

Use of calcimimetic drugs

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GUIDELINES

- a. Treatment with cinacalcet reduces levels of parathyroid hormone (PTH), calcium, phosphate and the calcium x phosphate product in patients with secondary hyperparathyroidism (SHPT) due to dialysis-dependent chronic kidney disease (CKD). (Level II evidence)
- b. Treatment with cinacalcet is not reported to influence requirements for standard drug therapy of SHPT. However, a greater proportion of patients treated with the addition of cinacalcet achieve K/DOQI and CARI target levels of PTH, calcium, phosphate and the calcium x phosphate product. (Level II evidence)
- c. When using cinacalcet, patients on dialysis with mild or moderate SHPT are more likely to achieve target levels of PTH, calcium, phosphate and the calcium x phosphate product than patients with severe SHPT. (Level II evidence)
- d. Rates of treatment withdrawal and the incidence of nausea and vomiting are higher for cinacalcet than for placebo. (Level II evidence)

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

- The use of cinacalcet in patients on dialysis is associated with a reduction in bone turnover and bone marrow fibrosis. (Level III evidence)
- Cinacalcet should not be used in patients on dialysis with intact-PTH levels below the target range (Opinion). The use of cinacalcet may be associated with development of adynamic bone disease when iPTH values are < 10.6 pmol/L (< 100 pg/mL). (Level III evidence)
- Cinacalcet therapy of SHPT may reduce rates of parathyroidectomy and fracture but has not been shown to influence hospitalisation, cardiovascular mortality, all-cause mortality or quality of life. (Post-hoc analysis of Level II evidence)

- **A therapeutic trial of cinacalcet is warranted for dialysis-dependent patients with SHPT when sustained levels of iPTH and the calcium x phosphate product remain above target levels despite optimal standard therapy. (Opinion)**
- **Parathyroidectomy should be considered for patients given a therapeutic trial of cinacalcet who do not achieve target levels of PTH, calcium, phosphate or the calcium x phosphate product. In particular, parathyroidectomy should be considered for patients with sustained levels of iPTH > 85 pmol/L (> 800 pg/mL), or sustained levels of iPTH > 50 pmol/L (> 470 pg/mL) in addition to levels of corrected serum calcium, phosphate or the calcium x phosphate product above the target ranges. (Opinion)**
- **Cinacalcet should be available for use in patients who require but are medically unfit for parathyroidectomy, or who are waiting for elective parathyroidectomy. (Opinion)**

BACKGROUND

The development of SHPT commonly accompanies declining glomerular filtration rates in patients with CKD. Progressive SHPT can increase bone turnover and reduce bone architectural integrity, can adversely influence haematopoiesis and may increase levels of serum calcium, phosphate and the calcium x phosphate product. Severe SHPT is likely to have an adverse impact on a variety of other organ systems.

Standard management of SHPT includes the use of calcium salts, calcitriol or vitamin D analogues, phosphate-lowering drugs and parathyroidectomy. However, many patients fail to meet biochemical targets suggested by CARI or the K/DOQI bone guidelines using standard medical therapy (Young et al 2005, Young et al 2004a). These patients are at increased risk of high turnover renal osteodystrophy and association studies suggest an increased risk of cardiovascular mortality when levels of serum calcium, phosphate, the calcium x phosphate product and adjusted PTH are above the suggested CARI or K/DOQI target ranges (Marco et al 2003, Block et al 2004). Limited prospective data suggests that achievement of target values for phosphate and the calcium x phosphate product may reduce cardiovascular morbidity and all cause mortality (Jaar et al 2004, Young Chang et al 2004).

The calcium sensing receptor (CaR) is a G-protein-coupled receptor, which recognises extracellular ionised calcium as its physiological ligand. Calcimimetics, including NPS R-467, NPS R-568 and cinacalcet HCl, are synthetic small organic compounds that bind to the transmembrane region of the CaR and act as positive allosteric modulators, shifting the calcium set-point of PTH to the left and leading to reduced PTH release across a wide range of ionised calcium concentrations. The introduction of the calcimimetic cinacalcet HCl provides a novel therapeutic intervention in the management of SHPT.

