (Cheng, Dehmel, Kewalramani, Sun, Wang); University College London, London, United Kingdom (Cunningham); Inserm, Université de Picardie, Amiens, France (Drueke); Klinikum Coburg-GmbH, Coburg, Germany (Ketteler); St Louis University, St Louis, Missouri (Martin); Indiana University, Indianapolis (Moe); Duke University, Durham, North Carolina (Patel); Hadassah Hebrew University Medical Center, Jerusalem, Israel (Silver); Stanford University, Stanford, California (Chertow).

Corresponding Author: Glenn M. Chertow, MD, MPH, Stanford University School of Medicine, 1070 Arastradero Rd, Ste 313, Palo Alto, CA 94034 (gchertow@stanford.edu).

- In two parallel randomized trials: etelcalcetide was compared with placebo among a total of 1023 hemodialysis patients with hyperparathyroidism
- Etelcalcetide was more effective than placebo in reducing PTH (with 74 to 75 percent of patients achieving >30 percent reduction in PTH versus 8.3 to 9.6 percent in placebo) by 27 weeks
- etelcalcetide-treated patients had more side effects compared with placebo (hypocalcemia, muscle spasms, nausea and vomiting)

JAMA | Original Investigation

Effect of Etelcalcetide vs Cinacalcet on Serum Parathyroid Hormone in Patients Receiving Hemodialysis With Secondary Hyperparathyroidism

A Randomized Clinical Trial

Geoffrey A. Block, MD; David A. Bushinsky, MD; Sunfa Cheng, MD; John Cunningham, MD; Bastian Dehmel, MD; Tilman B. Drueke, MD; Markus Ketteler, MD; Reshma Kewalramani, MD; Kevin J. Martin, MB, BCh; Sharon M. Moe, MD; Uptal D. Patel, MD; Justin Silver, MD; Yan Sun, MS; Hao Wang, PhD; Glenn M. Chertow, MD, MPH

IMPORTANCE Secondary hyperparathyroidism contributes to extraskeletal calcification and is associated with all-cause and cardiovascular mortality. Control is suboptimal in the majority of patients receiving hemodialysis. An intravenously (IV) administered calcimimetic could improve adherence and reduce adverse gastrointestinal effects.

OBJECTIVE To evaluate the relative efficacy and safety of the IV calcimimetic etelcalcetide and the oral calcimimetic cinacalcet.

DESIGN, SETTING, AND PARTICIPANTS A randomized, double-blind, double-dummy active clinical trial was conducted comparing IV etelcalcetide vs oral placebo and oral cinacalcet vs IV placebo in 683 patients receiving hemodialysis with serum parathyroid hormone (PTH) concentrations higher than 500 pg/mL on active therapy at 164 sites in the United States, Canada, Europe, Russia, and New Zealand. Patients were enrolled from August 2013 to May 2014, with end of follow-up in January 2015.

INTERVENTIONS Etelcalcetide intravenously and oral placebo (n = 340) or oral cinacalcet and IV placebo (n = 343) for 26 weeks. The IV study drug was administered 3 times weekly with hemodialysis; the oral study drug was administered daily.

MAIN OUTCOMES AND MEASURES The primary efficacy end point was noninferiority of etelcalcetide at achieving more than a 30% reduction from baseline in mean predialysis PTH concentrations during weeks 20-27 (noninferiority margin, 12.0%). Secondary end points included superiority in achieving biochemical end points (>50% and >30% reduction in PTH) and self-reported nausea or vomiting.

RESULTS The mean (SD) age of the trial participants was 54.7 (14.1) years and 56.2% were men. Etelcalcetide was noninferior to cinacalcet on the primary end point. The estimated difference in proportions of patients achieving reduction in PTH concentrations of more than 30% between the 198 of 343 patients (57.7%) randomized to receive cinacalcet and the 232 of 340 patients (68.2%) randomized to receive etelcalcetide was −10.5% (95% CI, −17.5% to −3.5%, *P* for noninferiority, <.001; *P* for superiority, .004). One hundred seventy-eight patients (52.4%) to randomized etelcalcetide achieved more than 50% reduction in PTH concentrations compared with 138 patients (40.2%) randomized to cinacalcet (*P* = .001; difference in proportions, 12.2%; 95% CI, 4.7% to 19.5%). The most common adverse effect was decreased blood calcium (68.9% vs 59.8%).

