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ON BEHALF OF THE RENAL ASSOCIATION

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Cinacalcet HCl for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy

Background

Cinacalcet has been approved for treatment of secondary hyperparathyroidism in patients with chronic kidney disease on haemodialysis. It is also approved for the treatment of hypercalcaemia associated with parathyroid carcinoma, a rare cancer that causes significant elevations in serum calcium levels.

Cinacalcet is the only available drug in a class of new compounds known as the calcimimetics. By it's unique mode of action cinacalcet directly lowers parathyroid hormone (PTH) concentrations by increasing the sensitivity of the calcium sensing receptors of the parathyroid glands to extracellular calcium.

Hyperparathyroidism is a complication of chronic kidney disease which affects 70-90% of patients[1] even when managed by currently available treatments viz. diet, dialysis, and medication. It is associated with an increased morbidity and mortality in dialysis patients. Large cross sectional epidemiological studies have demonstrated an increased mortality rate in dialysis patients with higher serum PTH, phosphorous, calcium and calcium x phosphate (Ca x P) products[2-4]. If untreated or unresponsive to treatment hyperparathyroidism leads to progressive bone destruction and multiple fractures; spinal and long bone fractures in renal failure are a threat to both life and mobility.

The control of the parathyroid gland function is complex. Derangements in calcium, phosphate and vitamin D all contribute to the development of secondary hyperparathyroidism in renal failure. The reduced production of active vitamin D by the kidney causes reduced calcium absorption from the gastrointestinal tract and also has a direct effect on the parathyroid glands to drive up PTH. In addition failure of the kidneys to excrete phosphate results in hyperphosphataemia, which has the direct effect of stimulating PTH production.

The Ca x P product is a measure of the amount of calcium and phosphorus in the blood, and when elevated, causes harmful deposition of calcium in various parts of the body including soft tissues, joints and blood vessels (including the coronary arteries[5]). This must also be taken into account when managing secondary hyperparathyroidism.

Current therapy and effectiveness

The management of secondary hyperparathyroidism in dialysis patients is difficult with the current treatment available. Only 66% of patients achieve a PTH below the recommended upper level in the Renal Association Standards published in 2002[6], 63% of patients achieve the target for calcium and 64% the Kidney Disease Outcome and Quality Initiatives (KDOQI) American Standards published in 2003[7] recommendations for Ca x P product.. Data from Dialysis Outcomes and Practice Patterns Study (DOPPS)[8] has shown that less than 10% of patients achieve all (KDOQI) targets relating to bone and mineral metabolism[7].

The 7th annual report of the UK Renal Registry[9] shows a year on year improvement in serum phosphate control however only 59% of haemodialysis patients achieve the Renal Association standard of <1.8 mmol/L. The Renal Registry also shows there is a wide variation between units in controlling hyperparathyroidism. For example with serum phosphorus control (one of the main drivers for developing and perpetuating secondary hyperparathyroidism) the range is from 76% to 39% of patients achieving target. Investigation at the best unit indicates that a dietetic prescribing team with support from a pharmacist was largely responsible for this. Despite optimal current treatment though, a large number of patients continue to have poorly controlled hyperparathyroidism while on dialysis.

Current medical interventions available include dietetic advice regarding dietary phosphate intake the use of phosphate binders vitamin D sterols and changing the dialysis prescription.

The calcium containing phosphate binders, calcium carbonate and calcium acetate are associated with an increase in Ca x P product and metastatic calcification. These are by far the commonest binders used in the UK and world-wide. Aluminium containing binders are effective but associated with significant toxicity if used long-term so these are now infrequently used. Newer phosphate binders include sevelamer and lanthanum carbonate.

There are significant problems with patient non-compliance with taking phosphate binders. These include having to take the medication at meal times, taste, large pill size and tablet burden.