These calcimimetic guidelines and Suggestions for Clinical Care aim to assess the therapeutic role of cinacalcet in the following areas, based on data available at the search date (May 2005):

- the ability of cinacalcet to significantly reduce levels of PTH, calcium, phosphate and the calcium x phosphate product and the achievement of biochemical targets suggested by the CARI and K/DOQI bone guidelines;
- the effectiveness of cinacalcet with increasing severity of SHPT;
- whether cinacalcet use alters the use of standard therapy;
- whether differences in patient-level outcome have been reported for cinacalcet versus standard therapy of SHPT;
- the effects of cinacalcet treatment on bone histomorphometry, bone mineral density, fracture or surrogate endpoints of renal bone disease;
- the effects of cinacalcet treatment on rates of parathyroidectomy, hospitalisation, cardiovascular or all-cause mortality or surrogate endpoints of cardiovascular disease;
- the effects of cinacalcet treatment on quality of life;
- the role of cinacalcet versus standard medical or surgical treatment of SHPT, based on studies published at the time of writing; and
- the risk of adverse side effects with cinacalcet.

SEARCH STRATEGY

Databases searched: Medline, Embase, the Cochrane Controlled Trials Register and conference proceedings were searched for clinical trials of calcimimetics in patients with chronic kidney disease, using the terms calcimimetics, cinacalcet HC1, AMG 073 and R-568. The Cochrane Collaboration search strategy was used to identify randomised controlled trials (RCTs) of calcimimetics against placebo or other agents. Searches were conducted for clinical trials of calcimimetics and secondary hyperparathyroidism, renal osteodystrophy, bone histomorphometry, fracture, bone mineral density, calcium, phosphate, the calcium x phosphate product, parathyroid hormone, parathyroidectomy, cardiovascular disease, hospital admission, mortality, quality of life and adverse side effects. In addition, Amgen Australia forwarded a list of all peer-reviewed publications and abstracts available in their database.

Latest search date: May 2005.

WHAT IS THE EVIDENCE?

Comments on the methodological quality of the included RCTs are found in Table 1 (Appendix).

Guidelines:

How effective is treatment with cinacalcet in achieving significant reductions in levels of PTH, calcium, phosphate and the calcium x phosphate product?

(Guideline a)

How effective is treatment with cinacalcet in achieving K/DOQI and CARI biochemical targets? (Guideline b)

Goodman et al (2002) reported 2 short-term dose-finding studies with small patient numbers. The first assessed biochemical responses to a single oral dose of cinacalcet or placebo. The second assessed biochemical responses during an 8-day study, in which 23 patients took cinacalcet at 10, 25 or 50 mg doses and 7 took placebo. In the 8-day study, patients taking cinacalcet were reported to have lower levels of PTH ($P = 0.05$), calcium, phosphate and the calcium x phosphate product.

Quarles et al (2003) reported a Phase 2 study that included 71 patients, of whom 36 were treated with cinacalcet and 35 with placebo. The study was conducted over 18 weeks with cinacalcet doses ranging from 25-100 mg/day. Compared with placebo, levels of iPTH and calcium reduced significantly ($P \leq 0.001$), as did the calcium x phosphate product ($P < 0.05$). More patients on cinacalcet achieved $> 30\%$ reduction in levels of PTH ($P \leq 0.01$) or PTH levels < 26.5 pmol/L (250 pg/mL) [$P < 0.05$].

Lindberg et al (2003) reported a Phase 2 study that included 78 subjects on haemodialysis with 39 assigned to cinacalcet and 39 to placebo. This study was conducted over 18 weeks and cinacalcet doses were titrated from 10 to 50 mg/day. Baseline iPTH levels were > 31.8 pmol/L (300 pg/mL). Compared with placebo, levels of iPTH, calcium and the calcium x phosphate product reduced significantly ($P \leq 0.001$). More patients on cinacalcet achieved $> 30\%$ reduction in PTH levels ($P \leq 0.01$) or PTH levels < 26.5 pmol/L (250 pg/mL) [$P \leq 0.01$].

