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Cost-Effectiveness of Early versus Late Cinacalcet Treatment in Addition to Standard Care for Secondary Renal Hyperparathyroidism in the USA

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ABSTRACT

Objectives: The objective of this research was to estimate lifetime cost-effectiveness of treating patients with cinacalcet early (when parathyroid hormone [PTH] levels are in the range of 300–500 pg/ml) versus delaying treatment with cinacalcet (cinacalcet initiated when PTH levels are >800 pg/ml) in patients with secondary hyperparathyroidism (SHPT) in the US setting.

Methods: A Markov model was developed to simulate the effects of early versus delayed use of cinacalcet (plus standard of care). Four different PTH ranges (≤300 pg/ml; 301–500 pg/ml; 501–800 pg/ml; >800 pg/ml) were used to represent four different health states within the Markov model. Associated with each Markov state (PTH range) were varying risks of major SHPT complications, including cardiovascular disease (CVD), fracture (Fx), and parathyroidectomy (PTx). Baseline cohort characteristics and risks of CVD, Fx, and PTx by PTH category were derived from a large US renal database and published sources. Costs were estimated from the US Renal Data System database and reported in 2006 US Dollars ($). Clinical and economic outcomes were discounted at 3.0% per annum.

Results: Early treatment was projected to improve quality-adjusted life years (QALYs) by 0.337 years compared to delaying treatment. The incremental cost-effectiveness ratio was $17,275 per QALY gained.

Conclusions: Early treatment with cinacalcet was associated with improvements in QALYs and would represent good value for money compared to delaying treatment with cinacalcet.

Keywords: cinacalcet, cost-effectiveness, cost, ESRD, modeling, secondary hyperparathyroidism, US.

Introduction

End-stage renal disease (ESRD), defined as a life-threatening reduction in renal function requiring dialysis or a renal transplant, affects over 335,000 patients in the USA [1]. Recent estimates from the US Renal Data System (USRDS) have shown that treating ESRD patients is a considerable burden on health-care payers, exceeding $20 billon or approximately 6.7% of the total Medicare budget [2]. Cardiovascular disease (CVD) in this population continues to be the single largest cause of mortality and morbidity, accounting for about 45% percent of all deaths [2] and as much as one-third of the hospitalizations. Numerous cardiovascular (CV) risk factors are present in patients with kidney disease, including hypertension, extracellular fluid volume overload, diabetes, glucose intolerance, dyslipidemia, and alterations in homocysteine metabolism [1,3–7]. Nevertheless, even when these factors are considered together with other established CV risk factors, including advanced age, gender, obesity, and tobacco use, the risk for CV mortality in patients with advanced kidney disease exceeds that which would be predicted [4,8,9].

Common among patients with ESRD are high levels of parathyroid hormone (PTH) (secondary hyperparathyroidism [SHPT]), and an imbalance of calcium and phosphorus metabolism [10], which are all closely linked to CV morbidity and mortality [11–15]. Several studies have found that increased levels of PTH are associated with an increased risk of both CVD morbidity and mortality [4,15–18]. Similarly, associations between increased levels of calcium (Ca) [15,16,19], phosphorus (P) [15–19], and calcium-phosphorus product (Ca × P) [15,17,19] and an increased risk of both CVD morbidity and mortality have been established [4].

The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI™) has recently published guidelines for patients with SHPT, in an attempt to improve their management. The K/DOQI guidelines recommend that patients be treated to PTH levels between 150 and 300 pg/ml, corrected serum calcium levels of 8.4 to 9.5 mg/dl, serum phosphorus

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of 3.5 to 5.5 mg/dl, and Ca × P levels below 55 mg^2/dl^2 [20]. Historically, treatments for patients with SHPT included restricted phosphate consumption, oral phosphate binders, and calcium and vitamin D supplements [21–24]. Nevertheless, the complex metabolic relationship between PTH, Ca, and P makes treatment difficult, oftentimes with one or more of the treatments canceling out the effect of another [25–28].

A recent advancement to the historical treatments is cinacalcet HCL (cinacalcet), a calcimimetic, which has been demonstrated to control all four biomarkers linked to CV morbidity and mortality (PTH, Ca, P, and Ca × P) [24,29–33]. Currently in the USA, the use of cinacalcet is skewed toward patients with more severe PTH levels. Nevertheless, recent studies have indicated that treating patients with cinacalcet early (before PTH levels become severely uncontrolled) may be clinically beneficial [20]. Pooled data from three, similarly designed, 26-week clinical trials with a total 1136 patients randomized to receive either cinacalcet or placebo in addition to standard of care indicated that cinacalcet-treated patients were more likely to reach K/DOQI target ranges than those receiving placebo [24]. Further analysis also revealed that the patients who were administered cinacalcet for PTH levels between 300 and 500 pg/ml had a larger proportion of them reaching K/DOQI targets as compared to the patients who were administered cinacalcet for PTH levels between 500 and 800 pg/ml (or >800 pg/ml). Given that uncontrolled PTH levels have been associated with increased risk of mortality, CVD, and fracture events, there may be a sound clinical rationale for the early initiation of cinacalcet treatment, before PTH levels become substantially elevated [4,29,34].

