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Biopharmaceutical Aspect of Etelcalcetide to Treat Secondary Hyperparathyroid in Chronic Kidney Disease : A Review

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Abstract
Chronic kidney disease (CKD) describes the abnormalities of kidney structure or function, present for more than 3 months. Seconday hiperparathyroid (SHPT) is one of clinical manifestation of CKD. SHPT characterized by excessive secretion of parathyroid hormone (PTH) and a combination of vitamin D deficiency, phosphate retention, high FGF23 and decreased total serum levels of 1,25-dihydroxy vitamin D and calcium. SHPT with high levels of calcium and phosphate causes renal osteodystrophy, erythropoietin resistance, vascular calcification, and left ventricular hypertrophy. Etelcalcetide is a novel calcimimetic agent that suppresses the secretion of PTH by binding to and activating the calcium-sensing receptor on the parathyroid gland. Etelcalcetide indicated for the treatment of SHPT with CKD on hemodialysis. The treatment is given by intravenous (IV) bolus injection three times per week at the end of each dialysis session. FDA approved on february 2017 for SHPT in adults with chronic kidney disease on hemodialysis. Etelcalcetide be the first calcimimetic agent that can be administered intravenously. Adverse event occuring among 5% or more of patient treated with etelcalcetide included nausea, vomiting, hypocalcemia. Among patients receiving hemodialysis with moderate to severe SHPT, the use of etelcalcetide was not inferior to cinacalcet in reducing serum PTH concentrations over 26 weeks. Further studies are needed to assess clinical outcomes as well as longer-term efficacy and safety. In this study, we aimed to review the use of Etelcalcetide in patients with SHPT in CKD.

Keywords: *Calcimimetic, Cronic Kidney Disease, Etelcalcetide, Secondary Hyperparathyroid*

I. INTRODUCTION

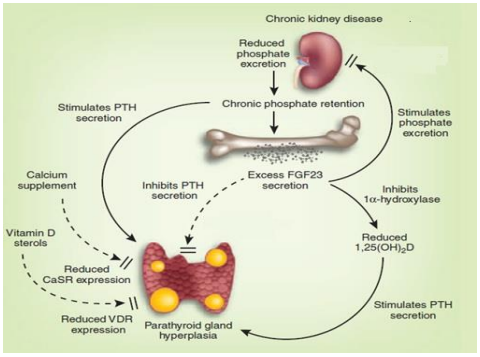
Chronic kidney disease (CKD) discribes the abnormalities of kidney structure or function, present for more than 3 months (Watnick & Dirkx, 2016). CKD is classified based on cause, GFR category, and albuminuria category (KDIGO, 2013). The pathogenesis of CKD is a progressive mechanism, involving hyperfiltration and hypertrophy of the remaining viable nephrons that are mediated by vasoactive hormones, cytokines, and growth factors. This adaptation become maladaptive because of increased pressure and flow within the nephron. In long term condition, it will caused distortion of glomerular architecture, abnormal podocyte function, and disruption of the filtration barrier. Protein and macromulecul can through the filtration barrier and caused proteinuria. The disruption and increases RAAS leading to nephrotoxic inflamatation, sclerosis and dropout of remaining nephron (Kasper, Fauci, Hauser, & Longo, 2015).

The etiology of CKD can be divided into initiation factors and progression factors. Initiation factors are factors that directly cause damage to the kidneys and can be prevented by pharmacological therapy. Including initiation factors are diabetes mellitus, hypertension, autoimmune disease, polycystic kidney disease, systemic infections, urinary tract infections, urinary stones, upper urinary tract obstruction and drug toxicity. In the United States of several initiation factors above, the three major causes of chronic kidney disease are diabetes mellitus, hypertension and glomerular disease. Progression factors are factors that aggravate kidney damage. These factors include proteinuri, increased blood pressure and smoking (Watnick & Dirkx, 2016).

