Outcomes of cinacalcet withdrawal in Australian dialysis patients

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Key Words

End-stage kidney disease, secondary hyperparathyroidism, dialysis, parathyroid hormone, cinacalcet

Abbreviations:

ALP alkaline phosphatase
CKD chronic kidney disease
CKD-MBD chronic kidney disease mineral bone disorder
CRP C-reactive protein
CUA calcific uremic arteriolopathy
Abstract

Background: Secondary hyperparathyroidism (SHPT) in chronic kidney disease is associated with cardiovascular and bone pathology. Measures to achieve parathyroid hormone (PTH) target values and control biochemical abnormalities associated with SHPT require complex therapies, and severe SHPT often requires parathyroidectomy or the calcimimetic cinacalcet. In Australia, cinacalcet was publicly funded for dialysis patients from 2009 to 2015 when funding was withdrawn following publication of the EVOLVE study, which resulted in most patients on cinacalcet ceasing therapy. We examined the clinical and biochemical outcomes associated with this change at Australian renal centres.
Methods: We conducted a retrospective study of dialysis patients who ceased cinacalcet after August 2015 in 11 Australian units. Clinical outcomes and changes in biochemical parameters were assessed over a 24- and 12-month period respectively from cessation of cinacalcet.

Results: 228 patients were included (17.7% of all dialysis patients from the units). Patients were aged 63±15 years with 182 patients on haemodialysis and 46 on peritoneal dialysis. Over 24 months following cessation of cinacalcet, we observed 26 parathyroidectomies, 3 episodes of calciphylaxis, 8 fractures and 50 deaths. Seven patients recommenced cinacalcet, meeting criteria under a special access scheme. Biochemical changes from baseline to 12 months after cessation included increased levels of serum PTH from 54 (IQR 27-90) pmol/L to 85 (IQR 41-139) pmol/L (p<0.0001), serum calcium from 2.3±0.2mmol/L to 2.5±0.1mmol/L (p<0.0001) and alkaline phosphatase (ALP) from 123 (92-176) IU/L to 143 (102-197) IU/L (p<0.0001).

Conclusion: Significant increases in serum PTH, calcium and ALP occurred over a 12-month period following withdrawal of cinacalcet. Longer term follow-up will determine if these biochemical and therapeutic changes are associated with altered rates of parathyroidectomies and cardiovascular mortality and morbidity.
Introduction

Secondary hyperparathyroidism (SHPT) begins early in the course of chronic kidney disease (CKD) and is characterized by progressive parathyroid gland hyperplasia, excessive parathyroid hormone (PTH) secretion and abnormalities in calcium and
phosphate metabolism. As renal function declines SHPT becomes almost ubiquitous and results in bone and endocrine abnormalities, together with extra-osseous calcification. SHPT has been associated with left ventricular dysfunction (1), myocardial fibrosis (2), dyslipidemia (3), peripheral neuropathy (4) and anaemia as a result of reduced red blood cell survival and bone marrow fibrosis (5). SHPT is a significant component of the well-recognized broader clinical syndrome encompassing mineral, bone and cardiovascular abnormalities that develop as a complication of CKD - Chronic Kidney Disease Mineral and Bone Disorder (CKD-MBD).

Traditional management of SHPT is aimed at controlling phosphate by means of restricting intake, optimizing dialysis and administering phosphate binders, as well as modulating calcium balance and suppressing PTH release with activated vitamin D. Despite traditional management, patients with severe and progressive disease may require surgical management with a parathyroidectomy. Although parathyroidectomies improve biochemical parameters and clinical symptoms related to severe SHPT, they are associated with an increased 30-day mortality and risk of re-hospitalization with hypocalcaemia (6). Surgical management also may not be suitable for older patients with complex co-morbidities, which encompasses a large proportion of dialysis patients in the Western world. In some cases, the effect of parathyroidectomy is also transient, with recurrence in up to 14% (7).
The only oral calcimimetic available to date is cinacalcet which provides a medical alternative to parathyroidectomy and acts as a positive allosteric modulator of the calcium sensing receptor (CaSR) reducing PTH secretion. Cinacalcet reduces PTH (8-11) and, in patients on dialysis, cinacalcet plus low doses of activated vitamin D reduces progression of coronary artery calcification score volume when compared to higher activated vitamin D therapy (12). In Australia, government reimbursement for cinacalcet was introduced in 2009, but was contingent on proof of efficacy and cost-effectiveness from the pivotal Effect of Cinacalcet on Cardiovascular Disease in Patients Undergoing Dialysis (EVOLVE) trial (13).