Therefore, we performed a simulation modeling analysis based on the available clinical data to evaluate the cost-effectiveness of early treatment with cinacalcet (initiated when PTH levels were between 300 and 500 pg/ml) compared to delaying treatment (initiated once PTH levels increased above 800 pg/ml) in ESRD patients with SHPT.

Methods

Model

A Markov model was developed in TreeAge Pro 2006 0.4 (TreeAge Software, Williamstown, MA) to compare two treatment regimens in patients with ESRD and SHPT. The two treatment regimens simulated in the model were: 1) early treatment with cinacalcet in addition to standard of care (phosphate binders and vitamin D sterols)—with cinacalcet treatment initiated at the start of the simulation and then maintained over patient lifetimes; and 2) standard of care followed by delayed treatment with cinacalcet—with cinacalcet treatment initiated once PTH-levels increased above 800 pg/ml and then maintained over patient lifetimes. Cinacalcet lowers all four key K/DOQI targets; however, it is indicated for the treatment of SHPT based on PTH levels, and therefore, the model was constructed accordingly to account for the effect of cinacalcet by patients' current PTH levels. The model was designed to estimate life expectancy and quality-adjusted life expectancy, and account for the direct medical costs associated with each treatment regimen and treating disease-related complications.

Four PTH ranges (below 300 pg/ml, 301–500 pg/ml, 501–800 pg/ml, and above 800 pg/ml) were used to represent four different health states within the model. Associated with each health state (PTH range) were differential risks of developing complications because of SHPT (CVD event, fracture, parathyroidectomy) and all cause mortality. Simulated patients in both treatment regimens were assumed to enter the model with PTH levels between 301 and 500 pg/ml, and then transition to other PTH levels according to their respective treatment regimen. The cycle length of the model was 6 months.

If patients in the model experienced a CVD event or a major fracture, the costs of hospitalization related to its management were applied. Associated follow-up and maintenance costs in subsequent cycles, however, were not captured in the present analysis. These patients also experienced a reduction in their quality of life after CVD events or fractures. Patients who underwent a parathyroidectomy procedure were assumed to undergo immediate hospitalization for surgery. They incurred a reduction in quality of life for the year after surgery and then they assumed the quality of life associated with their PTH level. After surgery, PTH levels were assumed to be controlled (PTH levels below 300 pg/ml) for 6 months and then they could increase again and be treated with cinacalcet at the dose before surgery. Patient history and the occurrence of multiple complications were modeled by having patients enter each cycle of the model in a specific health state defined by PTH levels and history of CVD hospitalization, fracture, and parathyroidectomy. Risk factors for initial and subsequent events (CVD, fracture or parathyroidectomy) were assumed to be the same regardless of patient history. Nevertheless, if a patient experienced multiple complications, the cumulative effect of reduction in quality of life was taken into account by applying all corresponding quality of life utilities as multiplicative factors to the patient's current utility.

Event Rates and Risk Adjustments

Probabilities (by PTH category) for the occurrence of complications were derived from clinical trial data, when sample size permitted. When clinical trial data were not available, information was derived from published sources and a large US-based dialysis database was used. The probability of a parathyroidectomy procedure (for each PTH level) was derived from the

placebo arms of four pooled clinical trials which were conducted in the USA, Europe, and Australia and consisted of 487 patients that were randomly allocated to receive placebo [29]. There were approximately 324 patient-years of exposure [29]. The probability of a major fracture (for each PTH level) was derived from published data from 9007 dialysis patients (included in the Waves 1–4 of the Dialysis Morbidity and Mortality Study). The probability of a major fracture (for each PTH level) was derived from the pooled clinical trial data using a weighted occurrence rate of hip, vertebral, and pelvic fractures [29]. The model only made use of hip, vertebral, and pelvic fractures as they were determined to have the largest impact on quality of life and costs. The probability of a CVD event (for each PTH level) was derived from a large US database of ESRD dialysis patients.

Transition Probabilities

Transition probabilities within the model were used to capture changes in PTH levels in both treatment arms. In the early cinacalcet treatment arm, all patients entered the model in the health state representing PTH levels between 300 and 500 pg/ml and were assumed to receive cinacalcet treatment at the beginning of the simulation. Subsequently, 81% of patients were assumed to reach the K/DOQI target range of PTH levels below 300 pg/ml and were assumed to maintain this PTH level for the remainder of the simulation. The assumptions were based on pooled data from three, similarly designed, 26-week clinical trials with a total of 1136 dialysis patients randomized to receive either cinacalcet or placebo in addition to standard of care [24], and an extension study with up to 3 years of follow-up where patients on cinacalcet were shown to maintain their response [35]. The maintenance data are substantial when considering the life expectancy of patients on dialysis is approximately 5 years. The remaining proportion of patients in the early cinacalcet treatment group (19%) were assumed to transition to other PTH level health states at probabilities observed in a national renal database and continued to receive cinacalcet [36].

