

Cost Effectiveness of Paricalcitol Versus Cinacalcet with Low-Dose Vitamin D for Management of Secondary Hyperparathyroidism in Haemodialysis Patients in the USA

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Abstract

Background The IMPACT SHPT [Improved Management of Intact Parathyroid Hormone (iPTH) with Paricalcitol-Centered Therapy Versus Cinacalcet Therapy with Low-Dose Vitamin D in Hemodialysis Patients with Secondary Hyperparathyroidism] study compared the effectiveness of paricalcitol and cinacalcet in the management of secondary hyperparathyroidism in haemodialysis patients but did not report the costs or cost effectiveness of these treatments.

Aim The aim of this study was to compare the cost effectiveness of a paricalcitol-based regimen versus cinacalcet with low-dose vitamin D for management of secondary hyperparathyroidism in haemodialysis patients from a US payer perspective, using a 1-year time horizon.

Methods This was a post hoc cost-effectiveness analysis of data collected for US patients enrolled in the IMPACT SHPT study—a 28-week, randomized, open-label, phase 4, multinational study (ClinicalTrials.gov identifier: NCT00977080). Patients eligible for the IMPACT SHPT study were aged ≥ 18 years with stage 5 chronic kidney disease, had been receiving maintenance

haemodialysis three times weekly for at least 3 months before screening and were to continue haemodialysis during the study. Only US patients who reached the evaluation period (weeks 21–28) were included in this secondary analysis. US subjects in the IMPACT SHPT study were randomly assigned to receive intravenous paricalcitol, or oral cinacalcet plus fixed-dose intravenous doxercalciferol, for 28 weeks. Patients in the paricalcitol group could also receive supplemental cinacalcet for hypercalcaemia. The primary effectiveness endpoint in the IMPACT SHPT study was the proportion of subjects who achieved a mean intact parathyroid hormone (iPTH) level of 150–300 pg/mL during the evaluation period. In this secondary analysis, we estimated the incremental cost-effectiveness ratio (ICER), comparing paricalcitol-treated patients with cinacalcet-treated patients on the basis of this primary endpoint and several secondary endpoints. Costs were estimated by examining the dosage of the study drug (paricalcitol or cinacalcet) and phosphate binders used by each participant during the trial. Nonparametric bootstrap analysis was used to examine the accuracy of the ICER point estimates.

Results The percentages of patients achieving the treatment goal of a mean iPTH level between 150–300 pg/mL during weeks 21–28 of therapy were 56.9 % in the paricalcitol group and 34.0 % in the cinacalcet group (a difference of 23 %, $p = 0.0235$). Paricalcitol was also more effective for each of the secondary endpoints. When annualized, the total drug costs were US\$10,153 in the paricalcitol group and US\$15,967 in the cinacalcet group, a difference of US\$5,814 (57.3 %, $p = 0.0053$). Because the paricalcitol-based treatment was less expensive and more effective, it was ‘dominant’, compared with cinacalcet, in this cost-effectiveness analyses. In our bootstrap analysis, 99.1 % of bootstrap replicates for the ICER of the primary

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endpoint fell within the lower right quadrant of the cost-effectiveness plane—where paricalcitol is considered dominant. For all of the other endpoints, paricalcitol was dominant in 100 % of replicates.

Conclusion On the basis of dosing and effectiveness data from US patients in the IMPACT SHPT study, we found that a regimen of intravenous paricalcitol was more cost effective than cinacalcet plus low-dose vitamin D in the management of iPTH in patients with SHPT requiring haemodialysis.

1 Introduction

Because of the aging of the population and the increased prevalence of hypertension, diabetes and obesity, chronic kidney disease (CKD) is impacting a greater proportion of US society [1–3]. Many patients with CKD progress to end-stage renal disease (ESRD) and require dialysis. As a result, CKD is very expensive for individual patients, insurance companies and Medicare [4]. Many CKD patients also develop elevated intact parathyroid hormone (iPTH) levels or secondary hyperparathyroidism (SHPT), which further adds to the burden of their disease [5]. SHPT results in imbalances in serum calcium and phosphorous levels, and in alternations in vitamin D metabolism, and can lead to renal osteodystrophy, fractures, cardiovascular disease and even death [6–10].