Following publication of EVOLVE, which showed no change in the unadjusted composite primary end-point of cardiovascular mortality and morbidity in patients on cinacalcet, government reimbursement for cinacalcet in Australia was withdrawn in August 2015 due to the lack of evidence of cost-effectiveness. Secondary analyses of the study did report benefits, including reduced cardiovascular mortality in patients over 65 years of age (14), a reduction in the risk of calciphylaxis (15) and possibly fracture risk (16). Globally, predictive Markov models were able to demonstrate cost effectiveness in Italy (17) and Japan (18), especially for patients unsuitable for parathyroidectomy. Economic analysis in Australia showed benefit in reducing parathyroidectomy rates, as well as clinical benefits in those over 65 years, however given financial feasibility was not met, funding of this medication was not continued. The hypothesis of our present study was that withdrawal of cinacalcet in dialysis

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patients with SHPT in Australia may be associated with changes to biochemical and clinical outcomes, including parathyroidectomy rates and prescribing practices.

**Methods**

*Study design*

We performed a retrospective observational study involving maintenance dialysis patients who had ceased cinacalcet therapy after August 2015. The aim was to assess the impact on clinical outcomes and biochemical parameters of mineral metabolism after withdrawal from cinacalcet in patients on dialysis. The study protocol was approved by the local ethics committee at Melbourne Health (The Royal Melbourne Hospital). Reciprocal ethics and governance approval was arranged at each site involved in the study.

*Study Population*

Eleven nephrology units across Australia (The Royal Melbourne Hospital, Royal Hobart Hospital, Princess Alexandra Hospital, Sunshine Coast Hospital, Canberra Hospital, Westmead Hospital, Blacktown Hospital, Nepean Hospital, St Vincent’s Health, Sir Charles Gairdner Hospital and Western Health) participated in the study. There were no specific exclusion criteria. Each centre provided data regarding
patient demographics, changes in prescription practices and biochemical changes over a 12-month period from August 2015. Mortality and morbidity data, including rates of parathyroidectomies, rates of clinically-evident vertebral or non-vertebral fractures, and episodes of calciphylaxis were collected at each centre over 24 months following medication cessation.

Study endpoints

The primary endpoint was change in biochemical outcome measures over a 12-month period. Patients were excluded from final analysis if they underwent a renal transplant, had a parathyroidectomy or restarted cinacalcet, via an industry-sponsored special access scheme, within 12 months of withdrawal of the medication. Comparison analysis between deceased and non-deceased participants was performed to ensure demographics, clinical outcomes and biochemical characteristics were not confounded.

Biomarker assessment

Biochemical data was obtained from each nephrology unit. All hospitals measure intact PTH, although a variety of testing platforms for PTH are currently used by pathology departments. All patients had measurements over the course of 12-month study period performed at the same centre and on the same platform which reduced
intra-sample variability. There remains some variability between different intact PTH platforms currently available (19), however variability between different platforms used across units in different states was unavoidable.

Statistical analysis

All data are summarised and results reported as mean (+/-standard deviation [SD]) or median (inter-quartile range [IQR]) for continuous data and number (percentage, %) for categorical variables. Paired t-test and Wilcoxon signed-rank test were used for between group comparisons. Categorical variables were analyzed with Chi-square test. Continuous variables were compared with one-way repeated measure ANOVA if normally distributed or with Freidman test if the distribution was skewed. Two-tailed P values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 21.0 for Macintosh (SPSS, Chicago, IL).