Similarly, in the delayed use of cinacalcet treatment arm, all patients entered the model with PTH levels between 300 and 500 pg/ml. The placebo arm of the pooled clinical trial data was used to obtain the probability of transitioning to the K/DOQI target (below 300 pg/ml) [24]. Transitions to the other PTH levels were obtained from a large US dialysis database [36]. Treatment with cinacalcet was initiated once patients transitioned to the health state representing PTH levels above 800 pg/ml, and continued to receive the medication until death or the patient underwent a parathyroidectomy procedure. Within the first 6 months of receiving cinacalcet therapy, there was a 22% probability that patients would transition to the PTH level health state below 300 pg/ml based on the pooled clinical trial data, and would remain there for the duration of the simulation [24,35]. The remaining proportion of patients would transition to the other PTH level health states at rates observed in the dialysis database.

Table 1 Mortality rates

Annual mortality rate per 1000 patient years at risk			
Age (years)	Mean (years)	Standard error	Reference
Below 19	68.8	8.25	[2]
20–44	101.7	3.32	[2]
45–64	173.9	3.78	[2]
65–74	286.4	6.93	[2]
Above 75	426.8	9.38	[2]
PTH level-based relative risk of death			
PTH level	Value (relative risk)		Reference
Below 300 pg/ml	1.00		[16]
300–500 pg/ml	1.0613		[16]
500–800 pg/ml	1.1824		[16]
Above 800 pg/ml	1.1824		[16]

PTH, parathyroid hormone.

Mortality

Estimates for the annual probability of death were derived from the USRDS 2005 annual report, with risks applied during each cycle and adjusted to increase with age to reflect the increased mortality of patients with ESRD (Table 1). To account for the increased risk of death with higher PTH levels, PTH level-specific relative risk of mortality rates reported by Block et al., derived from 40,538 dialysis patients in the USA, was multiplied by the age-specific all-cause mortality to calculate patients annual probability of death (Table 1) [16].

Simulation Cohorts

Baseline cohort characteristics of simulated patients included in the model were based on those included in the clinical trials reported by Cunningham et al. All patients were assumed to have ESRD, be treated with either hemodialysis or peritoneal dialysis, and have SHPT treated with standard care.

Costs

Costs were accounted in the analysis from the perspective of the third party health-care payer (Medicare) in the USA (Table 2). Pharmacy costs of cinacalcet and the costs associated with the occurrence of complications attributed to SHPT in patients with ESRD were included in the analysis. All costs were inflated to 2006 US dollars (as required) using the medical component of the US consumer price index (http://www.bls.gov/cpi/home.htm).

The average doses of cinacalcet applied in the model were taken from the measured doses from the pooled clinical trials [37–39]. Doses were determined by

Table 2 Summary of input cost data

Variable	Cost	Reference
CV hospitalization and follow-up	$20,001 ± 23,159	[52]
Major fracture and follow-up	$19,818 ± 21,509	[34]
Parathyroidectomy and follow-up	$15,247 ± 13,715	[52]
PTH test	$15.60	[53]
Cost of cinacalcet (per mg)	$0.374	(Data provided by Amgen)

CV, cardiovascular; PTH, parathyroid hormone.

whether patients transitioned to a PTH level health state below 300 pg/ml immediately after the initiation of the medication. The cost of a CVD hospitalization was applied in the model using a weighted average of complications as observed in the clinical trials. The weighted frequency of each CVD event was matched with the corresponding event costs derived from a large database of ESRD patients. A similar method was employed to derive the cost of a major fracture. The individual costs of a hip, pelvic or vertebral fracture were derived from Medicare claims data [35].

The costs of renal dialysis were not included in the model because the modeling study focused on the incremental costs of adding cinacalcet therapy and the occurrence of complications (Fig. 1).

Utilities

Changes in quality of life associated with the condition of ESRD, SHPT, and the occurrence of events were derived from multiple sources (Table 3). Quality of life at baseline for all patients in the analysis was derived from a European-based study estimating utility values for patients treated with both peritoneal and hemodialysis [40]. To capture the decrement in quality of life associated with the occurrence of a CVD event, patients' current utility was multiplied by 0.97, which was the mean value of angina symptoms [41,42]. To account for the disutility associated with a major fracture, a multiplicative value of 0.90 was applied in each subsequent year after the event which was derived from a systematic review of health state utilities of osteoporosis-related fractures [43]. In the absence of specific disutility data associated with a parathyroidectomy procedure, the surgical procedure was assumed to impact quality of life as per reported decrements for general surgery [44]. Reduced quality of life associated with uncontrolled PTH levels was incorporated into the analysis by multiplying the overall utility at the end of each cycle by –5%, –10%, and –15% for patients in the PTH level health states of 301 to 500 pg/ml, 501 to 800 pg/ml, and above 800 pg/ml, respectively, after physician consultation. The application of PTH level-specific utility values was intended to reflect bone pain, a common symptom associated with hyperparathyroidism.