Seconday hiperparathyroid (SHPT) is one of clinical manifestation of CKD. SHPT characterized by excessive secretion of parathyroid hormone (PTH) and a combination of vitamin D deficiency, phosphate retention, high FGF23 and decreased total serum levels of 1,25-dihydroxy vitamin D and calcium (Ca) (Sprague, Crwaford, & Melnick, 2016). Dysregulated mineral homeostasis due to CKD leads to decreased renal phosphate excretion, increased fibroblast growth factor level 23, and reduction of calcitriol synthesis. This change causes consistent PTH hormone secretion that contributes to the occurrence of parathyroid hyperplasia and SHPT in End Stage Renal Disease (ESRD). SHPT with high levels of calcium and phosphate causes renal osteodystrophy, erythropoietin resistance, vascular calcification, and left ventricular hypertrophy. Clinical symptoms are closely related to increased morbidity and mortality in ESRD disease. It is therefore important to maintain PTH levels and also to control calcium and phosphate levels (Jeong, Kim, & Oh, 2016).

II. ROLE OF CALCIUM SENSING-RESEPTORS IN PATHOGENENIS OF SHPT

Calcium and phosphate balance are controlled primarily by PTH and 1,25(OH)2D. More than 60% of calcium ion reabsorption occurs in the proximal tubule. Like calcium, most of the phosphate ion that is filtered is reabsorbed in the proximal tubule. Decrease of renal mass in CKD cause progressive reduction in 1,25(OH)2D synthesis and decreased phosphate ion reabsorption in the gastrointestinal tract. Fibroblast growth factor-23 (FGF-23), which increases early in the course of CKD possibly as a consequence of phosphorus retention, has been found to suppress calcitriol synthesis, in turn leading to increased PTH. Excretion phosphate reduction cause chronic phosphate retention and it stimulates PTH secretion. When plasma calcium is low, it will stimulates PTH secretion. Thus, reduction phosphate excretion, increase of FGF23 and hypocalcemia in CKD leading to SHPT (Widmaier, Raff, & Strang, 2014).



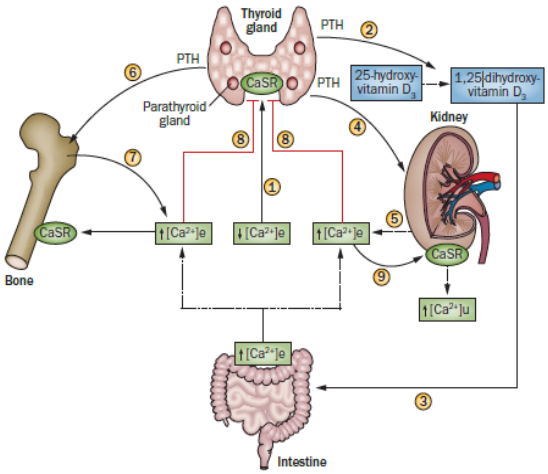
Picture 1. Pathogensis of SHPT in CKD (Komaba & Fukagawa, 2010)

Phosphate restriction with diet phosphat 800 - 1000 mg per day is recomended for patient with SHPT. The pharmacology therapy include phosptahe binder, active vitamin D (1,25[0H] vitamin D / calcitriol) or active vitamin D analogs and Calcium-sensing receptors (Hwang, Choi, & Oh, 2015) .

III. PHARMACOLOGY OF ETELCALCETIDE

Etelcalcetide is a novel calcimimetic agent that suppresses the secretion of PTH by binding to and activating the calcium-sensing receptor on the parathyroid gland. Etelcalcetide specifically indicated for the treatment of SHPT with CKD on hemodialysis. The treatment is given 5 mg administered by intravenous (IV) bolus injection intravenously three times per week at the end of each dialysis session. Recomendation dose is 2.5-15 mg three times per week (Block, et al., 2017).

Etelcalcetide is a 1048 Da synthetic peptide. In two phase III studies in patients with SHPT on hemodialysis, approximately 75 % of those administered etelcalcetide achieved > 30 % PTH reduction from baseline versus 8–10 % of those receiving placebo. In clinical studies, the importance of renal clearance was indicated by a prolonged etelcalcetide t ½ in patients with CKD on hemodialysis (81.7–175 h) compared with healthy volunteers (18.4–20.0 h) (Subramanian, et al., 2016).



