The cost-utility of cinacalcet in addition to standard care compared to standard care alone for secondary hyperparathyroidism in end-stage renal disease: a UK perspective

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Abstract

Background. Secondary hyperparathyroidism (SHPT) is a common side effect of end-stage renal disease (ESRD) and is associated with increased risk of fracture and cardiovascular events (CV). Current standard treatment includes dietary control, phosphate binders and vitamin D. However, many patients do not have their parathyroid hormone (PTH), calcium and phosphate levels controlled by this regimen. Cinacalcet is the first of a new class of calcimimetic drugs which suppress PTH production. Although there is convincing evidence of the impact of cinacalcet on serum biomarkers, the long-term clinical implications of treatment are less clear. The aim of this study is to estimate the cost-utility of cinacalcet as an addition to standard treatment of SHPT compared with standard treatment alone.

Methods. A Markov model was developed to estimate the incremental cost-utility of cinacalcet. Uncertainty was explored through extensive sensitivity analysis.

Results. Compared with standard treatment, cinacalcet incurs average additional lifetime costs of £21 167 per person and confers an additional 0.34 quality adjusted life years, resulting in an incremental cost-effectiveness ratio of £61 890 (approximately €89 000) per quality-adjusted life-year (QALY). Extensive one-way sensitivity analysis showed that cinacalcet was only likely to be considered cost-effective if the relative risk of mortality for people with very high levels of PTH was 2.2 compared with people whose PTH reached target levels, or if drug costs were considerably reduced. Probabilistic sensitivity analysis showed cinacalcet was very unlikely to be cost-effective at usual levels of willingness to pay in the National Health Service (NHS).

Conclusion. Unless the cost of cinacalcet is considerably reduced, it is unlikely to be considered a cost-effective treatment for people with SHPT.

Keywords: cinacalcet; cost-effectiveness; cost-utility; end-stage renal disease; modelling studies; secondary hyperparathyroidism

Introduction

Secondary hyperparathyroidism (SHPT) is common in end-stage renal disease (ESRD) [1]. It usually develops early in chronic kidney disease (CKD) and progresses as renal function deteriorates [2]. There is an increased risk of vascular disease due to calcification in SHPT [3], and SHPT is also the main cause of renal osteodystrophy which increases the risk of fracture [4]. The relative impacts of serum calcium, phosphate and PTH, being complex, are unclear. Advanced SHPT can cause bone pain, muscle weakness and itching [4]. Currently, the UK’s Renal Registry reports that 72% of people meet target levels for PTH, 60% for phosphate and 63% for calcium [5].

Cinacalcet (Mimpara®, Amgen Inc.) is the first of a new class of calcimimetic drugs, which act on parathyroid calcium receptors to increase their sensitivity to serum calcium. This suppresses the production of PTH. This, in turn, reduces serum calcium and phosphate levels [6]. Cinacalcet was licensed by the European Agency for the Evaluation of Medicinal Products (EMEA) in July 2004. There is convincing evidence of the impact of cinacalcet on serum biomarkers such as PTH and calcium-phosphate product from the literature. However, the long-term clinical implications of this are unclear. Crucially, evidence for an impact on clinical events such as mortality, cardiovascular event (CV), fracture and parathyroidectomy (PTX) is based on one, short-term,
post hoc analysis [7]. Modelling is one way of investigating this further.

The aim of this study is to estimate the cost-utility of cinacalcet as an addition to standard treatment with phosphate binders and vitamin D for the treatment of SHPT compared with standard treatment alone. The report was produced for the National Institute for Health and Clinical Excellence (NICE) who used it to help inform the decision-makers about SHPT treatment in England and Wales. Healthcare is free at the point of delivery through the National Health Service (NHS) in the UK. NICE makes decisions about whether or not treatments will be funded through the NHS based on assessments of their clinical and cost-effectiveness. NICE is unlikely to consider treatments cost-effective if they cost more than £30 000 (£43 200) for an additional quality-adjusted life-year (QALY).