It is possible to increase phosphate loss in the dialysate by increasing the amount of dialysis delivered The majority of patients receive 4 hours of dialysis three times weekly. A small number of centres in the world where slow prolonged (8 hours plus) dialysis or daily dialysis is performed improves phosphate clearance[10]. This approach is not feasible in the UK with the limited dialysis facilities available.

The main vitamin D sterols prescribed in UK are oral calcitriol or alphacalcidol. Though effective at suppressing PTH, side effects include hypercalcaemia, hyperphosphataemia, over-suppression of PTH and adynamic bone disease. In order to minimise these side effects intermittent oral and intravenous preparations are sometimes used.

Another vitamin D sterol which directly suppress the parathyroid gland with less of a calcaemic effect is Paracalcitol. This vitamin D analogue was approved for treatment of hyperparathyroidism in chronic renal failure in 1998 in the US and has recently obtained a license in the UK.

Failed medical therapy of hyperparathyroidism will necessitate an in-patient admission for parathyroidectomy. Parathyroidectomy, partial or total, in renal failure patients has a much higher incidence of post-operative problems and complications in renal failure compared to routine endocrine parathyroid surgery[11]. Stabilisation of post-operative calcium with a combination of vitamin D and calcium supplementation may take many months and may never be achieved in all patients. In addition all glands may not be located and further, frequently more difficult surgery is required at a later date.

Therapeutic effectiveness of Cinacalcet

In randomised, double-blind, placebo-controlled clinical studies in over 1000 patients cinacalcet is clearly effective in controlling secondary hyperparathyroidism in haemodialysis patients. Three, 6-month, randomised, double-blind, placebo-controlled clinical studies were conducted in haemodialysis patients with uncontrolled secondary hyperparathyroidism (n=1136)[12-14]. Sixty-six percent of patients were receiving vitamin D sterols at study entry, and > 90% were receiving phosphate binders. Significant reductions in iPTH, Ca x P product, calcium, and phosphorus were observed in the cinacalcet (plus standard care) treated patients compared with placebo (plus standard care) treated patients, and the results were consistent across the 3 studies. In each of the studies, the primary endpoint (proportion of patients with an iPTH ≤ 26.5 pmol/l) was achieved by 41%, 46%, and 35% of patients receiving cinacalcet, compared with 4%, 7%, and 6% of patients receiving placebo. Approximately 60% of cinacalcet treated patients achieved a ≥ 30% reduction in iPTH levels, and this effect was consistent across a range of baseline iPTH levels. The mean reductions in serum Ca x P product, calcium and phosphorus were 14%, 7% and 8%, respectively. Reductions in iPTH and Ca x P product were maintained for up to 12 months of treatment [14]. Cinacalcet decreased iPTH and Ca x P product, calcium and phosphorus levels regardless of baseline iPTH or Ca x P product level, dialysis modality (PD versus HD), duration of dialysis, and whether or not vitamin D sterols were administered.

Potential impact of Cinacalcet on managing secondary hyperparathyroidism.

Cinacalcet reduces the numbers of patients requiring a parathyroidectomy. Post-hoc analysis has indicated a reduction in the parathyroidectomy rate from 4.1 to 0.3 events/100 patient years [15]. A post-hoc analysis from the three trials mentioned above has also demonstrated significant reductions in the risk of fractures[15]. Experience with the use of cinacalcet indicate a reduction in the requirement for the use of phosphate binders (calcium carbonate/calcium acetate/sevelamer) though the extent of this is difficult to quantitate from the published reports. There are no published controlled data analysing improvement in symptoms or quality of life in patients treated with cinacalcet treatment yet published. The implication is that achievement of the KDOQI and Renal Association standards will reduce morbidity, hospital admissions and mortality. The

impact of cinacalcet on long term (5-10 years) morbidity and mortality is obviously unknown at present.

Who should get it?

Treatment with cinacalcet should be considered in haemodialysis patients with secondary hyperparathyroidism where the condition is not controlled by currently available treatment.