Block et al (2004a) reported a study that combined results of two Phase 3 studies carried out in North America, Europe and Australia. Patients were on haemodialysis and continued their standard therapy. Baseline levels of iPTH were > 31.8 pmol/L (300 pg/mL) on 3 measures over 30 days, but no more than 20% of patients were entered with PTH > 84.8 pmol/L (800 pg/mL). The total number of patients was 741, of whom 371 were treated with cinacalcet and 370 with placebo. The study was conducted over 26 weeks. This consisted of a 12-week dose titration period, in which daily doses were increased from 60 mg to 90 mg, 120 mg or 180 mg if PTH was > 21.2 pmol/L (200 pg/mL) and patients were not hypocalcaemic. This was followed by a 14-week efficacy period. The 26-week treatment protocol was completed by 68% of patients taking cinacalcet and 78% of those taking placebo. Compared with patients taking placebo, patients taking cinacalcet were reported to have significant reductions in levels of PTH (intact and bio-intact), calcium (7%), phosphate (8%), the calcium x phosphate product (15%) ($P \leq 0.001$ for each) and bone specific alkaline phosphatase. More patients on cinacalcet achieved $> 30\%$ reduction of PTH levels. A limitation is that 27% of subjects did not complete the study

Lindberg et al (2005) reported a Phase 3 study that included 395 patients on haemodialysis and peritoneal dialysis. Of the 349 patients on haemodialysis, 260 were randomised to cinacalcet and 89 to placebo. Of the 46 patients on peritoneal dialysis, 34 were randomised to cinacalcet and 12 to placebo. The study was conducted over 26 weeks with doses titrated from 30 to 180 mg/day. Cinacalcet was reported to have similar efficacy for haemodialysis and peritoneal dialysis patients. Compared with placebo, patients treated with cinacalcet had reduced levels of iPTH, calcium, the calcium x phosphate product, PTH reduction $> 30\%$ and PTH reduction to < 31.8 pmol/L (300 pg/mL) [$P \leq 0.001$] and phosphate ($P < 0.05$). A limitation is that 26% of patients did not complete the study.

Moe et al (2005) reported a secondary analysis of the three Phase 3 studies carried out in North America, Europe and Australia reported by Block and Lindberg (Block et al 2004b, Lindberg et al 2005). At entry, the number of patients with levels of PTH over 85 pmol/L (800 pg/mL) was restricted to 20%. The total number of patients was 1136 of which 665 were treated with cinacalcet and 471 with placebo. The studies comprised 12- or 16-week dose titration periods and 10- or 14-week drug evaluation phases. Titration continued until a dose of 180 mg was reached or the level of iPTH was < 21.2 pmol/L (200 pg/mL). Dosing stopped or was reduced if iPTH levels fell to < 10.6 pmol/L (100 pg/mL) or symptoms developed that were likely to be related to hypocalcaemia. Patients continued standard therapy including vitamin D. Reductions were reported for levels of PTH, calcium, phosphate and the calcium x phosphate product, with significantly more patients achieving K/DOQI biochemical bone targets ($P \leq 0.001$ for each). Compared with placebo, more patients on cinacalcet achieved a reduction in levels of PTH < 31.8 pmol/L (300 pg/mL) [$P \leq 0.001$]. These analyses are limited by the assessed trials having similar but non-identical design and the high drop-out rate of 26%.

Does treatment with cinacalcet alter requirements for standard therapy of SHPT? (Guideline b)

Moe et al (2005) reported that patients treated with cinacalcet and placebo did not differ in the proportion requiring a change in vitamin D sterol dose (based on mean intake over the efficacy-assessment phase versus baseline), calcium-based phosphate binder dose or a change in the dose of sevelamer. Limitations of this study include the exclusion of patients using more than one vitamin D sterol and of patients using more than one calcium-based phosphate binder. Szczech (2004) assessed the studies of Quarles et al (2003), Lindberg et al (2003) and Block et al (2004) and reported the same conclusion.

How effective is cinacalcet with increasing severity of SHPT? (Guideline c)

Moe et al (2005) reported on the achievement of K/DOQI targets determined according to subgroups defined by baseline iPTH: mild=iPTH 32-53 pmol/L (300-500 pg/mL); moderate=iPTH 53-85 pmol/L (501-800 pg/mL) and severe=iPTH > 85 pmol/L (800 pg/mL). The percentage of patients in mild, moderate and severe groups who achieved the target iPTH of < 32 pmol/L (300 pg/mL) was 81%, 60% and 22%, respectively. For achievement of both the PTH and calcium x phosphate targets, the percentages were 59%, 42% and 18%, respectively.