Methods

A Markov (state transition) model was developed in Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA). The structure of the model was informed by current research literature and clinical expert opinion on SHPT in ESRD and its treatment. Estimates of the effectiveness of cinacalcet were taken from a systematic review of the literature by the authors [8]. Other parameters were identified through systematic literature searches and, where no relevant published data was identified, the project’s expert advisory group was consulted. The model estimates the incremental cost-utility of adding cinacalcet to the current standard treatment of SHPT in ESRD.

The modelled population is people with SHPT. The treatments compared are cinacalcet as an addition to standard treatment and standard treatment alone. Standard treatment includes dietary control, phosphate binders and vitamin D. A hypothetical cohort of 1000 people with SHPT are modelled until the whole cohort has died. The starting age is 55 years, based on the mean age of cinacalcet trial participants [9]. The model uses a cycle length of 3 months. A half-cycle correction was not added to the model, as the cycle length is sufficiently short for this not to be necessary.

UK costs from 2004 are used as these are the most recent available data for many standard sources. The exception is drug costs, where currently available 2005 costs are used.

Extensive one-way sensitivity analyses were undertaken to explore which of the input parameters, when varied independently of the other model inputs, have the greatest impact on the incremental cost-effectiveness of cinacalcet.

Probabilistic sensitivity analysis (PSA) was also undertaken using Monte Carlo simulation to explore the impact of underlying parameter uncertainty on cost-effectiveness [10]. In this stochastic approach, the Markov model is run 1000 times using input values randomly drawn from probability density functions for each uncertain parameter.

Model structure

Figure 1 (see online supplement) shows the influence diagram for the model. Populations in both arms are the same at baseline: all have hyperparathyroidism, defined as a PTH level of more than 32 pmol/l (>300 pg/ml). After a 3-month titration period, where people are treated with either standard treatment alone, or with the addition of cinacalcet, PTH levels are considered to be ‘controlled’, ‘uncontrolled’ or ‘very uncontrolled’ based on trial data from the authors’ systematic review [8]. The outcomes for these groups are then estimated over time, with assumptions regarding the control of progression of HPT with cinacalcet. A stratified approach is taken to assess the risk of people with different degrees of PTH control. People are considered ‘controlled’ if they have a PTH level of 32 pmol/l or less (<300 pg/ml), in accordance with Renal Association standards [5]. They are defined as ‘uncontrolled’ if they have a PTH of between 33 and 84 pmol/l (311–792 pg/ml), and ‘very uncontrolled’ if they have a PTH level of 85 pmol/l or more (≥800 pg/ml). Those with ‘very uncontrolled’ PTH are further divided into those eligible or ineligible for parathyroidectomy. Two ‘post-surgical’ outcomes are modelled—with or without adverse effects. Parathyroidectomy only occurs in people with ‘very uncontrolled’ levels of PTH.

The seven health states shown for ‘controlled’ PTH levels in Figure 1 are replicated for all degrees of PTH control and the two post-parathyroidectomy strata. Thin arrows between boxes represent possible transitions experienced by the cohort within each of the strata, with transitions permitted in the direction of the arrows and circular arrows representing staying in the same health state for further model cycles.

The natural history of SHPT is that PTH levels are likely to become progressively more uncontrolled over time. This is shown by the thicker, double arrows representing movement between model strata in Figure 1. In the base case, those treated with cinacalcet are assumed not to experience this deterioration of control.

Differences in costs and benefits between the arms of the model (the incremental cost-effectiveness ratio, ICER) are based on the different proportions of people who have ‘controlled’, ‘uncontrolled’ or ‘very uncontrolled’ levels of PTH after standard treatment alone or with cinacalcet. Relative risks (RRs) of having a fracture, cardiovascular event or of mortality depend on the PTH level and previous history of such events and are taken from the literature.