Guidelines for the management of SHPT have been published by the National Kidney Foundation (NKF) and recommend control of iPTH levels with vitamin D receptor (VDR) activators [11, 12]. The 2003 Kidney Disease Outcomes Quality Initiative (KDOQI) recommended a serum iPTH target of 150–300 pg/mL, while the 2009 Improving Global Outcomes (KDIGO) guidelines suggested an iPTH goal of 2–9 times the upper limit of normal (which corresponds to a range of 130–600 pg/mL) [11]. Control of iPTH levels with VDR activators—which include calcitriol, doxercalciferol, paricalcitol and alfacalcidol—is associated with improved outcomes [13, 14]. Among the VDR activators, the evidence is strongest for paricalcitol, which is associated with reduced hospitalization and improved survival [15–17]. Cinacalcet, a calcimimetic agent, is also effective in reducing PTH levels and, when used concomitantly with low-dose vitamin D, it may minimize hypercalcaemia [18, 19].

The effectiveness of paricalcitol and cinacalcet was compared in the recent multinational IMPACT SHPT (Improved Management of iPTH with Paricalcitol-Centered Therapy Versus Cinacalcet Therapy with Low-dose Vitamin D in Hemodialysis Patients with Secondary Hyperparathyroidism) study. Paricalcitol was found to be superior to cinacalcet plus low-dose vitamin D in

controlling iPTH levels [20]. While the IMPACT SHPT study was important for understanding the comparative effectiveness of the two drugs, knowing the cost effectiveness is also essential. A recent secondary analysis of the IMPACT SHPT data found that a paricalcitol-based regimen was less expensive than cinacalcet from a global perspective (with costs expressed in Euros) [21]. However, because of differences in international drug pricing, these data may not be relevant to US patients, clinicians and payers. Moreover, what is needed most for evidence-based decision making is a direct comparison of the cost effectiveness of these agents.

Here, we provide an examination of the US patients in the IMPACT SHPT study, and we extend the previous analysis by examining not just the costs but also the cost effectiveness of paricalcitol compared with cinacalcet. While there are other studies that have compared the cost effectiveness of treatments for SHPT, none have compared paricalcitol and cinacalcet directly [22, 23]. Thus, the objective of this study was to evaluate, from a payer perspective, the cost effectiveness of paricalcitol versus cinacalcet with low-dose vitamin D for management of SHPT in haemodialysis patients in the USA.

2 Methods

This was a secondary cost-effectiveness analysis of data from US patients collected during the IMPACT SHPT study. The methods of the IMPACT SHPT study are described in detail elsewhere [24]. In brief, the IMPACT SHPT study was a 28-week, randomized, open-label, phase 4, multinational study (ClinicalTrials.gov identifier: NCT00977080). US subjects were randomly assigned to receive intravenous paricalcitol (the paricalcitol group), or oral cinacalcet plus fixed-dose intravenous doxercalciferol, for 28 weeks. Patients in the paricalcitol group could also receive supplemental cinacalcet for hypercalcaemia [used only if the serum calcium level was ≥ 10.5 mg/dL (2.61 mmol/L) in two consecutive blood tests in the presence of a high iPTH level]. At weeks 21–28 (the ‘evaluation period’), patients were evaluated for clinical response. For the purposes of this secondary analysis, only those patients who reached the evaluation period were included.