The use of cinacalcet should be part of an overall strategy for prevention and treatment of secondary hyperparathyroidism :-

1. Dialysis units should have the necessary staffing to allow proper counselling and follow up of patients by renal trained dieticians to optimise the management of renal bone disease and disorders relating to mineral metabolism.
2. Patients must be educated with regard to diet and the correct use of phosphate binders and compliance with treatment monitored.
3. Dialysis adequacy should be assessed by conventional methods and the dialysis prescription optimised.
4. It is reasonable to wait for 6 months after the start of dialysis before considering treatment unless the clinical need is considered urgent.

Biochemical measures that should serve as criteria for instituting treatment with cinacalcet should be: persistent (> 6 months) elevation in parathyroid hormone, calcium, phosphate and Ca x P product (above Renal Association Standards) despite compliance with maximal medical therapy. The Renal Association Standards regarding bone and mineral metabolism are currently being revised and will now also include a standard for Ca x P product. The standards are likely to be broadly similar to the evidence based KDOQI guidelines (serum calcium of >2.54 mmol/L., serum phosphorus > 1.8 mmol/L., calcium x phosphate product > 4.4 and an intact assay PTH >300pg/ml).

It is likely that the PTH target ranges will require revision with the introduction of new PTH assays. There is evidence that the current most commonly used “intact” PTH assays in addition to detecting the 1-84 aminoacid peptide also measure a 7-84 fragment of PTH (cyclase inactive PTH or CIP) which accumulates in chronic kidney disease. The identification of this inhibitory fragment has led to new assays being developed utilizing an antibody to the 1-7 region of the molecule combined with an antibody to the 39-84 region thus eliminating cross-reactivity from 7-84 fragments. The 1-84 molecule has been termed cyclase activating PTH (CAP) or “whole molecule” PTH. The reference range for these new assays is 7 – 36 ng/L. (about half that for intact PTH). Target ranges for “whole molecule” PTH are not yet established.

An alternative to treatment with cinacalcet is surgical parathyroidectomy. Parathyroidectomy in patients with chronic kidney disease has generally been reserved for patients with severe autonomous hyperparathyroidism. Usually iPTH blood levels are greater than 1000 pg/ml and by this stage bone disease is advanced and metastatic calcification is present. It is clear that earlier treatment with cinacalcet will prevent many patients developing such severe disease. There are no randomised trials

comparing parathyroidectomy with cinacalcet in the management of secondary hyperparathyroidism. With the increasing numbers of elderly patients with additional co-morbid conditions requiring dialysis any surgery will be associated with a higher morbidity and mortality. A greater number of patients will also be medically unfit for surgery. Informed patient choice should also be factored into the decision when considering medical (cinacalcet) or surgical intervention.

It would therefore be appropriate to use cinacalcet for the following indications in dialysis patients with autonomous hyperparathyroidism:-

1. Patients not fit for parathyroid surgery when this is indicated or in whom parathyroid surgery should be postponed.

2. Patients in whom recurrent hyperparathyroidism has developed after previous parathyroid surgery.

3. Patients with autonomous hyperparathyroidism in whom Renal Association Guidelines on bone and mineral metabolism are not being achieved despite optimal use of standard therapy.

4. Calciphlaxis is a rare but life-threatening condition of skin and soft tissue necrosis caused by calcium phosphate deposition in the small blood vessels of the skin and soft tissues. Cinacalcet should be used to treat this condition provided the patient is not hypocalcaemic

There will be a proportion of patients who will have such significant co-morbidity and limited life expectancy on dialysis that the physician may choose to ignore asymptomatic hyperparathyroism.

With the use of cinacalcet more haemodialysis patients will avoid fractures and parathyroid surgery and achieve Renal Association Standards for calcium, phosphate and calcium phosphate product reducing ectopic calcification. This new unique therapeutic agent will significantly improve the management of hyperparathyroidism in patients on haemodialysis and should be made available

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