Death may occur from any of the health states. The death rate is modelled as a time-dependent variable to reflect the aging of the cohort. Death from cardiovascular causes and death from other causes is possible in all of the model strata. In addition, there is a small risk of death as a complication of parathyroidectomy.

In accordance with current guidance from the UK Treasury and NICE, costs and benefits were discounted at 3.5% [11].

Sources of estimates used in the analysis

Transition probabilities. It was not clear how data on fracture, cardiovascular event and mortality from a single short-term study should be extrapolated to the longer-term [7]. In addition, the death rates in this study were much lower than reported by the Renal Registry for a similar age group, indicating that the trial populations may not be representative of those in clinical practice. We therefore
sought alternative methods and used data from large cohort studies about the risk of clinical events in relation to PTH.

Data on the effectiveness of cinacalcet and standard care at reducing PTH to target levels were taken from a systematic review of the literature [5]. Details of search strategies are available from the authors. Cinacalcet trials report achievement of PTH control, but the proportion of people ‘uncontrolled’ or ‘very uncontrolled’ were not reported. These were estimated using data supplied by the Renal Registry. This showed that, of those who did not have PTH levels below the target level, 70% had PTH levels between 33 and 84 pmol/l while 30% had PTH levels of more than 85 pmol/l (Dr David Ansell, personal communication 24 February 2006). These data were used to distribute people who did not achieve target PTH levels between the two uncontrolled PTH strata of the model. The proportion of people with ‘controlled’, ‘uncontrolled’ and ‘very uncontrolled’ PTH levels at 3 months is 5, 67 and 29%, respectively in the standard treatment arm and 40, 42 and 18% in the cinacalcet arm reflecting initial effectiveness of cinacalcet shown in randomized clinical trials (RCTs) (Table 1– see online supplement).

Annual mortality rates are derived from the Renal Registry for those with controlled PTH levels [12]. Three types of mortality are modelled: cardiovascular death, death from other causes and periperoative mortality following parathyroidectomy. Death from other causes represents a relatively stable background level of mortality within the model. This varies slightly based on the level of PTH control and age, but is consistent for all the health states at a given degree of PTH control. Cardiovascular death is the main source of differential death rates between the health states at each degree of PTH control. Cardiovascular death is the main source of differential death rates between the health states at each degree of SHPT severity. For each health state within the model the transition probabilities for cardiovascular death have been calculated according to the two basic constraints: first, the total number of cardiovascular deaths from each of the strata is based on the expected proportion of cardiovascular deaths in this population and, second, the RR of cardiovascular deaths between health states in each strata is maintained.

Reduced cardiovascular mortality risk in the cinacalcet arm arises through more of the population having ‘controlled’ PTH levels, with associated lower overall mortality. In addition, a lower proportion of the population at all levels of PTH control occupy health states related to cardiovascular events and fractures, which carry higher mortality risk. RR of mortality, cardiovascular events and fracture at various levels of PTH control were derived from a large cohort study of people on dialysis [13].

The risk ratio for subsequent cardiovascular events after an initial cardiovascular event is derived from a retrospective cohort study of 1995 US dialysis patients, examining the risk factors associated with both initial and subsequent hospitalizations for people with and without prior congestive heart failure (CHF) [14]. Annual event rates for a first CV event among those with ‘controlled’ PTH levels is 0.108, and for subsequent events, after an initial event, this rises to 0.244.

We did not identify any data on the pattern of fractures in people with renal osteodystrophy. We therefore used data about the risk of hip fracture within this population, and assumed that additional minor fractures would occur in the same proportions as found in the general population. The RR of having a fracture at different levels of PTH control was then applied, derived from the Kim and colleagues’ [15] study of 10018 patients on dialysis in the USA. In the absence of condition-specific data, the risk of subsequent fracture was taken from a review of osteoporosis [16]. For those with controlled PTH levels, the annual rate of hip fracture is 0.0029 and, concerning subsequent fractures, the rate rises to 0.0067.