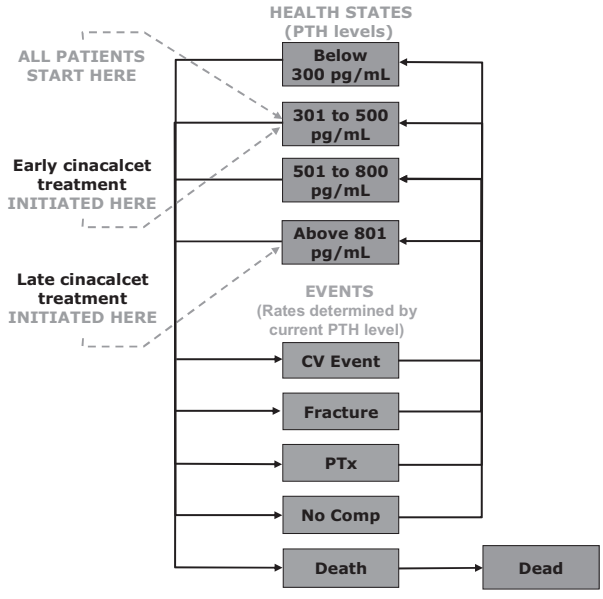

Figure 1 Model diagram. CV, cardiovascular; PTH, parathyroid hormone; PTx, parathyroidectomy.

Discounting and Time Horizon

All costs and clinical benefits were discounted at an annual rate of 3.0% in the base case analysis to correspond with current recommendations for health economic analyses in the US setting [45,46]. A patient lifetime horizon was used to capture all costs and events associated with the progression of SHPT in the simulation cohort.

Sensitivity Analyses

Sensitivity analyses were performed to investigate the impact of key input parameters and assumptions on the results of the base case analysis. The following

Table 3 Quality of life utilities

Event	Utility	Reference
ESRD state utility	0.6735 (0.58–0.78)	[40]
CVD hospitalization	×0.97	[41,42]
Major fracture	×0.90	[43]
300–500 pg/ml	×0.95	Assumption
500–800 pg/ml	×0.90	Assumption
Above 800 pg/ml	×0.85	Assumption

CVD, cardiovascular disease; ESRD, end-stage renal disease.

sensitivity analyses were performed: 1) the annual rate used to discount future costs and clinical benefits was varied between 0 and 6% per annum; 2) the dose of cinacalcet was varied by applying a multiplier to the dose in both treatment arms by ±20%; 3) adjusting the annual mortality rate of patients with ESRD by ±20%; 4) baseline event rates for both CVD and fracture events were varied by ±20%; 5) utility estimates applied to the three levels of uncontrolled PTH levels were removed; 6) after a parathyroidectomy, patients were assumed to not continue receiving cinacalcet treatment 6 months after surgery; and 7) probabilistic sensitivity analysis was performed, involving 1000 random samples from the distributions between the lower and upper bounds of 95% confidence intervals for clinical event rates, effectiveness, dosages of cinacalcet, costs, and utilities. This was in contrast to the deterministic calculation method applied in the base case analysis, which used mean or most likely values for the input parameters.

Results

Clinical Outcomes

In the base case analysis, early treatment with cinacalcet was projected to improve mean discounted quality-adjusted life expectancy by 0.337 quality-adjusted life years (QALYs) (3.002 vs. 2.665 QALYs) compared to late treatment with cinacalcet (Table 4). Similar improvements in life expectancy were estimated for early versus late cinacalcet treatment (4.638 vs. 4.372 years, difference of 0.266 years). Undiscounted life expectancy was estimated to be 5.294 years for early cinacalcet treatment and 4.961 years with late treatment, an improvement of 0.334 years.

Economic Outcomes

Early cinacalcet treatment was projected to result in total direct medical costs (discounted at 3% per annum) of $98,499 compared to $92,674 for patients treated with late cinacalcet, an increase of $5825 over patient lifetimes (Table 4). Medication costs of cinacalcet were projected to account for 50% of total costs in the early treatment arm and 46% in the late treatment arm over patient lifetimes.

Early treatment with cinacalcet was associated with higher medication costs, and because of the increased life expectancy, slightly higher CVD, and fracture treatment costs compared to late treatment. Nevertheless, these costs were partially offset by a reduction in the costs of patients undergoing a parathyroidectomy procedure because of lower PTH levels. Increased costs of treating CVD and fracture complications were attributed to the survival paradox, whereby patients in the early cinacalcet arm lived longer and, although these patients were more likely to achieve controlled PTH levels than late treatment (resulting in lower CVD event rates), patients were exposed to the risk of complications for a longer time period, leading to higher complication costs.

Cost-Effectiveness

The incremental cost-effectiveness ratio (ICER) was estimated to be $17,275 per QALY gained for early versus late cinacalcet treatment, when total direct medical costs were taken into account. When only medication costs were considered, early cinacalcet treatment was projected to result in an ICER of $20,860 per QALY gained, compared to late cinacalcet treatment. When life expectancy was considered (rather than quality-adjusted life expectancy), the ICER was $21,881 per life year gained for early versus late cinacalcet treatment.

Sensitivity Analyses

Sensitivity analysis performed on key input parameters in the base case analysis indicated that the results were robust under variation within a range of plausible assumptions (Table 5). Varying the annual rate used to discount future costs and clinical benefits between 0 and 6% (base case 3%) had little impact on the ICER. When outcomes were not discounted, early treatment with cinacalcet was projected to remain cost-effective compared to late treatment, with an ICER of $13,018 per QALY gained. Applying a discount rate of 6% to all clinical and economic outcomes increased the ICER to $21,723 per QALY gained for early versus late cinacalcet treatment.