Are treatment side effects and is treatment withdrawal more common with cinacalcet than with placebo? (Guideline d)

Moe et al (2005) reported that for patients taking cinacalcet, the incidence of nausea (31%) or vomiting (27%) was higher than for patients taking placebo (19% and 15%, respectively). Withdrawal rates from cinacalcet (15%) were higher than for placebo (8%). It should be noted that cinacalcet HCl inhibits cytochrome P-450 2D6. Consequently, patients taking tricyclic antidepressants, flecainide and thioridazine were excluded from studies, as were patients with elevated bilirubin or hepatic transaminases.

Suggestions for clinical care (1-3):

- 1. The use of cinacalcet in patients on dialysis is associated with a reduction in bone turnover and bone marrow fibrosis.**
- 2. Cinacalcet should not be used in patients on dialysis with intact-PTH levels below the target range. The use of cinacalcet may be associated with the development of adynamic bone disease if iPTH values are suppressed < 10.6 pmol/L (< 100 pg/mL).**

Malluche et al (2004) described in abstract form, a study of patients with PTH > 32 pmol/L (300 pg/mL) assigned 2 :1 to cinacalcet (n = 32) or placebo (n = 16). Bone biopsies were performed at baseline and at 1 year.

Baseline histomorphometry was available for 19 patients taking cinacalcet. Of these, 16 were reported to have changes of hyperparathyroidism, one had adynamic bone disease and two were not reported. At 1 year, 12 showed no change, three were adynamic, two had mixed pathology, and results for two were unreported. Of the patients with adynamic changes, two of the three had sustained levels of PTH < 10.6 pmol/L (100 pg/mL). Percentage of bone marrow fibrosis was 4.69% (first biopsy) and 2.70% (second biopsy). PTH, ALP and N-telopeptide were significantly reduced.

Baseline histomorphometry was available for 13 patients taking placebo. Of these, 11 were reported to show changes of hyperparathyroidism, one adynamic bone disease, and one was not reported. At completion, there was no change in seven, mixed pathology in four, and two were unreported. Bone marrow fibrosis was reported to be 6.99% in the first biopsy and 9.12% in the second biopsy. The abstract concluded that cinacalcet HCl improved control of PTH, associated with reductions in bone turnover markers and bone marrow fibrosis. Limitations of this small study included a 33% dropout, and incomplete reporting of data.

Cunningham et al (2004) described in abstract form, an analysis of data from five similar, randomised controlled trials with 6-12 months follow-up. All patients were on dialysis with PTH ≥ 32 pmol/L (300 pg/mL). Cinacalcet was taken by 697 patients and placebo by 487. Doses were adjusted for a target iPTH < 26.5 pmol/L (250 pg/mL). Patients receiving cinacalcet were reported to have a lower incidence of fracture than those receiving placebo, with a hazard ratio of 0.46 (95% CI: 0.22-0.95, P = 0.04). The significant limitation of this assessment is that it represents a post hoc analysis of combined trials that vary in length and which were not designed or powered to assess fracture outcomes. Data on the nature or site of fractures was unavailable in the abstract.

At the cut-off date for literature searches, there was no available evidence for the effect of cinacalcet on bone mineral density.

3. Cinacalcet therapy of SHPT may reduce rates of parathyroidectomy and fracture but has not been shown to influence hospitalisation, cardiovascular mortality, all-cause mortality or quality of life.

In the abstract of Cunningham et al (2004), parathyroidectomy rates were lower in patients taking cinacalcet than those on placebo, with a hazard ratio of 0.07 (95%CI: 0.01-0.55, P = 0.009). However, the follow up of 6–12 months was relatively short for this outcome and the number of patients with severe SHPT entering the studies was

arbitrarily limited to 20%. No significant between-group differences were reported for all-cause hospitalisation, cardiovascular hospitalisation or mortality. However, the assessed studies were not designed or powered for parathyroidectomy or cardiovascular outcomes.