After parathyroidectomy, 92% of people are assumed to gain control of PTH. Those who have unsuccessful surgery remain with ‘very uncontrolled’ PTH levels. In addition, 1% of those receiving parathyroidectomy experience a serious adverse event, such as vocal cord damage and they enter the ‘post-parathyroidectomy—adverse effects’ stratum of the model. Here, they attract the same risks and benefits as those who continue to have ‘very uncontrolled’ levels of PTH.

Utility values. Quality of life was incorporated into the assessment through the use of utility values, where one represents perfect health and zero, death. We searched for values assigned by general population samples, as a societal perspective is preferred by policy makers (search strategy available from the authors) [17,18]. We did not identify any papers that reported utility value by PTH level. Bone pain and pruritus are common symptoms of hyperparathyroidism and studies have reported an increase in QoL after parathyroidectomy as a result of these symptoms resolving. Advice from clinical experts suggested that there was not likely to be an impact on QoL with ‘uncontrolled’ PTH compared with ‘controlled’, but that people with ‘very uncontrolled’ PTH levels would be adversely affected. The model therefore incorporates a scaled reduction of 15% in utility for those in the event-free health state who have ‘very uncontrolled’ PTH.

We did not identify any studies describing the utility values for people with ESRD experiencing fracture or cardiovascular event. These were incorporated using data from other populations which was applied as a scaled reduction to the utility for having ESRD alone (i.e. in the ‘event-free’ health state). See Table 2 in the online supplement for details of utility values used.

Resource use. Costing was conducted using a variety of data sources for the amount and valuation (unit costs) of resources used. A UK NHS perspective was used.

Resources included were the cost of cinacalcet, the cost of standard care for SHPT (vitamin D supplements and phosphate binders); hospital resources needed to treat cardiovascular-related adverse effects, major and minor fractures, parathyroidectomy and blood tests for biochemical serum levels. Dialysis costs were not included in the base case. We assess the impact of this in sensitivity analysis.

It is currently unclear whether prescription of vitamin D and phosphate binders would change with the inclusion of cinacalcet in SHPT management. The dosage included in the cinacalcet trials was largely fixed by study protocol. However, cinacalcet might reduce the need for phosphate binders and, in particular, might result in less use of expensive drugs, notably sevelamer. We therefore assumed that sevelamer would be reserved for patients with ‘very uncontrolled’ PTH levels.

Costs for cardiovascular events and fractures were based on weighted averages for common types of relevant event based on NHS national costs data [19]. Details of the resources and unit costs used in the model are shown in Tables 3 and 4 of the online supplement.
Results

Base case cost-effectiveness of cinacalcet

Base case results for the incremental cost-effectiveness of cinacalcet are shown in Table 5 on a per patient basis. For the modelled cohort, cinacalcet improves QALY by 11% (0.34 QALYs or 18 quality-adjusted life-weeks per patient), but costs an additional £21 167 per patient, giving an ICER of €61 890 per QALY (approximate value in Euros, assuming a conversion rate of £1.00 to €1.44, =€89 000 per QALY).

Event counts. Few differences in health outcomes are predicted by the model (Table 6). The exception is parathyroidectomy; a significant number of operations are avoided by the use of cinacalcet (P < 0.001). In both arms of the model, the number of multiple cardiovascular events is high. Approximately 2% of both arms experience a major fracture and about 20% a minor fracture. The costs of treating enough people with cinacalcet in addition to standard care in order to avoid a cardiovascular event is around £490 000 (€705 600), while the cost of avoiding a major fracture is £5 290 000 (€7 617 600) and of avoiding a parathyroidectomy is £140 000 (€201 600).

Although there are few differences in the number of cardiovascular outcomes between the model arms, the timing is affected by cinacalcet. People taking cinacalcet have a small survival advantage that increases slightly over time (Table 7). Over 80% of the cohort is dead in both arms by 10 years of follow-up.