Results

Demographics and clinical characteristics

The study included 228 patients in whom cinacalcet had been ceased between August and December 2015. This represents 17.7% of dialysis patients across the
11 units. Baseline characteristics are shown in Table 1. The mean age and median time on dialysis were 63 ± 15 years and 5.7 (IQR 3-8) years respectively. Thirty-seven percent of patients had diabetes, 74% had a history of hypertension and 38% had a history of ischaemic heart disease.

Clinical outcomes

Over a 2-year period, 26 patients underwent parathyroidectomies, 19 of which occurred within the first 12-month period. There were three episodes of calciphylaxis, eight non-vertebral fractures and 50 deaths (26 in the first 12 months and 24 in the subsequent 12 months), with an annual overall mortality rate of 11.0%. Deceased patients were older, with a mean age of 69 ± 11 years (p=0.005), however the median time on dialysis (6 [IQR3-7] years, p=0.9) and associated comorbidities including hypertension (p=0.70), diabetes (p=0.14) and ischaemic heart disease (p=0.14) were similar in both cohorts.

Biochemical outcomes

Thirty-five patients were excluded from 12-month analysis of biochemical changes and prescribing practices. Demographics and clinical features of this cohort are described in Table 2. Nineteen underwent parathyroidectomies, seven re-
commenced cinacalcet therapy, with access to medication via an industry-sponsored special access scheme, and seven received a kidney transplant.

There was an increase in PTH from 54 pmol/L (27 -90 pmol/L) to 85 pmol/L (41 -139 pmol/L) at 12 months (p<0.001), with the greatest change occurring by 6 months (p<0.001) (Figure 1). Correspondingly, serum calcium increased from 2.30±0.2 mmol/L to 2.50±0.1 mmol/L (p<0.001), and phosphate remained unchanged over the observation period (p=0.84). There were 54 episodes of hypercalcaemia (serum corrected calcium > 2.6mmol/L) at 6 months, with 31 episodes occurring at 12 months, this was significantly increased from 19 episodes of hypercalcaemia identified at baseline (p=0.002). There was an increase in alkaline phosphatase (ALP) from 123 IU/L (92-176 IU/L) to 143 IU/L (102-197 IU/L) at 12 months (p<0.001). Inflammatory markers, including C-reactive protein (CRP) and ferritin remained stable over 12-months, and there was a fall in serum albumin from 35.5+/4.6 g/L to 34.5+/4.5 g/L, p=0.01. Table 3 summarizes baseline, 6-month and 12-month values for biochemical outcomes in the study cohort.

Changes in prescribing practices

The median daily dose of cinacalcet prior to medication cessation was 30mg [30-60mg]. At baseline, 38% of patients (n=74) were on a calcium-based phosphate binder and 66% (n=127) on a non-calcium based phosphate binder. Twenty-six
percent (n=56) were on two phosphate binders and 21% percent (n=46) were not taking any phosphate binder. At baseline, active vitamin D use was high at 65% (n=125) and 26% (n=51) were on nutritional vitamin D. By 12 months following cinacalcet withdrawal, phosphate binder use was significantly reduced, with 29% (n=52, p=0.01) on a calcium based binder and 50% (n=97, p=0.008) on a non-calcium based binder. Active vitamin D use also reduced by 12 months to 48% (n=93), p=0.03. However, of the patients who remained on active vitamin D their dose was increased from 1.6+/−0.8 mcg/week to 2.2+/−1.3 mcg/week (p=0.005). There was no change in cholecalciferol administration (p=0.23). Table 4 describes prescribing practice changes following cinacalcet withdrawal. There were no significant changes in prescribing practice results with or without death censoring of data. There was no change to time on dialysis following cinacalcet withdrawal or any change in dialysis modality amongst individuals in the cohort.

Discussion

Our study of 228 dialysis patients from 11 nephrology centres across Australia is the first to show clinical and biochemical outcomes of cinacalcet withdrawal in a large cohort. We report that cinacalcet cessation, when previously used for the management of SHPT, was not associated with increased clinical outcomes after 2 years from withdrawal when compared to reported outcomes in the Australian dialysis population, apart from the rate of parathyroidectomy. Associated biochemical
changes however included a rise in PTH, calcium and ALP, no corresponding change in serum phosphate, and a fall in serum albumin in the first 12 months after medication withdrawal.