When the average dose of cinacalcet was reduced by 20% in both treatment arms, the ICER was reduced to $13,103 per QALY gained, whereas increasing the average dose in both treatment arms, increased the ICER to $21,447 per QALY gained for early versus late cinacalcet treatment. A similar analysis was

Table 4 Base case results

	Early cinacalcet	Late cinacalcet	Difference
Quality-adjusted life expectancy	3.002	2.665	0.337
Life expectancy	4.638	4.372	0.266
Total costs	$98,499	$92,674	$5825
ICER (with quality-adjusted life expectancy)	$17,275 per QALY gained		
ICER (with life expectancy)	$21,881 per life year gained		

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Table 5 Sensitivity analysis

Assumption	Quality-adjusted life expectancy (QALYs)			Lifetime direct medical costs ($)			Outcome/ICER ($ per QALY gained)
	Early cinacalcet	Late cinacalcet	Difference	Early cinacalcet	Late cinacalcet	Difference	
Base case	3.002	2.665	0.337	$98,499	$92,674	$5,825	$17,275
0% discount rate	3.422	3.018	0.404	$111,977	$106,719	$5,257	$13,018
6% discount rate	2.675	2.388	0.287	$88,002	$81,768	$6,235	$21,723
Dose of cinacalcet −20%	3.002	2.665	0.337	$88,648	$84,229	$4,418	$13,103
Dose of cinacalcet +20%	3.002	2.665	0.337	$108,350	$101,118	$7,232	$21,447
Overall ESRD mortality −20%	3.562	3.178	0.384	$116,583	$113,312	$3,271	$8,526
Overall ESRD mortality +20%	2.580	2.282	0.298	$84,903	$77,530	$7,372	$24,722
CVD event rates −20%	3.009	2.671	0.338	$89,168	$83,425	$5,743	$17,015
CVD event rates +20%	2.997	2.660	0.337	$107,829	$101,930	$5,900	$17,521
Fracture event rates −20%	3.007	2.668	0.338	$98,103	$92,318	$5,786	$17,103
Fracture event rates +20%	2.998	2.661	0.336	$98,894	$93,030	$5,864	$17,445
PTH level utility removed	3.052	2.878	0.174	$98,499	$92,674	$5,825	$33,557
No cinacalcet treatment after a parathyroidectomy	3.002	2.665	0.337	$96,821	$86,403	$10,418	$30,897
Only pharmacy costs	3.002	2.665	0.337	$49,255	$42,221	$7,034	$20,860

CVD, cardiovascular disease; ESRD, end-stage renal disease; ICER, incremental cost-effectiveness ratio; PTH, parathyroid hormone; QALY, quality-adjusted life year.

performed by varying overall ESRD mortality rates by 20%. Increasing and decreasing the overall mortality rate by 20% produced ICERs of $8526 and $24,722 per QALY gained, respectively, for early versus late cinacalcet treatment over patient lifetimes.

To determine the impact of changes in CVD complication rates on final outcomes, CVD rates were reduced 20% in a sensitivity analysis. This produced an ICER of $17,015 per QALY gained. Increasing the risk of CVD complications by 20% generated an ICER of $17,521 per QALY gained for early versus late cinacalcet treatment. Similarly, variation in the rate of fractures had relatively little impact on overall outcomes. When the rate of fractures was varied by the same proportions, the ICERs for early versus late cinacalcet treatment varied between $17,103 and $17,445 per QALY gained over patient lifetimes.

Sensitivity analysis was also performed by removing disutility values applied in the base case analysis to explicitly account for increasing levels of bone pain in patients with uncontrolled PTH levels (above 300 pg/ml). When these disutility values were removed, the ICER increased to $33,557 per QALY gained for early versus late cinacalcet treatment.

In the base case analysis, patients were assumed to resume their previous dose of cinacalcet treatment 6 months (one cycle) after a parathyroidectomy, in both treatment arms. In a sensitivity analysis where patients were assumed to not receive cinacalcet treatment after a parathyroidectomy, the ICER increased to $30,897 per QALY gained for early versus late cinacalcet treatment.

Probabilistic sensitivity analysis (second-order Monte Carlo simulation) was also performed which involves random sampling between the lower and upper bounds of the 95% confidence intervals for clinical event rates, effectiveness, dosages of cinacalcet, costs, and utilities. Sampling did not substantially change the outcomes of the base case analysis where a deterministic approach (mean values) had been used. When 1000 mean values of incremental costs versus incremental effectiveness in terms of quality-adjusted life expectancy were plotted on a scatter-plot diagram, a majority of the points fell in the upper right quadrant of the cost-effectiveness plane, indicating increased costs and increased effectiveness. These mean values were used to generate an acceptability curve over a range of willingness to pay values which indicated that there was about a 99% probability that early cinacalcet treatment compared to later treatment (both in addition to standard care) would be considered cost-effective assuming a willingness to pay of $50,000 per QALY gained (Fig. 2) [47].

