Cinacalcet hydrochloride for the management of secondary hyperparathyroidism in patients with end stage kidney disease on maintenance dialysis therapy.

Author: Dr Indranil Dasgupta on behalf of **British Renal Society**.

Cinacalcet in the management of renal bone disease: The current evidence.

Secondary hyperparathyroidism (SHPT) is a common complication of chronic kidney disease (CKD); the prevalence is particularly high in dialysis patients. Clinical manifestations of SHPT include renal osteodystrophy and vascular calcification, which probably contributes to the high cardiovascular morbidity and mortality observed in this group of patients. A number of recent studies have shown association between cardiovascular mortality and high Ca x P product, serum parathyroid hormone (PTH) and phosphate levels. Current therapy for SHPT includes the use of phosphate binders and vitamins D with a view to suppress PTH secretion. However, hypercalcaemia and high Ca x P product often limit the use of these drugs. The UK Renal Registry data show that serum PTH level is above the target range in about 50% of patients[4].

The calcimimetic Cinacalcet HCL is a new treatment option for SHPT that has been shown to reduce PTH while simultaneously lowering serum calcium and phosphorus in study subjects undergoing haemodialysis. Cinacalcet acts upon the calcium sensing receptor (CaR) located on the chief cells of the parathyroid glands. This CaR is the principal regulator of PTH secretion and is, therefore, an ideal target for therapies to treat SHPT. Recent clinical trials have clearly shown that cinacalcet lowers PTH and improves calcium-phosphorus homeostasis in patients on haemodialysis with uncontrolled SHPT.

Four randomised control trials (n=890, 2 phase II and 2 phase III) evaluated the efficacy of cinacalcet (in addition to standard therapy with vitamin D and phosphate binders) compared with placebo (+ standard therapy) in dialysis patients with SHPT. The main outcome measures were proportion of patients achieving ≥ 30% reduction in serum PTH, proportion achieving PTH level ≤ 250 ng/l, and reduction in Ca X P product[5,6,7]. In all trials significantly greater number of patients treated with cinacalcet achieved the PTH targets – 30% reduction in serum PTH (38 to 60% vs. 8 to 23% for placebo, $p \leq 0.01$) and

PTH level $\leq$ 250 ng/l (43% vs. 5 to 20% for placebo, $p \leq 0.05$). Another more recent study involving 395 patients on haemodialysis (n = 349) and peritoneal dialysis (n = 46) made similar observations[8].

None of these studies looked directly at clinical outcomes like improvement in bone pain, reduction of fracture risk, parathyroidectomies, cardiovascular risk reduction, hospitalisations and mortality. However, a combined post-hoc analysis of 4 similarly designed randomised, double blind, placebo controlled trials enrolling 1184 subjects with uncontrolled secondary hypertension has shown significant reductions in the risk of parathyroidectomy, fracture and hospitalisation due to cardiovascular disease. There were also improvements in self-reported physical function and diminished pain[9]. Another secondary analysis[10] of 3 placebo controlled trials (n = 1136) showed that in subjects with SHPT on haemodialysis cinacalcet facilitated achievement of NKF-K/DOQI recommended targets[11] for PTH, Ca, P, and Ca x P targets.

Licensed indications in the UK

Cinacalcet is a licensed calcimimetic compound for the treatment of SHPT in patients with end stage renal disease (ESRD) on maintenance dialysis therapy, and may be used as part of a therapeutic regimen including phosphate binders and/or Vitamin D sterols, as appropriate. It is also licensed for use in hypercalcaemia in parathyroid carcinoma.

Dosage and Administration

It is a film coated tablet available in three strength (30mg, 60mg, 90mg) and is taken with food or shortly after a meal once a day.

DOSE: IN ADULT over 18 years, 30 mg once daily, adjusted every 2–4 weeks to max. 180 mg daily to achieve a target PTH level of 150 to 300 ng/l.

Side Effects

The most commonly reported adverse events from the clinical trials were nausea and vomiting. Less common side effects reported were: anorexia, dizziness, paraesthesia, rash, myalgia, asthenia, hypocalcaemia, reduced testosterone levels and seizures.

Cost

At current prices, one year's treatment with cinacalcet (30 to 180 mg daily) costs between £1200 and £8400.

Advantages of cinacalcet therapy:

Direct inhibitor PTH secretion.

Effective therapy for SHPT in haemodialysis patients.

Reduces serum calcium, phosphate and Ca X P product.

Disadvantages of cinacalcet therapy:

Cost – expensive therapy.

Likely to be long-term and hence unlikely to replace parathyroidectomy altogether.

Requires close monitoring of serum Ca, P and PTH levels.

Not suitable for use in the primary care.

Lack of good outcome studies.

Recommendations:

In the light of the evidence available currently, the lack of studies directly looking at clinical outcomes, and the high cost of treatment which is likely to be long-term the **British Renal Society** feel that the use of cinacalcet should be restricted to:

1. **Severe secondary hyperparathyroidism (PTH > 800 ng/l) either resistant to standard therapy or the standard therapy is associated with high serum Ca or Ca x P product <u>where the patient is at a high risk for parathyroidectomy.</u> (Long-term treatment)**
2. **Severe secondary hyperparathyroidism (PTH > 800 ng/l) resistant to standard therapy where the patient is awaiting live kidney transplantation. (Short-term treatment until kidney transplantation)**
3. **Severe secondary hyperparathyroidism where the patient suffers from calciphylaxis awaiting parathyroidectomy.**
   (Short-term treatment until parathyroidectomy)

References

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