Picture 2. Calcium-Sensing Receptors in SHPT (Goltzman & Hendy, 2015)

Decreased in calcium levels causes decreased activation of CaSR in the parathyroid gland (1), enhancing the release of PTH (2), which converts active 25-hydroxyvitamin D3 to active 1,25-dihydroxyvitamin D3. This increases absorption of calcium in the intestinal (3) and elevated levels of calcium. Increased levels of PTH also increase reabsorption of calcium in the kidneys (4) and this increases bone turnover (6). This effect increases the resabsorption (especially in the cortical bone) and the release of calcium, thereby increasing the levels of calcium (7). Increased levels of calcium may stimulate CaSR in bone resulting in a cumulative rise in calcium which then activates CaSR in the parathyroid glands (8), and inhibits the release of PTH. Excessive levels of calcium will activate CaSR in the kidney (9) to increase calcium levels (Goltzman & Hendy, 2015).

IV. CLINICAL TRIALS OF ETELCALCETIDE

The FDA accepted application for etelcalcetide in 2015 based on data from three Phase 3 studies, two of them placebo-controlled trials involving more than 1,000 patients, and a head-to-head study evaluating etelcalcetide compared with orally administered calcimimetic drug cinacalcet. The contents have not been revealed and reject on August 2016 (Mooro, 2016). FDA approved on february 2017 for secondary hyperparathyroidism in adults with chronic kidney disease on hemodialysis. Etelcalcetide be the first calcimimetic agent that can be administered intravenously (Block, et al., 2017).

The FDA approval was based on two 26-week, randomized, double-blind, placebo-controlled studies. An aggregate of 1,023 patients with moderate-to-severe secondary HPT (PTH greater than 400 pg/mL) on hemodialysis were randomized to receive intravenous Etelcalcetide or placebo three times a week, at the end of their dialysis sessions in addition to standard of care that could include vitamin D and/or phosphate binders. The primary endpoint of both studies was the proportion of patients achieving greater than 30 percent reduction from baseline in PTH during the Efficacy Assessment Phase (EAP), defined as weeks 20 through 27. Secondary endpoints included the proportion of patients with PTH less than or equal to 300 pg/mL during the EAP (Mooro, 2016).

The two studies showed that etelcalcetide more significantly than placebo patients in : greater than 30 percent reduction from baseline in PTH during the EAP: 77% versus 11% in Study 1, and 79% versus 11% in Study 2; PTH levels of 300 pg/mL or less during the EAP: 52% versus 6% in Study 1, and 56% versus 5% in Study 2; and greater percent reduction from baseline was achieved in Etelcalcetide-treated patients than placebo-treated patients during the EAP, for PTH, corrected calcium and phosphate in both studies (Mooro, 2016).

A study randomized, double-blind, active clinical trial was conducted comparing IV etelcalcetide vs oral placebo and oral cinacalcet vs IV placebo in 683 patients receiving hemodialysis with serum PTH concentrations >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. 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. The result in patients achieving reduction in

PTH concentrations of more than 30% is 68.2% vs 57.7%. Etelcalcetide was noninferior to cinacalcet on the primary end point (Block, et al., 2017).

V. SAFETY DATA OF ETELCALCETIDE

Adverse event occuring among 5% or more of patient treated with etelcalcetide included nausea, vomiting, hypocalcemia. Adverse effect to GI such as nausea and vomiting, not differ significanly between etelcalcetide and cinacalcet (13,3% vs 13,8%). Reduced corrected serum calcium was common with this two drugs, but it was more common with etelcalcetide than with cinacalcet. Hypocalcemia in etelcalcetide and cinacalcet (5% vs 2,3%) (Block, et al., 2017) (FDA, 2017).