Sensitivity analyses

One-way sensitivity analyses. Extensive one-way sensitivity analyses of transition probability, utility and cost values were used to examine the impact of the uncertainty associated with individual inputs. In this (deterministic) analysis, the model appears particularly sensitive to:

(i) Transition probabilities

(a) The difference between model arms in the proportion of people that have ‘very uncontrolled’ levels of PTH (>85 pmol/l).

(b) The differential rate of disease progression (loss of PTH control) between the cinacalcet and standard care arms.

(c) The percentage of patients who withdraw from cinacalcet treatment.

(d) The RR of death for people with ‘uncontrolled’ levels of PTH.

(e) The RR of death for people with ‘very uncontrolled’ levels of PTH.

(ii) Utilities

(a) The difference in quality of life for people with ‘very uncontrolled’ PTH levels compared with people with ‘controlled’ PTH levels.

(iii) Costs

(a) The price of cinacalcet.

(b) Differential cost of cinacalcet depending on the degree of PTH control.

Table 5. Discounted base case cost-effectiveness results per patient for cinacalcet (dialysis costs excluded)

<table>
<thead>
<tr>
<th></th>
<th>Costs (£)</th>
<th>QALYS</th>
<th>Incremental costs (£)</th>
<th>Incremental QALYs</th>
<th>ICER (£/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard care only</td>
<td>6533</td>
<td>3.04</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Cinacalcet plus standard care</td>
<td>27 700</td>
<td>3.39</td>
<td>21 167</td>
<td>0.34</td>
<td>61 890</td>
</tr>
</tbody>
</table>

Discounted base case cost-effectiveness results per patient for cinacalcet (dialysis costs included)

<table>
<thead>
<tr>
<th></th>
<th>Costs (£)</th>
<th>QALYS</th>
<th>Incremental costs (£)</th>
<th>Incremental QALYs</th>
<th>ICER (£/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard care only</td>
<td>81 523</td>
<td>3.04</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Cinacalcet plus standard care</td>
<td>106 946</td>
<td>3.39</td>
<td>25 423</td>
<td>0.34</td>
<td>74 334</td>
</tr>
</tbody>
</table>

Table 6. Number of people experiencing different outcomes in the economic model for 1000 people

<table>
<thead>
<tr>
<th></th>
<th>Standard treatment alone n (%)</th>
<th>Standard treatment plus cinacalcet n (%)</th>
<th>Difference n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>One major fracture</td>
<td>25 (2.5)</td>
<td>21 (2.1)</td>
<td>4 (0.4)</td>
</tr>
<tr>
<td>More than one major fracture</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
<td>0</td>
</tr>
<tr>
<td>One CV event</td>
<td>438 (43.8)</td>
<td>434 (43.4)</td>
<td>4 (0.4)</td>
</tr>
<tr>
<td>More than one CV event</td>
<td>726 (72.6)</td>
<td>687 (68.7)</td>
<td>39 (3.9)</td>
</tr>
<tr>
<td>Parathyroidectomy</td>
<td>211 (21.1)</td>
<td>64 (6.8)</td>
<td>147 (14.7)</td>
</tr>
<tr>
<td>Surgical mortality</td>
<td>9 (4.3% of surgeries)</td>
<td>3 (4.7% of surgeries)</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

Table 7. Survival predicted by the model base case

<table>
<thead>
<tr>
<th></th>
<th>Survival 25th centile (years)</th>
<th>Median survival (years)</th>
<th>Survival 75th centile (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard treatment plus cinacalcet</td>
<td>2.25</td>
<td>5.00</td>
<td>8.75</td>
</tr>
<tr>
<td>Standard treatment alone</td>
<td>2.00</td>
<td>4.50</td>
<td>8.00</td>
</tr>
</tbody>
</table>
Whether or not the cost of dialysis is included in the analysis.