CONCLUSIONS AND RELEVANCE Among patients receiving hemodialysis with moderate to severe secondary hyperparathyroidism, the use of etelcalcetide was not inferior to cinacalcet in reducing serum PTH concentrations over 26 weeks; it also met superiority criteria. Further studies are needed to assess clinical outcomes as well as longer-term efficacy and safety.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT1896232

JAMA. 2017;317(2):156-164. doi:10.1001/jama.2016.19468

Editorial page 139

Related article page 146

Supplemental content

Author Affiliations: Denver Nephrology, Denver, Colorado (Block); University of Rochester, Rochester, New York (Bushinsky); Amgen Inc, Thousand Oaks, California (Cheng, Dehmel, Kewalramani, Sun, Wang); University College London, London, United Kingdom (Cunningham); Inserm, Université de Picardie, Amiens, France (Drueke); Klinikum Coburg-GmbH, Coburg, Germany (Ketteler); St Louis University, St Louis, Missouri (Martin); Indiana University, Indianapolis (Moe); Duke University, Durham, North Carolina (Patel); Hadassah Hebrew University Medical Center, Jerusalem, Israel (Silver); Stanford University, Stanford, California (Chertow).

Corresponding Author: Glenn M. Chertow, MD, MPH, Stanford University School of Medicine, 1070 Arastradero Rd, Ste 313, Palo Alto, CA 94034 (gchertow@stanford.edu).

- A randomized trial compared intravenous etelcalcetide versus oral placebo (n = 340) and oral cinacalcet versus intravenous placebo (n = 343) among hemodialysis patients with hyperparathyroidism

- Etelcalcetide was superior to cinacalcet in reducing PTH by greater than 30 percent (68 in etelcalcetide groups versus 58 percent in cinacalcet group)

- Nausea and vomiting were comparable between groups
- hypocalcemia was more common in the etelcalcetide group and required interventions to increase serum calcium concentrations
- Etelcalcetide administration led to prolongation of corrected QT intervals in many patients
- Because it is administered intravenously, compliance can be assured

evocalcet

- Evocalcet is a new oral calcimimetic agent with long term efficacy and safety for SHPT

Evocalcet

- Evocalcet: noninferior to cinacalcet
- patients treated with evocalcet had a lower incidence of gastrointestinal drug-related AEs than with cinacalcet
- Evocalcet does not strongly inhibit major CYP isoforms; therefore, it is considered likely to become an easy-to-use treatment option in terms of drug interactions

- current evidence on evocalcet safety and efficacy for SHPT is from Japan only

- evocalcet might be a better alternative to cinacalcet for SHPT in East Asian hemodialysis patients with SHPT.

Treatment approach

- Both drug classes lower PTH levels
- disparate effects on calcium and phosphate levels
- different treatment approaches based on serum phosphate and calcium levels

2017 KDIGO guidelines

- **phosphate <5.5 mg/dL and calcium <9.5 mg/dL :** calcitriol monotherapy

(other vitamin D analogs are also effective in reducing PTH)

Some clinicians treat such patients with a calcimimetic rather than calcitriol or a synthetic vitamin D analog, although studies have not shown a convincing benefit of cinacalcet on important clinical outcomes

- Cinacalcet should not be used if the serum calcium level is <8.4 mg/dL since it lowers calcium concentration
- Such patients are treated with calcitriol.

- dosing strategy is empiric:

goal of administering increasing doses of calcitriol or synthetic vitamin D analogs to achieve target plasma PTH level while maintaining serum phosphate ≤5.5 mg/dL

- Measures to maintain goal serum phosphate values are used concurrently.

- Among patients with inadequate reduction of PTH on calcitriol:

- add cinacalcet, providing the calcium is >8.4 mg/dL

- Up to one-half of patients with severe hyperparathyroidism show little or no decline in plasma PTH levels with calcitriol therapy
- The addition of cinacalcet increases the chances of achieving target PTH values and allows the use of lower doses of the vitamin D analog, which are less likely to cause hypercalcemia or hyperphosphatemia

- Cinacalcet is initiated at a dose of 30 mg/day orally, with stepwise increments to 60, 90, and 180 mg/day

- The dose can be increased every four weeks until goals are achieved

- Patients with serum phosphate ≥5.5 mg/dL or serum calcium level ≥9.5 mg/dL and persistently elevated PTH, despite maximal therapies to reduce phosphate
- Initiate calcimimetic
- Calcitriol and synthetic vitamin D analogs **should not** be used in such patients at least initially, since they both raise serum calcium and phosphate levels.

- Cinacalcet should not be started if serum calcium is <8.4 mg/dL
- During treatments, serum levels of corrected total calcium should be maintained between 8.4 and 9.5 mg/dL
- Among patients who do not sufficiently reduce PTH with cinacalcet alone, **we add calcitriol or a synthetic vitamin D analog**, providing the phosphate <5.5 mg/dL and calcium <9.5 mg/dL

- **nondialysis CKD patients:** do not use the calcimimetics

- Although cinacalcet decreases PTH levels, it is associated with hypocalcemia, increased urinary calcium excretion, and increased serum phosphate levels
- Because of the risk of hypocalcemia, laboratory values require close monitoring (weekly after starting therapy or change in dose), which may be difficult in the outpatient setting
- The KDIGO 2017 guideline does not provide recommendations on the use of cinacalcet
- Prior KDIGO guidelines suggested that cinacalcet not be used given the paucity of data concerning efficacy and safety in predialysis patients with CKD