Following cinacalcet withdrawal, there was a statistically significant increase in ALP, which may represent increased bone turnover. Recent publications suggest cinacalcet use may improve bone metabolism and is associated with reduced bone turnover markers including bone specific ALP, osteocalcin and beta-crosslaps (20). Cunningham et al (21) reported reduced parathyroidectomy, fracture and cardiovascular hospitalization rates with cinacalcet use in a combined analysis of four clinical trials, and secondary analysis of the EVOLVE trial identified a trend towards reduced rates of fractures with cinacalcet use, particularly in older patients (16). The fracture rate in our cohort was relatively small with only eight clinically-evident fractures during the study period, although the incidence of fracture may have been under-reported by units. Fractures seen in primary care settings and asymptomatic vertebral fractures may have potentially not been included.

With regards to clinical outcomes, 11% of patients underwent a parathyroidectomy within 2 years of medication cessation, equating to an 86/1000-person year parathyroidectomy rate. There was no observed increase in calciphylaxis, with three episodes identified in the cohort over the 24-month study period. The mortality rate of the cohort was 11% per year which is comparable to current published Australian
dialysis mortality data for patients in a similar age group (22). As vascular calcification and associated cardiovascular mortality and morbidity related to SHPT may take many years to develop, this cohort requires further follow up to identify if there are potentially longer-term associations with cinacalcet withdrawal.

Parathyroidectomy rates are not currently recorded in the Australian and New Zealand Dialysis and Transplant registry (ANZDATA), unlike other parameters including cardiovascular disease and cancer. Therefore, this study is limited in being able to identify increased rates of parathyroidectomy since reimbursement of cinacalcet ceased. Certainly, within one centre at The Royal Melbourne Hospital, we have seen a 69% increase in the rate of parathyroidectomies since 2015. Data from Canada following the public formulary listing of cinacalcet showed a significant decrease in parathyroidectomy rates from 11.4/1000 persons-years to 3.6/1000 (23).

Multiple studies have highlighted the short-term risks associated with parathyroidectomies in patients on dialysis (6, 24). A review of clinical outcomes following parathyroidectomy using United States Renal Data System (USRDS) data, demonstrated a 2% 30-day mortality and 23.8% re-hospitalization rate following surgery, together with a 39% increase in hospitalization rate in the year following parathyroidectomy (24). Long term mortality in younger dialysis patients may be better with parathyroidectomy compared with medical management (25), however it is difficult to generalize this potential benefit to our study cohort, given the average
age in our study cohort was 63 years, with a higher percentage of co-morbidities including diabetes and ischaemic heart disease.

Patient preference in regards to treatment of SHPT with cinacalcet versus parathyroidectomy has not been assessed to our knowledge. The impact on quality of life with parathyroidectomy versus cinacalcet has recently been examined in a systematic review of eight studies (26). Although a direct comparison between the two interventions could not be made, parathyroidectomy was associated with improvement in short and long-term quality of life, including improvement in itch, joint pain and muscle weakness, whereas no difference was seen in quality of life with the use of cinacalcet. It is possible that reduction in PTH with surgery compared to medical suppression is more beneficial, however it is unlikely that a head-to-head comparison will ever be undertaken.

Reduced use of activated vitamin D from 65% to 48% was not unexpected, because use of cinacalcet allows clinicians to target lower PTH values by enabling increased dosing with activated vitamin D with a reduced risk of hypercalcaemia. Nevertheless, there was no associated increase in serum phosphate over a 12-month period after cinacalcet withdrawal, suggesting that cinacalcet alone was insufficient to overcome the biochemical effects of hyperphosphataemia resulting from increased calcitriol use. In fact, one consideration is whether cinacalcet availability emphasizes the potential to achieve lower PTH values leading to higher calcitriol and phosphate
binder requirements. Since oversuppression of PTH and higher phosphate binder use may have adverse consequences, particularly when calcium-based binders are used, the question arises as to longer term patient-level benefits of more complex combined therapies that include cinacalcet.