For quality of life, patient-reported outcomes were assessed in the controlled, Phase 3 studies using the KDQOL Cognitive Functioning scale and, as exploratory endpoints, scales in the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36). Mean KDQOL Cognitive Functioning scale scores from baseline to the efficacy-assessment phase did not differ between the cinacalcet and placebo groups in any Phase 3 study. Similar results were observed for the SF-36 Physical Component Summary scores. Current evidence does not support a significant effect of cinacalcet on haemoglobin or epoietin use. In 6-month studies, haemoglobin levels remained constant in both treatment and placebo groups with a non-significant increase of epoietin use in the placebo group.

Suggestions for clinical care (4-6):

There is little patient-level outcome data for the use of cinacalcet versus standard treatment of SHPT. However, association data described in the PTH, calcium, phosphate and calcium x phosphate product guidelines suggests that long-term attainment of suggested targets, which are more readily achieved with the use of calcimimetics, may improve patient outcomes. Suggestions for the use of cinacalcet or resorting to parathyroidectomy when sustained levels of PTH and/or levels of calcium, phosphate and the calcium x phosphate product remain elevated despite optimal standard therapy, are also based on association studies described in the PTH, calcium, phosphate and calcium x phosphate guidelines.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.

British Renal Association: No recommendation.

Canadian Society of Nephrology: No recommendation

European Best Practice Guidelines: No recommendation.

International Guidelines: No recommendation.

IMPLEMENTATION AND AUDIT

In Australia and New Zealand, the use of cinacalcet will depend on availability and the cost to dialysis patients. Cinacalcet should be used in conjunction with standard therapies to improve the proportion of dialysis patients who achieve target serum levels of PTH, calcium, phosphate and the calcium x phosphate product, as described elsewhere in the guidelines. Cinacalcet should be available for use by patients who require, but are medically unfit for parathyroidectomy or are waiting for elective parathyroidectomy (see Suggestions for Clinical Care).

SUGGESTIONS FOR FUTURE RESEARCH

Randomised controlled trials over longer time periods are needed to assess the continuing efficacy and safety of cinacalcet. Trial endpoints should include cardiovascular and all-cause mortality, hospitalisation, fracture and bone mineral density. A longer study with larger patient numbers is required to assess influences of cinacalcet on bone histomorphometry. The potential for cinacalcet to be used at earlier stages of CKD and following renal transplantation requires evaluation. To date, calcimimetics have been evaluated as an addition to standard therapy but studies to assess cinacalcet plus lower dose vitamin D are underway. An evaluation of cinacalcet versus standard therapies would be useful, particularly in early CKD when cinacalcet may reduce progression of parathyroid hyperplasia in addition to improving the attainment of biochemical targets.

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Appendix

Table 1. Assessment of the methodological quality of randomised controlled trials of cinacalcet. Adapted from a Cochrane Review of calcimimetics on secondary hyperparathyroidism by Strippoli G, Tong A, Palmer S, Elder G, Messa P and Craig J. (In press)

Reference	Allocation concealment*	Blinding			Intention-to-treat analysis	Loss to follow-up (%) [†]
		Participants	Investigators	Outcome assessors		
Goodman et al, 2002	Not stated	Yes	Yes	No	Yes	0/52 (0)
Quarles et al, 2003	Adequate	Yes	Yes	No	Yes	6/71 (8)
Lindberg et al, 2003	Not stated	Yes	Yes	No	No	11/78 (14)
Malluche, et al, 2004b	Not stated	Yes	Yes	No	NA [‡]	NA
Block et al, 2004	Not stated	Yes	Yes	No	No	202/741 (27)
Lindberg et al, 2005	Adequate	Yes	Yes	No	Yes	101/395 (26)

*Defined as adequate when sequentially labelled, sealed, opaque envelopes or a central or pharmacy randomization were used; inadequate when a pseudo-randomization method including alternation, date of birth, chart number was used; not stated if no information was available.

[†]Including patients who were stated as being lost to follow-up or those who were discontinued and could have had outcomes measured.

[‡]NA = Data not available in abstract form.