Through threshold analysis, we explored whether alterations in these key inputs individually could affect the ICER to such an extent that cinacalcet might be considered cost-effective at a willingness to pay (WTP) threshold of £30 000 (£43 200). Only two changes were found that would individually render cinacalcet cost-effective at this level: a reduction of cinacalcet costs from £0.145/mg to £0.08/mg (£0.21 to £0.12) or, if the RR of mortality for those with ‘very uncontrolled’ PTH levels were more than double that of those with ‘controlled’ PTH levels (RR = 2.2 compared with the base case RR = 1.1824).

Probabilistic sensitivity analysis

Graphic presentation of the Monte-Carlo outputs (Figure 2) shows the ICER values for 1000 simulations. A cost-effectiveness acceptability curve (CEAC) [20] has also been calculated showing, at different levels of WTP for an additional QALY, the probability that cinacalcet is cost-effective.

The simulation output shows that cinacalcet is cost-effective in just 0.5% of simulations undertaken. Although slightly more QALYs are always accrued, the additional costs of treatment means that the ICER is almost always greater than £30 000 per QALY. The CEAC shows that cinacalcet is unlikely to be the most cost-effective option below a WTP threshold of about £62 000 (£89 000).

We also ran probabilistic analysis for the base case including the cost of dialysis, which show similar results (Figure 3 – see online supplement).

Cost-effectiveness for people with different degrees of SHPT

Cinacalcet may have more impact on people who have ‘uncontrolled’ PTH (33 to 84 pmol/l) than those with ‘very uncontrolled’ PTH (≥85 pmol/l) [8]. Pooled trial data suggest that of those with ‘very uncontrolled’ PTH levels, 12% will become ‘controlled’ after treatment with cinacalcet compared to none of those treated by standard treatment alone; for those with ‘uncontrolled’ PTH levels, the percentage controlled by treatment are 51 and 7%, respectively. We investigated the cost-utility for these two groups separately. The results are shown in Tables 8 and 9. Although the ICER is lower in people with ‘uncontrolled’ PTH than in people with ‘very uncontrolled’ PTH levels, in neither case would cinacalcet be considered cost-effective.

Cost-effectiveness if stopping rules are employed

Currently, treatment of SHPT tends to continue even if PTH target levels are not met, as any increased risk of CV events and fractures are believed to be continuous, making any reduction or stabilization of PTH levels desirable. We undertook a sensitivity analysis to establish the cost-effectiveness of cinacalcet if stopping rules are employed. If those whose PTH levels remain ‘very uncontrolled’ after the 3-month titration period with cinacalcet revert to standard care alone after this

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**Table 8.** Cost-effectiveness of cinacalcet in people with ‘uncontrolled’ levels of PTH and colleagues (dialysis costs excluded)

<table>
<thead>
<tr>
<th></th>
<th>Costs (£)</th>
<th>QALYs</th>
<th>Incremental costs</th>
<th>Incremental QALYs</th>
<th>ICER (£/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard treatment only</td>
<td>6 466</td>
<td>3.06</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Standard treatment plus cinacalcet</td>
<td>27 905</td>
<td>3.43</td>
<td>21 438</td>
<td>0.37</td>
<td>57 442</td>
</tr>
</tbody>
</table>

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time, the ICER falls to £53 400 (€76 300). If only those who achieve target levels of PTH continue to receive cinacalcet whilst those with ‘uncontrolled’ and ‘very uncontrolled’ PTH levels revert to standard care alone, the ICER drops to £44 000 (€63 000). In both cases, the ICER is higher than usual WTP thresholds in the UK.