Limitations of our study include its retrospective observational nature and therefore we do not have a control group to compare identified clinical and biochemical changes. Comparing mortality and morbidity data in our cohort to published data in the general Australian dialysis population involves selection bias as we have studied a cohort of individuals previously prescribed cinacalcet based on clinical indication as determined by their treating clinicians. Also, not all units across Australia were involved in data collection and there was a short duration of follow up. Furthermore, we were unable to comprehensively collect all morbidity outcomes, including fracture rates and types of cardiovascular events, as well as changes in dosing of phosphate binders in all study participants, given the study’s retrospective nature. Another limitation is that given the variability between different PTH analysis platforms it is possible we have over or under-estimated the change in PTH over the study period. Strengths of our study include a large data set across 11 Australian centres with varying geographical locations, which provides a unique insight into the effects of cinacalcet withdrawal, perhaps not possible in many another countries. We have also collected comprehensive national biochemical parameters and
parathyroidectomy rates in Australia in the era following withdrawal of cinacalcet reimbursement.

In conclusion, for patients in the Australian dialysis population who withdrew from cinacalcet therapy, median values of PTH exceeded the Kidney Disease Improving Global Outcomes (KDIGO) CKD-MBD guidelines suggested upper target range of 9-times the upper range of the PTH assay, calcium and ALP values rose, and there was no change in serum phosphate. The parathyroidectomy rate was 86/1000 patient-years over the first 24 months from withdrawal. Longer term follow-up will allow greater insight into associated future cardiovascular morbidity, mortality and fracture rates.

**Authorship Page:**

**Authors**

Ruderman I, Holt S and Nigel T contributed to the conception, critical appraisal of paper and drafting of the work.

All authors contributed to the writing of the manuscript and approved the final copy of paper.

**Disclosures**

IR declares she has no competing interests. NDT and GJE have received honoraria, travel support and research funding from Amgen, Shire and Sanofi. SGH has
research funding, honoraria and travel support from Amgen, Astra-Zenica, Baxter and Sanofi. RK has received honoraria and travel support from Shire and Amgen.

References


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Table 1: Patient demographics and clinical characteristics

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Cinacalcet withdrawal patients (n=228)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>63 +/- 15</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>138 (60%)</td>
</tr>
<tr>
<td>Dialysis modality (haemodialysis)</td>
<td>182 (80%)</td>
</tr>
<tr>
<td>Time on dialysis, years</td>
<td>5.7 [3-8]</td>
</tr>
<tr>
<td>Diabetes</td>
<td>84 (37%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>170 (74%)</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>86 (38%)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>26 (11%)</td>
</tr>
</tbody>
</table>

Events during follow up (24 months)

<table>
<thead>
<tr>
<th>Event</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parathyroidectomy</td>
<td>26 (11%)</td>
</tr>
<tr>
<td>Non-vertebral fractures</td>
<td>8 (3.5%)</td>
</tr>
<tr>
<td>Calciphylaxis</td>
<td>3 (1.3%)</td>
</tr>
<tr>
<td>Deaths</td>
<td>50 (23%)</td>
</tr>
</tbody>
</table>

Data presented as number (percent), mean +/- standard deviation or median [interquartile range]
**Table 2**: Demographics and clinical characteristics of patients who underwent parathyroidectomy and renal transplantation or restarted cinacalcet during the study period

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Patients excluded from final analysis (n=35)</th>
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</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>55 +/- 13</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>20 (57%)</td>
</tr>
<tr>
<td>Dialysis modality (haemodialysis)</td>
<td>22 (63%)</td>
</tr>
<tr>
<td>Time on dialysis, years</td>
<td>4 [2-7]</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9 (26%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>28 (80%)</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>10 (28%)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>3 (8%)</td>
</tr>
<tr>
<td><strong>Baseline medications</strong></td>
<td></td>
</tr>
<tr>
<td>Calcium-based phosphate binder use</td>
<td>8 (23%)</td>
</tr>
<tr>
<td>Non-calcium-based phosphate binder use</td>
<td>23 (66%)</td>
</tr>
<tr>
<td>Active vitamin D use</td>
<td>20 (57%)</td>
</tr>
</tbody>
</table>
Nutritional vitamin D use 
7 (20%)
Erythropoietin-stimulating agent use 
20 (57%)