Discussion

Cinacalcet is the only drug currently available shown to lower all four mineral metabolism biomarkers (PTH,

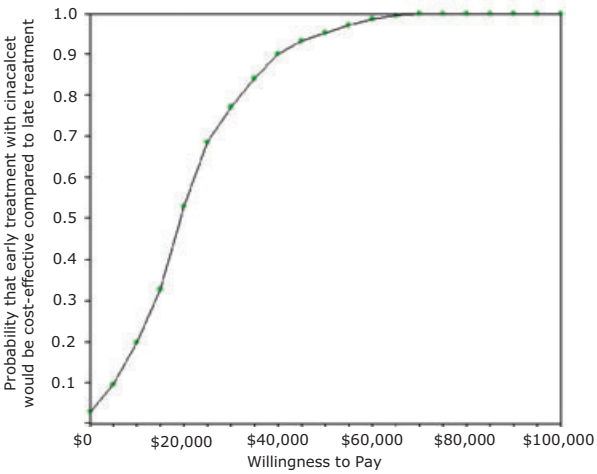

Figure 2 Acceptability curve.

Ca, P, Ca × P) [48] linked to CV morbidity and mortality [4,15,16,18,19,49]. Although use of cinacalcet is currently skewed toward patients with higher PTH levels, clinical trial results suggest there is sound clinical rationale for early use, and the results from the present analysis indicate that early treatment with cinacalcet is likely to be cost-effective compared to delaying treatment [24]. Initiation of treatment with cinacalcet when PTH levels were 300 to 500 pg/mL was estimated to increase both life expectancy and quality-adjusted life expectancy compared to treatment when PTH levels were above 800 pg/mL. Improvements in clinical outcomes were driven by PTH level-specific risk factors of developing complications and mortality and the larger proportion of patients achieving controlled PTH levels in the early cinacalcet treatment arm. Early treatment with cinacalcet was also associated with higher treatment costs. Nevertheless, with projected ICERs of $17,275 per QALY gained to $21,881 per life year gained, the present analysis indicated that early cinacalcet use is likely to be a cost-effective treatment option in the USA, compared to late treatment. This ICER is well below cost-effectiveness thresholds commonly referenced to indicate good value for money in the USA [47].

The concusions of the model are robust under variation in a wide range of assumptions. Sensitivity analyses revealed that outcomes from the model, in terms of cost per QALY gained for early versus late cinacalcet treatment, were most sensitive to reductions in mortality risk because of ESRD, removal of quality of life utilities for PTH levels, and assumptions regarding the continuation of cincacalcet treatment after a parathyroidectomy. Nevertheless, the corresponding ICERs in terms of cost per QALY gained were still within the range generally considered good value for money.

The costs associated with renal dialysis were not accounted for in the analysis. Had the considerable costs associated with renal dialysis been modeled, this may have biased against early cinacalcet because patients receiving this additional treatment tended to live longer, on average, and so would have accrued greater dialysis costs attributing to the so-called "survivor effect." A similar effect was seen with CVD and fracture costs, the early cinacalcet treatment arm, where the total costs attributed to treating these two complications were lower in shorter time horizons because of the increased life expectancy.

As with most health economic modeling analyses, certain assumptions were required to facilitate the modeling process. One assumption used in the primary analysis was that the risk of a subsequent fracture was not increased in patients who experienced an initial major fracture. No evidence was identified indicating that fracture risks would differ between initial and subsequent events and therefore the analysis assumed that there would be no difference. Similarly, any increased risk of a cardiovascular hospitalization subsequent to undergoing a parathyroidectomy procedure or incurring a major fracture was not known, and therefore not included in the analysis. Nevertheless, parathyroidectomy is rarely performed in patients with secondary renal hyperparathyroidism and remains an intervention of last resort [49,50]. It is known that parathyroidectomy is accompanied by a 1.5- to 2.7-fold increased risk of death during the first 3 months after surgery, accompanied by a decline in death rates toward 10% below the mortality rate observed in matched controls [49]. In the present analysis, the risk of death immediately after a parathyroidectomy was assumed to be 2.1 times higher than general ESRD mortality. Additionally, calcification in other soft tissues was not modeled which although very rare is a serious complication and associated with high degree of mortality.

The increased risk of death after a CVD or fracture event was not accounted for in the analysis. Mortality was assumed to be the same regardless of a patient's history of complications (except immediately after a parathyroidectomy) and was instead dependent upon patient age and PTH level. This assumption is likely to have favored late cinacalcet treatment as patients in the higher PTH levels experienced more CVD and fracture events.

A health economic model of cinacalcet treatment in the UK setting has been previously published by Garside et al. [51] where the authors concluded that cinacalcet treatment was unlikely to be cost-effective in the UK under the assumptions used to construct their model. It is noteworthy, however, that this was not the view of NICE in the recently published technology appraisal guidance (no. 117) where cinacalcet was indeed recommended for funding. Published literature has demonstrated a link between higher PTH levels and mortality [16]. The Garside model does not take this into account, whereas the current model does.

Despite acknowledging that bone pain and pruritis are common symptoms of hyperparathyroidism, the Garside model only applies a decrement in health state utility to "very uncontrolled" PTH levels (a value which is consistent with the current model), whereas the current model applies a gradually increasing health state utility decrement as PTH levels increase above an uncontrolled state.

In summary, this economic model suggests that it is cost-effective to initiate treatment with cinacalcet as soon as patients' PTH levels rise above 300 pg/ml rather than delaying treatment until their PTH levels are severely out of control.

