A Review of Parsabiv™ (Etelcalcetide) for Secondary Hyperparathyroidism in Hemodialysis Patients

By: Lana Nesheiwat, BS, 2014 Pharm. D Candidate Class of 2018
FDU School of Pharmacy
230 Park Avenue M-SP1-01 Florham Park 07932
(602)-810-3433
lananesh@student.fdu.edu

Introduction

Secondary hyperparathyroidism (sHPT) is a chronic and serious disease characterized by increasing levels of parathyroid hormone (PTH) with low calcium levels in the blood. It occurs when patients cannot absorb enough calcium from the gut or in the context of kidney failure.[1] PTH helps control calcium, phosphorous, and vitamin D levels within the blood and bone. The excessive secretion of PTH causes more calcium to be taken from the bone.[2] Certain disease states that lead to hypocalcemia or cause an interference with the body's ability to excrete phosphate can result in sHPT. One of the main causes of sHPT is renal failure requiring hemodialysis.[1] This medical condition affects approximately two million people throughout the world who are receiving hemodialysis, including 468,000 people in the U.S. Approximately 88 percent of patients with stage 5 chronic kidney disease (CKD) receiving hemodialysis are likely to develop sHPT.[3] It is often a silent disease, initially, and individuals usually present asymptomatically. For that reason, it is frequently under-diagnosed and undertreated. The percentage of patients who fail to reach laboratory targets necessary for controlling sHPT has more than doubled in the last five years.

Standard of care thera[y for patients with sHPT includes the administration of phosphate binders and active-vitamin D analogs, such as calcitriol. In 2004, FDA approved Sensipar® (cinacalcet), the first calcimimetic for the treatment of sHPT in patients with CKD undergoing hemodialysis.[4] The drug is effective in reducing PTH, however, because of its oral route of administration, lack of compliance is a common problem in CKD patients who are taking a large quantity of medications on a regular basis.

Etelcalcetide is a new calcimimetic that was approved by the FDA in February 2017, and is marketed in the U.S as Parsabiv™ (Amgen, Thousand Oaks, CA).[5] Etelcalcetide is indicated

for the treatment of sHPT in adult patients with CKD on hemodialysis. It is the first therapy approved for this medical condition in 12 years and is the only calcimimetic on the market that can be administered intravenously three times a week at the end of the hemodialysis session.

Pharmacology and Pharmacokinetics

Etelcalcetide is a calcium-sensing receptor (CaSR) agonist found on the surface of the chief cells of the parathyroid gland. It is a synthetic peptide calcimimetic agent that allosterically modulates CaSR.[5] It does this by binding to the CaSR, thus enhancing the activation of the receptor by extracellular calcium. It reduces PTH secretion through binding and activation of the CaSR. Reduction in PTH levels in the body leads to a decrease in both serum calcium and phosphate.

***Absorption*:** Since this medication is administered intravenously, etelcalcetide has 100 percent bioavailability.

Distribution: Etelcalcetide has a volume of distribution at steady state of approximately 796 L, and is predominately bound to plasma albumin by reversible covalent binding. The ratio of blood-to-plasma [14C]-etelcalcetide concentrations is approximately 0.6.

Metabolism: Etelcalcetide is not metabolized by CYP450 enzymes. It is bio-transformed in blood by reversible di-sulfide exchange with endogenous thiols, which predominantly form conjugates with serum albumin.

Elimination: Elimination occurs primarily via the kidneys in patients with normal renal function, whereas dialysis is the predominant elimination pathway in CKD patients who require hemodialysis. In CKD patients on hemodialysis, etelcalcetide was removed with a hemodialysis clearance value of 7.66 L/hr. Because it is cleared by hemodialysis, the drug is administered after dialysis sessions.