The primary effectiveness endpoint in the IMPACT SHPT study was the proportion of subjects who achieved a mean iPTH level of 150–300 pg/mL during the evaluation period. We used this endpoint as our primary effectiveness input in estimating cost effectiveness. We also included secondary effectiveness endpoints, namely the proportion of subjects achieving either a ≥ 30 or ≥ 50 % reduction in the iPTH level, the proportion of subjects with a normal serum calcium level (8.4–10.5 mg/dL) and the

Table 1 Unit prices of drugs included in the analysis

Drug name	Unit price [US\$] ^a
Study drugs	
Cinacalcet	0.46/mg
Intravenous paricalcitol	3.03/mcg
Intravenous doxercalciferol	3.13/mcg
Phosphate binders	
Calcium acetate	0.00095/mg
Calcium carbonate	0.00010/mg
Calcium gluconate	0.00285/mg
Lanthanum carbonate	0.0098/mg
Sevelamer	0.00427/mg

^a Unit prices were based on 2012 wholesale acquisition costs and were obtained from AnalySource, an online source of drug pricing data from First Databank, Inc. (San Francisco, CA, USA)

proportion of subjects with both an iPTH level of 150–300 pg/mL and a calcium level of 8.4–10.5 mg/dL during the evaluation period.

Costs were not measured directly in the IMPACT SHPT study but were estimated here by examining the dosage of the study drug (paricalcitol or cinacalcet) and phosphate binders used by each participant during the trial. Included in the cost of the study drugs was any supplemental cinacalcet administered to patients in the paricalcitol group and the use of fixed-dose intravenous doxercalciferol in the cinacalcet group. To estimate costs, we multiplied utilization by the unit price for each drug, which was based on the 2012 wholesale acquisition cost, to get the total cost per patient in US dollars. The wholesale acquisition cost was obtained from AnalySource, an online source of drug pricing data from First Databank, Inc. (San Francisco, CA, USA), and is shown in Table 1. We assumed that the dosage reached in the evaluation period was the maintenance dose, and we estimated annual costs by extrapolating the costs observed during the evaluation period. These annualized costs were then incorporated into our cost-effectiveness analysis so that the results assumed a 1-year time horizon.

Descriptive statistics, including means with standard deviations and percentages, were used to characterize the clinical and cost data in each group. Differences between demographic and baseline characteristics, costs and effectiveness outcomes were examined using chi-squared and Student *t* tests as appropriate. All statistical tests were two-tailed, with *p* values of <0.05 considered statistically significant. The data were summarized and analysed using SAS version 11.0 software (SAS Institute, Cary, NC, USA).

Incremental cost-effectiveness ratios (ICERs) were calculated for the primary and secondary effectiveness outcomes (separately). The ICER represents a ratio of the

difference in costs (the numerator) in the paricalcitol group relative to the cinacalcet group to the difference in effects (the denominator) of the two treatments. The formula is as follows: $ICER = (C_p - C_c)/(E_p - E_c)$, where C_p represents the total drug cost in the paricalcitol group and C_c represents the total drug cost in the cinacalcet group, and where E_p represents the effectiveness in the paricalcitol group and E_c represents the effectiveness in the cinacalcet group. Here, effectiveness is the proportion of patients in each group who achieved that particular endpoint.

To estimate the 95 % confidence intervals for the ICERs, we simulated 1,000 non-parametric bootstrap replicates by sampling with replacement from the original dataset. For each of the replicates, we calculated the ICER. The 95 % confidence intervals were determined by the 2.5th and 97.5th percentiles of all the bootstrap replicates. We also determined the proportion of bootstrap replicates that fell in each quadrant of the standard cost-effectiveness plane. We used this approach for both the primary effectiveness outcome and each of the secondary effectiveness outcomes.

3 Results

Table 2 describes the demographic and baseline characteristics of the patients in each treatment group. The two groups were comparable. The majority of patients were male—60.8 and 59.6 % in the paricalcitol and cinacalcet treatment groups, respectively—and their mean ages were 61.0 and 60.7 years, respectively. On average, the patients had been on dialysis for 3.9 years. Baseline laboratory values and the use of concomitant medications did not differ significantly between the groups. However, a significantly greater proportion of subjects in the paricalcitol group had angina and left ventricular hypertrophy.