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Supplementary materials for this article can be found at: http://www.ispor.org/publications/value/ViHsupplementary.asp

References

1 Sarnak MJ, Levey AS. Cardiovascular disease and chronic renal disease: a new paradigm. Am J Kidney Dis 2000;35(4 Suppl. 1):S117–31.
2 U.S. Renal Data System. USRDS 2004 Annual Data Report: Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. Bethesda, MD: US Renal Data System, 2006.
3 Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis 1998;32(5 Suppl. 3):S112–19.
4 Slinin Y, Foley RN, Collins AJ. Calcium, phosphorus, parathyroid hormone, and cardiovascular disease in hemodialysis patients: the USRDS waves 1, 3, and 4 study. J Am Soc Nephrol 2005;16:1788–93.
5 Kobus G, Malyszko J, Mysyliwiec M. [Cardiovascular risk factors in dialyzed patients]. Pol Arch Med Wewn 2004;112:1425–31.
6 Locatelli F, Pozzoni P, Del Vecchio L. Epidemiology of chronic kidney disease in Italy: possible therapeutical approaches. J Nephrol 2003;16:1–10.
7 Buccianti G, Baragetti I, Bamonti F, et al. Plasma homocysteine levels and cardiovascular mortality in patients with end-stage renal disease. J Nephrol 2004;17:405–10.
8 Fabbian F, Benussi P, Cacici G, et al. Relationship between diabetes mellitus and degree of coronary artery disease in uraemic patients investigated with coronary angiography. Int J Artif Organs 2003; 26:196–9.
9 Qunibi WY. Dyslipidemia and progression of cardiovascular calcification (CVC) in patients with end-stage renal disease (ESRD). Kidney Int 2005; 95(Suppl.):S43–50.
10 Slatopolsky E, Brown A, Dusso A. Pathogenesis of secondary hyperparathyroidism. Kidney Int Suppl 1999;73(Suppl.):S14–19.
11 Suliman ME, Qureshi AR, Barany P, et al. Hyperhomocysteinemia, nutritional status, and cardiovascular disease in hemodialysis patients. Kidney Int 2000; 57:1727–35.
12 Cases A, Vera M, Lopez Gomez JM. Cardiovascular risk in patients with chronic renal failure. Patients in renal replacement therapy. Nefrologia 2002;22 (Suppl. 1):S68–74.
13 Zoccali C. Cardiovascular risk in uraemic patients-is it fully explained by classical risk factors? Nephrol Dial Transplant 2000;15:454–7.
14 Haydar AA, Hujairi NM, Covic AA, et al. Coronary artery calcification is related to coronary atherosclerosis in chronic renal disease patients: a study comparing EBCT-generated coronary artery calcium scores and coronary angiography. Nephrol Dial Transplant 2004;19:2307–12.
15 Young EW, Albert JM, Satayathum S, et al. Predictors and consequences of altered mineral metabolism: the Dialysis Outcomes and Practice Patterns Study. Kidney Int 2005;67:1179–87.
16 Block GA, Klassen PS, Lazarus JM, et al. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J Am Soc Nephrol 2004;15:2208–18.
17 Ganesh SK, Stack AG, Levin NW, et al. Association of elevated serum PO (4), Ca x PO (4) product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. J Am Soc Nephrol 2001;12:2131–8.
18 Marco MP, Craver L, Betriu A, et al. Higher impact of mineral metabolism on cardiovascular mortality in a European hemodialysis population. Kidney Int 2003;85(Suppl.):S111–14.
19 Rubel JR, Milford EL. The relationship between serum calcium and phosphate levels and cardiac valvular procedures in the hemodialysis population. Am J Kidney Dis 2003;41:411–21.
20 Levey AS, Coresh J, Balk E, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann Intern Med 2003;139:137–47.
21 Aparicio M, Combe C, Lafage MH, et al. In advanced renal failure, dietary phosphorus restriction reverses hyperparathyroidism independent of changes in the levels of calcitriol. Nephron 1993;63:122–3.
22 Andress DL, Norris KC, Coburn JW, et al. Intravenous calcitriol in the treatment of refractory osteitis fibrosa of chronic renal failure. N Engl J Med 1989;321:274–9.
23 Martin KJ, Gonzalez EA, Gellens M, et al. 19-Nor-1-alpha-25-dihydroxyvitamin D2 (Paricalcitol) safely and effectively reduces the levels of intact parathyroid hormone in patients on hemodialysis. J Am Soc Nephrol 1998;9:1427–32.
24 Moe SM, Chertow GM, Coburn JW, et al. Achieving NKF-K/DOQI bone metabolism and disease treatment goals with cinacalcet HCl. Kidney Int 2005; 67:760–71.