Scenario analysis: exploration of the impact of cinacalcet through estimated impacts on calcium-phosphate product control

Due to limitations in the evidence base, we have based our model on a single bio-marker for risk of adverse events. This is a limitation for two reasons: first, it is known that the levels of PTH, Ca and Ph are interconnected, and second, PTH levels may not be the strongest marker of risk for cardiovascular events or mortality. However, the systematic review shows that there is very limited information about the impact of cinacalcet on other biochemical markers especially in relation to its impact on PTH [8]. The only available information is that 91% of those treated with cinacalcet who achieve PTH target levels also have a reduction in calcium-phosphate product (CaxP) levels from their baseline level.

We have explored the potential impact of this in our model although the analysis should be regarded as purely exploratory. We have assumed that all of those with controlled PTH also have controlled CaxP levels according to the KDOQI target level (<4.4 mmol²/l² or <55 mg²/ml²) while all of those with uncontrolled PTH levels also have uncontrolled CaxP levels. This is likely to create a bias in favour of cinacalcet. The major difference between this scenario and the base case is that the RR of cardiovascular event and mortality between levels of control increase, biased data from the large Block and colleagues study [13]. The RR of mortality for those with uncontrolled CaxP levels is 1.63 and RR of cardiovascular events is 1.38. Full details of inputs used, including ranges used in the PSA, are available from the authors.

Results for scenario analysis using data on calcium-phosphate product levels

The results for this speculative analysis are shown in Table 10. The ICER is considerably reduced from the original model that bases the risk of adverse effect solely on PTH levels. However it is still higher than is usually accepted as representing a cost-effective treatment option.

Results of PSA for scenario analysis based on calcium-phosphate product levels

Figure 4 shows the PSA results when dialysis costs are excluded. Cinacalcet is cost-effective at a WTP threshold of £30 000 per QALY (€43 200) in 5.8% of simulations. Cinacalcet only becomes likely to be cost-effective above a WTP threshold of around £40 000/QALY (€57 600).

Figure 5 shows the equivalent PSA results when the dialysis costs are included (see online supplement). None of the simulations show cinacalcet to be cost-effective at a WTP threshold of £30 000 per QALY (€43 200). Cinacalcet only becomes likely to be cost-effective above a WTP threshold of £60 000/QALY (€86 400).

Discussion

Cinacalcet is unlikely to be considered cost-effective at usual levels of WTP in the NHS [21]. The lack of large differences between comparator arms is largely explained by the relatively high background death rate for this population. Any differences in mortality risk between the arms depend on differences in the number of people who have ‘uncontrolled’ and ‘very uncontrolled’ PTH levels compared with those who have ‘controlled’ levels. The RR of adverse effects such as fracture, cardiovascular event and death are slight between these levels of PTH control. People with ‘very uncontrolled’ PTH have a higher RR of all major events than those with more controlled PTH levels.

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Table 9. Cost-effectiveness of cinacalcet in people with ‘very uncontrolled’ levels of PTH and colleagues (dialysis costs included)

<table>
<thead>
<tr>
<th></th>
<th>Costs (£)</th>
<th>QALYs</th>
<th>Incremental costs</th>
<th>Incremental QALYs</th>
<th>ICER (£/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard treatment only</td>
<td>6 667</td>
<td>3.02</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard treatment plus cinacalcet</td>
<td>27 155</td>
<td>3.27</td>
<td>20 488</td>
<td>0.25</td>
<td>81 479</td>
</tr>
</tbody>
</table>

Table 10. Scenario Analysis 2 for the cost-effectiveness of cinacalcet based on the impact on CaxP levels (dialysis costs excluded)

<table>
<thead>
<tr>
<th></th>
<th>Costs (£)</th>
<th>Utilities</th>
<th>QALYs</th>
<th>Incremental costs</th>
<th>Incremental QALYs</th>
<th>ICER (£/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard treatment only</td>
<td>5089</td>
<td>2.38</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard treatment plus cinacalcet</td>
<td>23 512</td>
<td>2.85</td>
<td>18 422</td>
<td>0.47</td>
<td></td>
<td>38 855</td>
</tr>
</tbody>
</table>
However, because parathyroidectomy is also likely for these people, the risk of a fracture quickly returns to the same level as those with ‘controlled’ PTH levels post-surgery, and the risk of death is reduced to a level close to that experienced by the controlled group. In order to assess the impact of parathyroidectomy on cost-utility, we assessed the impact of removing it as an option in the model. If parathyroidectomy ceases to be a treatment option for anyone, the ICER drops by 12%, but remains high at £54 119 per QALY (£77 900).