Clinical Trials: Placebo-Controlled Phase 3 studies

FDA approval of etelcalcetide was mainly based on two 26-week, randomized placebo-controlled Phase 3 clinical trials in patients with sHPT. A total of 1,023 patients with moderate-to-severe secondary HPT (PTH > 400 pg/mL) on hemodialysis were randomized to receive either a starting dose of Parsabiv 5 mg intravenously or placebo three times a week, at the end of their dialysis sessions.[5] Participants continued their standard of care regimen of vitamin D, alone, or in addition to phosphate binders, as prescribed by their physicians over the course of the studies. To achieve a goal PTH level of less than or equal to 300 pg/mL, the dose of Parsabiv was titrated every 4 weeks for the first 16 weeks of the study. In both studies, the primary end point was the percentage of patients with a greater than 30% reduction in PTH levels from baseline to the efficacy assessment phase (EAP). The EAP was defined in both studies as the mean PTH levels inclusive of weeks 20 through 27. The secondary end points were the proportion of patients with a mean PTH of less than or equal to 300 pg/mL, percent change from baseline in PTH, corrected serum calcium, and phosphate levels.[5] During the EAP, the two clinical trials showed a greater than 30% reduction from baseline in mean serum PTH in a significantly higher proportion of patients receiving IV Parsabiv (77% in Study 1, 79 % in Study 2, respectively) compared to placebo (11% in both studies) with a $p < 0.001$. Furthermore, Parsabiv was superior to placebo for the secondary endpoints of reduction in mean PTH, corrected serum calcium, and serum phosphate levels from baseline to the end of study. In Study 1 and Study 2, 52% and 56% of patients, respectively, who were given IV Parsabiv achieved a serum PTH level of 300 pg/mL or less compared to placebo where only 5% of patients in Study 1 (and 6% of patients in Study 2) were able to achieve this target ($p < 0.001$).

Clinical Trials: Head-to Head Study Comparing IV Etelcalcetide vs. Oral Cinacalcet

A head-to-head, randomized, double-blind, 26-week clinical trial comparing IV etelcalcetide to placebo (n = 340) and oral cinacalcet to placebo (n=343) was carried out to determine the efficacy and safety of both calcimimetic agents in 683 patients receiving dialysis.[6] The inclusion criteria for this study were patients whose serum PTH was higher than 500 pg/mL and on standard care of therapy. One hundred sixty-four sites in the US, Canada, Europe, Russia, and New Zealand, were included. Etelcalcetide was administered intravenously 3 times per week and cinacalcet was given orally daily. The primary efficacy end point was non-inferiority of etelcalcetide to cinacalcet in achieving a greater than 30% reduction from baseline in mean pre-dialysis serum PTH during weeks 20-27, inclusive. Secondary end points were superiority of etelcalcetide over cinacalcet in achieving greater than 30% and 50% reduction in PTH levels, and self-reported gastrointestinal adverse events such as nausea or vomiting. The results showed that Etelcalcetide met its primary end point of non-inferiority to cinacalcet. The study results showed that approximately 68.2 % of patients who received IV etelcalcetide achieved a greater than 30% reduction of serum PTH compared to 57.7 % for oral cinacalcet - 95% CI of -17.5% to −3.5% and a $p < 0.001$ for noninferiority (See Table 1). The secondary endpoint of superiority of etelcalcetide in achieving a greater than 30% reduction compared to the oral calcimimetic was met as well ($p = 0.004$). In addition, the secondary endpoint of etelcalcetide achieving greater than a 50% reduction in serum PTH compared to cinacalcet was also proven (52.4%, 40.2%, respectively; $p = 0.001$). The most common side effect was decreased blood calcium in 68.9% of patients randomized to IV etelcalcetide and 59.8% in oral cinacalcet group. From these results, it can be concluded that in patients with moderate to severe sHPT receiving hemodialysis, the use of etelcalcetide was proven to be not only non-inferior, but also superior to cinacalcet in reducing

serum PTH over a 26-week period. This study was published in 2017 and is the only study that was conducted to assess the efficacy and safety comparing these two calcimimetic agents. Therefore, further clinical studies are necessary to further confirm these findings.