Data presented as number (percent), mean +/- standard deviation or median [interquartile range]

**Table 3: Biochemical changes over 12-month period following cinacalcet withdrawal**

<table>
<thead>
<tr>
<th>Biochemistry</th>
<th>Baseline (n=193)</th>
<th>6 months (n=177)</th>
<th>12 months (n=167)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH, pmol/L</td>
<td>54 [27-90]</td>
<td>83 [40-115]</td>
<td>85 [41-139]</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Calcium, mmol/L</td>
<td>2.3 +/- 0.2</td>
<td>2.5 +/- 0.2</td>
<td>2.5 +/- 0.1</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Phosphate, mmol/L</td>
<td>1.6 +/- 0.58</td>
<td>1.6 +/- 0.47</td>
<td>1.6 +/- 0.57</td>
<td>p=0.84</td>
</tr>
<tr>
<td>ALP, IU/L</td>
<td>123 [92-176]</td>
<td>134 [101-184]</td>
<td>143 [102-197]</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Albumin, g/L</td>
<td>35.5 +/- 4.6</td>
<td>35.1 +/- 5.0</td>
<td>34.5 +/- 4.5</td>
<td>p=0.010</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>7 [3-16]</td>
<td>7 [3-19]</td>
<td>9.5 [4-29]</td>
<td>p=0.09</td>
</tr>
<tr>
<td>Ferritin, ug/L</td>
<td>312 [187-496]</td>
<td>309 [159-524]</td>
<td>367 [180-540]</td>
<td>p=0.08</td>
</tr>
<tr>
<td>Haemoglobin, g/L</td>
<td>110 +/- 14</td>
<td>111 +/- 14</td>
<td>110 +/- 117</td>
<td>p=0.67</td>
</tr>
<tr>
<td>Bicarbonate, mmol/L</td>
<td>23 +/- 3</td>
<td>22 +/- 3</td>
<td>23 +/- 3</td>
<td>p=0.42</td>
</tr>
</tbody>
</table>

Data presented as mean +/- standard deviation or median [interquartile range]

**Abbreviations:** ALP, alkaline phosphatase; CRP, C-reactive protein; PTH, parathyroid hormone
Table 4: Changes in prescribing practices

<table>
<thead>
<tr>
<th>Medications</th>
<th>Baseline</th>
<th>6 months</th>
<th>12 months</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium-based phosphate binders</td>
<td>74 (38%)</td>
<td>49 (25%)</td>
<td>52 (29%)</td>
<td>p=0.01</td>
</tr>
<tr>
<td>Non-calcium-based phosphate binders</td>
<td>127 (66%)</td>
<td>112 (58%)</td>
<td>97 (50%)</td>
<td>p=0.008</td>
</tr>
<tr>
<td>Active vitamin D</td>
<td>125 (65%)</td>
<td>112 (58%)</td>
<td>93 (48%)</td>
<td>p=0.03</td>
</tr>
<tr>
<td>Nutritional vitamin D</td>
<td>51 (26%)</td>
<td>33 (17%)</td>
<td>37 (19%)</td>
<td>p=0.23</td>
</tr>
<tr>
<td>Erythropoietin-stimulating agent use</td>
<td>127 (66%)</td>
<td>116 (60%)</td>
<td>100 (52%)</td>
<td>p=0.09</td>
</tr>
</tbody>
</table>

Data presented as number (percent)
Legends to figures:

**Figure 1**: Changes in biochemical mineral markers over 12 months following cinacalcet withdrawal. Changes in (a) parathyroid hormone, (b) calcium, (c) phosphate and (d) alkaline phosphatase over a 12-month period summarized in line graph (median, lower and upper quartile).
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