In the base case analysis, we did not include the background cost of dialysis which may favour cinacalcet; if cinacalcet leads to survival gains, there will be significant cost implications for the NHS due to the need for dialysis during those added years of life. The handling of health care costs in added years of life due to an intervention is a methodological issue of considerable controversy [22,23]. Current conventions recommend that medical costs that are ‘related to the intervention’ should be included in cost-effectiveness analysis. It could be debated to what extent dialysis is related to SHPT as opposed to being related to the more broad underlying condition of ESRD. In addition, dialysis is a very expensive treatment that has already been accepted as a standard for this population although it may not be deemed cost-effective.

It is possible to make a comparison between the number of events predicted by the PenTAG model and those reported by Cunningham and colleagues in their analysis of fractures, parathyroidectomy and CV events [7]. In all cases, confidence intervals in the two analyses of RR overlap.

A major challenge to modelling the effect of cinacalcet in the long-term is the need to account for the combined impact of changes in the different biochemical markers. Serum levels of biomarkers such as PTH, Ca and Ph are interrelated and complex. Furthermore, the relationship between combinations of biomarkers and long-term clinical outcomes is complex and has not been characterized. The covariance between markers is unknown. We identified only one study, based on routine data in a Canadian population, that examined the relationship between calcium, phosphate, PTH and dialysis duration in relation to mortality only [24]. We have therefore modelled PTH independently, which may over- or under-estimate the risk of clinical events. However, the assumptions used in modelling calcium-phosphate product with PTH levels probably provide an optimistic view for cinacalcet on the risk-reduction of long-term consequences.

It is not known whether control of PTH with cinacalcet will be sustained. It is possible that underlying disease progression will still occur, or that effectiveness may not be sustained over the long-term. Compliance is also a known problem, with up to 86% of people on dialysis non-compliant with at least one aspect of their treatment [25]. Cinacalcet is an additional treatment for people who may already be taking large amounts of medication. Further, cinacalcet is associated with increased nausea and vomiting. Our base case assumes that there is no loss of control with cinacalcet, but that disease progression does affect those treated with standard care. This would cause a bias in favour of cinacalcet.

A number of assumptions have had to be made in relation to fracture in this population. The pattern of fractures experienced in people with ESRD due to SHPT is not clear, so general population data has been used. The interaction between the risks of first fracture or cardiovascular events and subsequent events is also unclear. The risk of death from fractures in people with renal osteodystrophy from SHPT is not well understood and assumptions from a different condition have been included. The paucity of evidence in relation to many of these factors has led to the need to make a range of linked assumptions, about which much uncertainty must remain. The direction of any potential bias is not clear.

The model is based on cinacalcet trial populations which have an average age of 55 years. The average age of accepting RRT in the UK, however, is 65 years [5]. It is not known whether the effectiveness of cinacalcet...
Cost-utility of cinacalcet

vares by age. Younger age is likely to bias the model in favour of cinacalcet as background death rates would be relatively lower.

Quality of life in SHPT is not well understood and so assumptions based on clinical opinion have been made in the model. Quality of life values following cardiovascular events or fractures in this population are not known and may be different from values obtained in the general population or other disease groups, as may resource use. Assumptions based on different populations have been included in the model and the impact of any bias this may introduce is not clear.

**Conclusion**

Cinacalcet is unlikely to be considered cost-effective at usual levels of WTP in the UK NHS. However, if drug costs were reduced considerably, cinacalcet may become cost-effective.

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**References**


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