25 Reichel H, Drüeke T, Ritz E. Skeletal Disorders. Oxford Textbook of Clinical Nephrology (2nd ed.). Oxford: Oxford University Press, 1997.
26 Block GA, Port FK. Re-evaluation of risks associated with hyperphosphatemia and hyperparathyroidism in dialysis patients: recommendations for a change in management. Am J Kidney Dis 2000;35:1226–37.
27 Johnson CA, McCarthy J, Bailie GR, et al. Analysis of renal bone disease treatment in dialysis patients. Am J Kidney Dis 2002;39:1270–7.
28 Indridason OS, Quarles LD. Comparison of treatments for mild secondary hyperparathyroidism in hemodialysis patients. Durham Renal Osteodystrophy Study Group. Kidney Int 2000;57:282–92.
29 Cunningham J, Danese M, Olson K, et al. Effects of the calcimimetic cinacalcet HCl on cardiovascular disease, fracture, and health-related quality of life in secondary hyperparathyroidism. Kidney Int 2005; 68:1793–800.
30 Goodman WG, Hladik GA, Turner SA, et al. The Calcimimetic agent AMG 073 lowers plasma parathyroid hormone levels in hemodialysis patients with secondary hyperparathyroidism. J Am Soc Nephrol 2002;13:1017–24.
31 Quarles LD, Sherrard DJ, Adler S, et al. The calcimimetic AMG 073 as a potential treatment for secondary hyperparathyroidism of end-stage renal disease. J Am Soc Nephrol 2003;14:575–83.
32 Lindberg JS, Moe SM, Goodman WG, et al. The calcimimetic AMG 073 reduces parathyroid hormone and calcium x phosphorus in secondary hyperparathyroidism. Kidney Int 2003;63:248–54.
33 Block GA, Martin KJ, de Francisco AL, et al. Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. N Engl J Med 2004;350: 1516–25.
34 Danese MD, Kim J, Doan QV, et al. PTH and the risks for hip, vertebral, and pelvic fractures among patients on dialysis. Am J Kidney Dis 2006;47:149–56.
35 Moe SM, Cunningham J, Bommer J, et al. Long-term treatment of secondary hyperparathyroidism with the calcimimetic cinacalcet HCl. Nephrol Dial Transplant 2005;20:2186–93.
36 Belozeroff V, Borker R, Barder B, Pupim L, Hakim RM. Trends in parathyroid hormone in hemodialysis patients. National Kidney Foundation (NKF) 2007 Spring Clinical Meeting. 2007.
37 Lindberg JS, Culleton B, Wong G, et al. Cinacalcet HCl, an oral calcimimetic agent for the treatment of secondary hyperparathyroidism in hemodialysis and peritoneal dialysis: a randomized, double-blind, multicenter study. J Am Soc Nephrol 2005;16: 800–7.
38 Block GA, Martin KA, Turner SA. Phase 3 study results demonstrate efficacy and safety of calcimimetic cinacalcet HCL in hemodialysis patients with secondary hyperparathyroidism (HPT). J Am Soc Nephrol 2003;14:461A.
39 de Francisco AL, Suranyi MG, Cunningham J. Cinacalcet HCL (AMG 073) for the treatment of hemodialysis patients with secondary hyperparathyoidism (HPT): results of a European/Australian phase 3 study. J Am Soc Nephrol 2006;14:461A.
40 de Wit GA, Ramsteijn PG, de Charro FT. Economic evaluation of end stage renal disease treatment. Health Policy 1998;44:215–32.
41 Nease RF Jr, Kneeland T, O'Connor GT, et al. Variation in patient utilities for outcomes of the management of chronic stable angina. Implications for clinical practice guidelines. Ischemic Heart Disease Patient Outcomes Research Team. JAMA 1995; 273:1185–90.
42 Dolan P. Modeling valuations for EuroQol health states. Med Care 1997;35:1095–108.
43 Brazier JE, Green C, Kanis JA. A systematic review of health state utility values for osteoporosis-related conditions. Osteoporos Int 2002;13:768–76.
44 Tufts-New England Medical Center. Cost-effective analysis registry (CEA). Available from: https://research.tufts-nemc.org/cear/default.aspx [Accessed January 10, 2007].
45 Tarn T, Smith M. Pharmacoeconomic guidelines around the world. ISPOR Connections 2004;10:5–15.
46 Gold MR, Siegel JE, Russell LB, Weinstein MC. Cost-Effectiveness in Health and Medicine (1st ed.). New York: Oxford University Press, 1996.
47 Eichler HG, Kong SX, Gerth WC, et al. Use of cost-effectiveness analysis in health-care resource allocation decision-making: how are cost-effectiveness thresholds expected to emerge? Value Health 2004; 7:518–28.
48 Torres PU. Cinacalcet HCl: a novel treatment for secondary hyperparathyroidism caused by chronic kidney disease. J Ren Nutr 2006;16:253–8.
49 Kestenbaum B, Andress DL, Schwartz SM, et al. Survival following parathyroidectomy among United States dialysis patients. Kidney Int 2004;66:2010–16.
50 Goodman WG. Medical control of secondary hyperparathyroidism: we're not there yet. Kidney Int 2004;65:335–6.
51 Garside R, Pitt M, Anderson R, et al. 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. Nephrol Dial Transplant 2007;22:1428–36.
52 Doan QV, Dylan M, Griffiths R, et al. Economic impact of cardiovascular disease and fractures in patients with ESRD. National Kidney Foundation (NKF) 2007 Spring Clinical Meeting. 2007.
53 Watkins Memorial Health Center. Laboratory Services. 2006. Available from: http://www.da ksgov/purch/contracts/ContractData/06149 doc [Accessed February 8, 2007].