IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 22, Issue 9 Ser.3 (September. 2023), PP 53-55
www.iosrjournals.org

The Effect Of Etelcalcetide In Bulgarian Patients On Hemodialysis Treatment With SHPT

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Abstract.
Patients suffering from ESRD (End-stage renal disease) have reduced renal function, which alters the metabolism of calcium, phosphorus and vitamin D. These changes often lead to SHPT (secondary hyperparathyroidism), which is characterized by elevated levels of PTH and is often associated with hyperplasia of the parathyroid glands (Cunningham, et al. 2011; Goodman and Quarles 2008; Joy, et al. 2007; Ruda, et al. 2004). This chronic and progressive disease develops early in the course of CKD, worsens with reduced renal function, and affects most patients with CKD at an advanced stage.
Etelcalcetide is the only calcimimetic therapy for intravenous (i.v.) administration. In addition, etelcalcetide is an allosteric activator of CaSR that binds directly to the extracellular medium. Etelcalcetide is a calcimimetic that can achieve clinically significant and sustained reductions in PTH, calcium and phosphorus levels. In addition to this i.v. method of administration of etelcalcetide also addressed some of the non-clinical reasons why patients did not follow or discontinue other SHPT treatments. In this way, etelcalcetide can provide a treatment that addresses the unmet medical need of patients with CKD and CKD.

Key words : *hemodialysis patients; secondary hyperparathyroidism; Parsabiv (etelcalcetide)*

Date of Submission: 03-09-2023 Date of Acceptance: 13-09-2023

I. Introduction

Patients with CKD on haemodialysis treatment are at risk of complications such as anaemia, electrolyte disturbances (e.g. hyperkalaemia, hyperphosphataemia) and CKD-BMD, including secondary hyperparathyroidism, changes in vitamin D activation and renal osteodystrophy.

Secondary hyperparathyroidism (SHPT) is a complication of chronic kidney disease and end-stage renal disease that results in defective calcium (Ca) and phosphorus (P) homeostasis. In SHPT, excess amounts of parathyroid hormone (PTH) are continuously released from the enlarged parathyroid glands, thereby increasing blood PTH levels, and elevated concentrations of circulating PTH are associated with abnormalities in serum Ca, P, and FGF-23 (Cunningham et al., 2011). These biochemical changes worsen the progression of ICH and are associated with abnormal bone histology, increased risk of fractures, vascular and soft tissue calcification and increased mortality (Joy et al., 2007).

Control of elevated serum phosphorus, calcium levels, restoration of vitamin D levels and direct targeting to suppress PTH production remain targets for effective treatment of CKD-BMD.

Multiple classes of drugs including phosphate binders, vitamin D analogues and calcimimetics have been developed to directly or indirectly influence markers of CKD-BMD. In particular, within the class of calcimimetics - Cinacalcet (Sensipar, Amgen, Inc.) and etelcalcetide (Parsabiv, Amgen, Inc.) are two drugs available in the EU.

Etelcalcetide, an intravenous (i.v.) calcimimetic agent, received FDA approval in 2017 for the treatment of secondary hyperparathyroidism in adult patients with CKD on hemodialysis. Parsabiv is a synthetic peptide that allosterically activates the calcium-sensitive receptor (CaSR) in the extracellular domain of the receptor located on the principal cells of the parathyroid gland. By binding to CaSR, it enhances receptor activation by extracellular calcium, which results in decreased PTH secretion. In contrast to existing treatments, etelcalcetide can be administered to patients with chronic kidney disease intermittently and precisely at the end of each hemodialysis session, and blood levels of etelcalcetide remain constant until the next hemodialysis session, as etelcalcetide is cleared mainly by dialysis (Harada et al., 2017).

II. Material and methods

18 patients (12 females and 6 males) on hemodialysis treatment with Parsabiv i.v. were followed up for 12 months in the Clinic of Nephrology and Dialysis at the University Hospital "St. Marina" Varna.

Patients underwent haemodialysis 3 times a week for 4 hours - bicarbonate dialysis procedure. Their ages ranged from 44 - 68 years. The study patients had high baseline Ca, P and PTH values before starting their

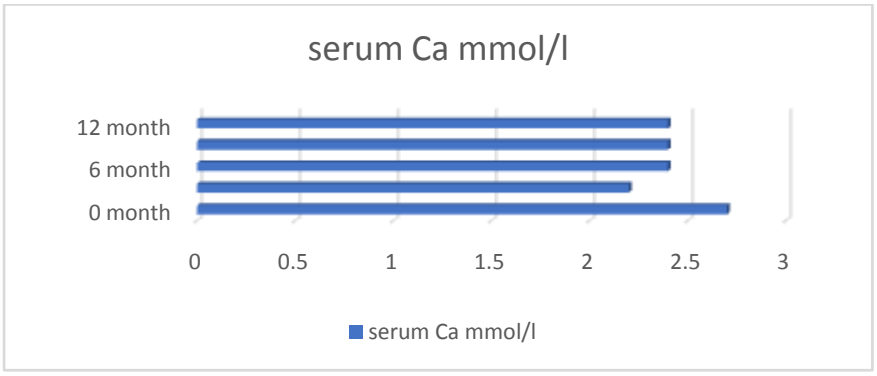
treatment.Parsabiv was administered at a dose of 12.5 mg/week and was given intravenously at the end of each dialysis session.