3.1 Effectiveness

The clinical results of the IMPACT SHPT study are presented in detail elsewhere [20]. The primary endpoint was the percentage of patients achieving the treatment goal of a mean iPTH level between 150–300 pg/mL during weeks 21–28 of therapy per stratum. As shown in Table 2, among US patients, 29 (56.9 %) in the paricalcitol group and 16 (34.0 %) in the cinacalcet group reached this endpoint (a difference of 23 %, *p* = 0.0235). Similarly, greater proportions of patients in the paricalcitol group than in the cinacalcet group achieved a ≥ 30 % reduction in the iPTH level (84.3 versus 48.9 %, a difference of 35 %, *p* = 0.0002) and a ≥ 50 % reduction in the iPTH level (64.7 versus 21.3 %, a difference of 43 %, *p* = 0.0001). Further, compared with those in the cinacalcet group, a greater proportion

Table 2 Demographic and baseline characteristics and concomitant medications by treatment group

Characteristic	Paricalcitol	Cinacalcet	<i>p</i> value ^a
Subjects [<i>n</i>]	51	47	
Age [years; mean ± SD]	61.0 ± 11.5	60.7 ± 11.6	0.8984
Male [<i>n</i> (%)]	31 (60.8)	28 (59.6)	0.9027
Race [<i>n</i> (%)]			0.3147
White	24 (47.1)	26 (55.3)	
Black	25 (49.0)	19 (40.4)	
Other	2 (4.0)	2 (4.3)	
Hispanic [<i>n</i> (%)]	11 (21.6)	13 (27.7)	0.4836
Diabetes [<i>n</i> (%)]			
Type 1	5 (9.8)	1 (2.1)	0.1133
Type 2	33 (64.7)	26 (55.3)	0.3429
Cardiovascular disease [<i>n</i> (%)]			
Angina	7 (13.7)	1 (2.1)	0.0362
Myocardial infarction	10 (19.6)	4 (8.5)	0.1168
Coronary artery disease	20 (39.2)	13 (27.7)	0.2265
Left ventricular hypertrophy	11 (21.6)	2 (4.3)	0.0116
Duration of dialysis [years; mean ± SD]	3.9 ± 3.3	3.9 ± 3.3	0.9948
Blood pressure [mmHg; mean ± SD]			
Systolic	142.8 ± 26.1	149.4 ± 24.7	0.2016
Diastolic	72.7 ± 12.9	76.5 ± 15.2	0.1839
Concomitant medications [<i>n</i> (%)]			
Angiotensin-converting enzyme inhibitors	20 (39.2)	18 (38.3)	0.9258
Angiotensin II receptor blockers	9 (17.6)	7 (14.9)	0.7126
Beta blockers	35 (68.6)	27 (57.4)	0.2514
Calcium channel blockers	26 (51.0)	24 (51.1)	0.9934
Diuretics	16 (31.4)	9 (19.1)	0.1655
Erythropoiesis-stimulating agents	43 (84.3)	38 (80.8)	0.6511
Baseline laboratory values			
Serum iPTH level [pg/mL; mean ± SD]	516.6 ± 147.9	524.3 ± 149.7	0.7984
Corrected calcium level [mg/dL; mean ± SD]	9.0 ± 0.5	9.1 ± 0.4	0.5402
Phosphorus level [mg/dL; mean ± SD]	4.8 ± 1.0	5.0 ± 1.0	0.4789
Alkaline phosphatase level [IU/L; mean ± SD]	111.9 ± 52.8	126.9 ± 52.4	0.1617
Bone-specific alkaline phosphatase level [U/L; mean ± SD]	35.7 ± 15.8	41.7 ± 26.7	0.1801
25-hydroxy vitamin D level [ng/mL; mean ± SD] ^b	23.0 ± 14.0	23.7 ± 9.7	0.8148
Creatinine level [mg/dL; mean ± SD] ^c	8.1 ± 2.3	9.0 ± 2.5	0.0994
Albumin level [g/dL; mean ± SD]	4.0 ± 0.2	4.0 ± 0.3	0.6989

iPTH intact parathyroid hormone, SD standard deviation

^a Differences between groups were considered statistically significant (indicated by **bold text**) if $p < 0.05$ on the basis of Pearson's chi-squared test or Student's *t* test