Table 1.

Description of Analysis	**Primary endpoint: non-inferiority of etelcalcetide to cinacalcet in achieving a > 30% reduction from baseline in mean pre-dialysis PTH during the Efficacy assessment period, defined as weeks 20-27, inclusive**		
	Treatment group	Oral Cinacalcet	IV Etelcalcetide
	Number of subjects	N = 343	N = 340
	Primary end point	57.7%	68.2 %
Description of Analysis	**secondary endpoint: superiority of etelcalcetide to cinacalcet in achieving > 50% reduction in PTH levels**		
	Treatment group	Oral Cinacalcet	IV Etelcalcetide
	Number of subjects	N = 343	N = 340
	Primary end point	40.2%	52.4%

Place of Therapy

Traditionally, most therapeutic regimens used to treat elevated PTH levels and control sHPT involved treatment with vitamin D sterols such as calcitriol or synthetic vitamin D analogues.[1]These standard-of-care medications have a role in reducing PTH levels, however, because they act by increasing GI absorption of calcium and phosphate, their use is complicated by increased calcium and phosphate levels in the blood. Contraindications of these agents include pre-existing hypercalcemia, and these agents carry a risk of vascular or metastatic calcification and toxicity from hypercalcemia, as well.[3] To address these issues, the FDA approved the first oral calcimimetic, cinacalcet, an alternative therapeutic drug to treat sHPT in those who are undergoing hemodialysis. Cinacalcet directly lowers PTH secretion by increasing the sensitivity of the CaSR to extracellular calcium, whereas vitamin D sterols inhibit the

synthesis and secretion of PTH.

Head-to-head clinical trials showed that IV etelcalcetide is superior to cinacalcet for sHPT patients on hemodialysis for two reasons - (1) it can be administered intravenously at the conclusion of a dialysis session, which ensures patient adherence, and (2) etelcalcetide is more effective in reducing serum PTH *versus* cinacalcet, despite full compliance. Of course, in the real world, adherence with an oral agent in the treatment of sHPT is very challenging since the average CKD patient with sHPT takes about 6-10 pills daily to control their medical conditions.[7]

To illustrate the challenges of patient adherence in this disease state, Ogna, V et.al conducted a prospective, randomized controlled open-label study in nine dialysis clinics in Switzerland. This study assessed whether an integrated care (IC) approach leads to improved therapeutic control of cinacalcet in patients with sHPT on hemodialysis compared to a usual care (UC) approach. To monitor adherence, the study employed a Medication Event Monitoring System (MEMS) for 6 months in both arms, followed by 3 months where no monitoring was performed. Intact PTH (iPTH) in the IC group decreased from a baseline of 417 ng/L to 339 ng/L after 6 months of monitoring (p-value =0.03). No significant reductions in iPTH were found in the UC group, 419 ng/L at baseline and 436 ng/L after 6 months of using MEMS. At 6 months, approximately 84% of the IC group achieved iPTH levels within the KDIGO guidelines (PTH <300 pg/mL) compared to 55% in the UC group (p-value=0.04).[1, 8] During the 3 months that monitoring was discontinued in both groups, iPTH levels rose slightly in the IC group and the UC group (p = 0.2, p = 1, respectively). This study reinforces the compliance benefits of IV etelcalcetide immediately post-hemodialysis as compared to the utility of once daily oral cincalcet.[7]

Conclusion

The IV formulation of etelcalcetide given 3 times weekly was specifically designed to be delivered at the conclusion of hemodialysis, which increases convenience and ensures compliance. sHPT is often not controlled because of poor drug adherence.[7] Intravenous etelcalcetide is a proven effective and highly convenient treatment for sHPT that can enable healthcare providers to maximize therapeutic results CKD patients.

References

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