Ca and P levels were measured monthly and iPTH levels were measured every 3 months. Serum calcium concentrations were quantified by the automated Arsenazo III photometric method, and those of inorganic phosphorus by the automated phosphomolybdate/UV method, adapted on a fully automatic ADVIA 1800 biochemical analyzer, Siemens. Serum concentrations of modified intact parathyroid hormone were quantified by the two-step automated chemiluminescent immunoassay (CLIA) using two polyclonal antibodies as an application of LIAISON/ DIASORIN.

III. Results and discussion

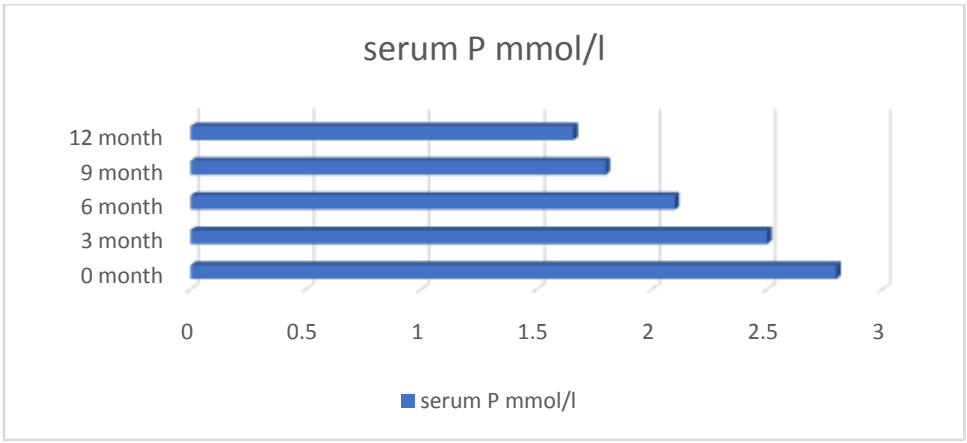
The present analysis of the results obtained is based on the comparison of Ca, P and iPTH values every 3 months for a period of 12 months from the initiation of Parsabiv 12.5mg/week.

Figure1. Comparison of mean calcium values before Parsabiv treatment and every 3 months of Parsabiv 12.5mg/week i.v. treatment.



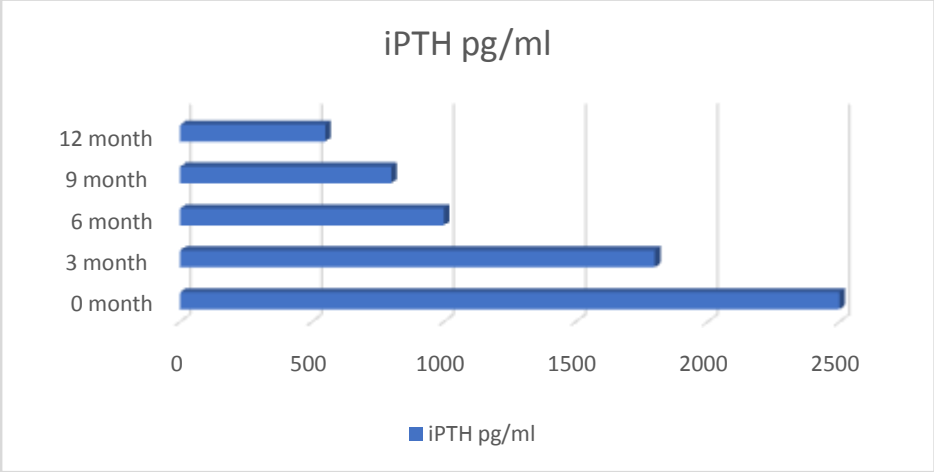
From the results obtained, it was found that after the third month of treatment with Parsabiv, serum calcium concentrations decreased in 14 patients and treatment with calcium carbonate 600mg 2x600 mg/day was also started and adjustment was made in dialysis solution of patients from A11 - 1.25 Ca2+ to A13.0 - 1.50 Ca2+ twice a week and A13.1 - 1.75 Ca2+ once a week.

Table 2 Comparison of mean phosphorus values before treatment with Parsabiv and every 3 months of treatment with Parsabiv 12.5mg/week i.v.



At the third month of Parsabiv treatment, patients were also started on Sevelamer 800mg 3x1tb/day p.os. After the sixth month, 80% of patients achieved normal serum phosphorus values.

Table 3 Comparison of mean PTH values before treatment with Parsabiv and every 3 months of treatment with Parsabiv 12.5mg/week i.v.



From the results obtained, it was found that more than 50% of patients on etelcalcetide (Parsabiv) achieved more than 30% reduction in PTH in the first trimester of treatment and after 12 months more than 70% of patients achieved more than 60% reduction in PTH.

In patients with CKD, current guidelines recommend controlling PTH levels so that they remain below 600 pg/mL to reduce the potential clinical consequences of IHT as well as the accompanying disturbances in calcium and phosphorus levels (KDIGO 2009).

IV. Conclusion

SHPT is a chronic disease that develops early in CKD when decreased kidney function alters calcium, phosphorus and vitamin D levels. SHPT worsens with worsening renal function and is prevalent in the dialysis population, characterized by elevated parathyroid hormone levels.

Parsabiv (etelcalcetide) represents another option for controlling elevated parathyroid hormone levels in the treatment of CKD-BMD in hemodialysis patients. The availability of a parenteral formulation offsets the need to administer another oral medication for these patients, and post-dialysis seance administration ensures compliance. It has demonstrated comparable efficacy to cinacalcet in clinical trials, with reduced potential for drug-drug interactions and a favorable safety profile.

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