In several placebo controlled trials, cinacalcet therapy resulted in higher rates of adverse gastrointestinal effects, principally nausea and vomiting. In 2 large placebo-controlled trials of etelcalcetide, nausea was reported at rates 1.7-fold and vomiting at rates 1.5-fold higher than those of placebo. Overall safety and tolerability were similar between treatment groups. Although there were numerically more episodes of heart failure in the etelcalcetide group, overall event rates were similar to rates observed in the EVOLVE trial. Initially, there were concerns that cinacalcet might lead to heart failure and sudden death owing to the effects of reduced serum calcium on myocardial contractility and the QT interval, respectively. However, rates of heart failure and sudden death were reduced in patients randomized to cinacalcet in the EVOLVE trial (Block, et al., 2017).

VI. CONCLUSION

Etelcalcetide is a novel calcimimetic agent that suppresses the secretion of PTH, binding to and activating the calcium-sensing receptor on the parathyroid gland. FDA approved etelcalcetide on february 2017 for SHPT in adults with chronic kidney disease on hemodialysis. Calcimimetics are a class of drugs that activate the parathyroid calcium-sensing receptor to inhibit PTH secretion. Cinacalcet better than etelcalcetide in reduction PTH level. The adverse effect not differ significanly between cinacalcet and etelcalcetide. Etelcalcetide is an add-on drug of calcimimetic in treatment SHPT. 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.

References

Block, G., Bushinsky, D., Cheng, S., J, C., Dehmel, B., Drueke, T., Chertow, G. (2017). Effect of Etelcalcetide vs Cinacalcet on Serum Parathyroid Hormone in Patients Receiving Hemodialysis With Secondary Hyperparathyroidism-A Randomized Clinical Trial. JAMA, 156-164.
FDA. (2017, March 3). Retrieved from http://www.accessdata.fda.gov/drugsatfda_docs

Goltzman, A., & Hendy, G. (2015). The calcium-sensing receptor in bone —mechanistic and therapeutic insights. *Nat. Rev. Endocrinol*, 1-10.

Hwang, E., Choi, B., & Oh, K.-H. (2015). Management of chronic kidney disease–mineral and bone disorder. *Kidney Res Clin Pract, 34*, 4-12.

Jeong, S., Kim, I.-W., & Oh, K.-H. H. (2016). Pharmacogenetic analysis of cinacalcet response in secondary hyperparathyroidism patients. *Drug Design, Development and Therapy*, *10*, 2211–2225.

Kasper, D., Fauci, Hauser, & Longo. (2015). *Harrison's Principles of Internal Medicine* (19th ed.). New York: McGraw-Hill Education.

KDIGO. (2013). KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Official Journal of the International Society of Nephrology*, *3*(1).

Mooro. (2016). *FDA Indicates Parsabiv for Kidney Disease Treatment Not Approved in Present Form*. Retrieved from CKDnews: https://ckdnews.com/2016/08/29/fda-amgens-chronic-kidney-disease-treatment-parsabiv-rejects

Sprague, S., Crwaford, P., & Melnick, J. (2016). Use of Extended-Release Calcifediol to Treat Secondary Hyperparathyroidism in Stages 3 and 4 Chronic Kidney Disease. *Am J Nephrol*, *44*, 316–325.

Subramanian, R., Zhu, X., Hock, B., Sloey, B., Wu, B., Wilson, S., . . . Skiles, G. (2016). Pharmacokinetics, Biotransformation, and Excretion of [14C]Etelcalcetide (AMG 416) Following a Single Microtracer Intravenous Dose in Patients with Chronic Kidney Don Hemodialysisisease . *Clin Pharmacokinet*, 1-14.

Watnick, S., & Dirkx, T. (2016). Kidney Disease. In M. Papadakis, S. McPhee, & M. Rabow (Eds.), *Current Medical Diagnosis and Treatment 2016* (pp. 898-937). New York : McGraw-Hill Education.

Widmaier, E. P., Raff, H., & Strang, K. T. (2014). *VANDER'S Human Physiology The Mechanisms of Body Function* (13th ed.). New York: McGraw-Hill.