^b Not all subjects had a baseline value recorded for this item— $n = 36$ in the paricalcitol group and $n = 36$ in the cinacalcet group

^c Not all subjects had a baseline value recorded for this item— $n = 46$ in the paricalcitol group and $n = 50$ in the cinacalcet group

of those in the paricalcitol group maintained a normal serum calcium level (92.2 versus 53.2 %, a difference of 39 %, $p < 0.0001$). Finally, more patients in the paricalcitol group than in the cinacalcet group both met the primary endpoint (an iPTH level of 150–300 pg/mL) and were normocalcaemic (52.9 versus 17.0 %, a difference of 36 %, $p = 0.0002$).

3.2 Costs

When annualized on the basis of the evaluation period, the mean total drug costs were US\$10,153 in the

paricalcitol group and US\$15,967 in the cinacalcet group, a difference of US\$5,814 (57.3 %, $p = 0.0053$), as shown in Table 3. The mean annualized costs of phosphate binders were US\$7,173 and US\$6,703 in the paricalcitol and cinacalcet groups, respectively, which was not statistically different ($p = 0.7645$). However, the mean annualized cost of the study drug for those in the cinacalcet group was three times that in the paricalcitol group (US\$2,979 and US\$9,264 in the paricalcitol and cinacalcet groups, respectively, a difference of US\$6,285, $p < 0.0001$).

Table 3 Effectiveness and costs by treatment group

Characteristic	Paricalcitol	Cinacalcet	<i>p</i> value ^a
Subjects [<i>n</i>]	51	47	
Effectiveness [<i>n</i> (%)]			
Primary endpoint			
iPTH level 150–300 pg/mL ^b	29 (56.9)	16 (34.0)	0.0235
Secondary endpoints			
≥30 % reduction in iPTH level ^c	43 (84.3)	23 (48.9)	0.0002
≥50 % reduction in iPTH level ^d	33 (64.7)	10 (21.3)	<0.0001
Calcium level 8.4–10.5 mg/dL ^e	47 (92.2)	25 (53.2)	<0.0001
iPTH level 150–300 pg/mL and calcium level 8.4–10.5 mg/dL ^f	27 (52.9)	8 (17.0)	0.0002
Costs [US\$; mean ± SD] ^g			
Cost of study drugs	2,979 ± 2,422	9,264 ± 7,275	<0.0001
Cost of phosphate binders	7,173 ± 6,987	6,703 ± 8,380	0.7645
Total drug cost	10,153 ± 7,751	15,967 ± 11,734	0.0053

iPTH intact parathyroid hormone, SD standard deviation

^a Differences between groups were considered statistically significant (indicated by **bold text**) if $p < 0.05$ on the basis of Pearson's chi-squared test or Student's *t* test

^b Proportion of subjects achieving a mean iPTH level of 150–300 pg/mL during the evaluation period (weeks 21–28)

^c Proportion of subjects achieving ≥30 % reduction in the mean iPTH level during the evaluation period compared with baseline

^d Proportion of subjects achieving ≥50 % reduction in the mean iPTH level during the evaluation period compared with baseline

^e Proportion of subjects with a mean calcium level of 8.4–10.5 mg/dL during the evaluation period

^f Proportion of subjects achieving both a mean iPTH level of 150–300 pg/mL and a mean calcium level of 8.4–10.5 mg/dL during the evaluation period

^g Costs were annualized on the basis of dosages in the evaluation period

3.3 Cost Effectiveness

Table 4 provides the results of our cost-effectiveness analysis. The table includes the difference between the paricalcitol and cinacalcet groups in terms of the mean total drug costs (based on data in Table 3). This is the numerator in the ICER calculations. Because paricalcitol was less expensive, the difference in cost was negative (representing the savings associated with paricalcitol). Note that the costs were the same for each of the ICER calculations. Table 3 also shows the difference between the paricalcitol and cinacalcet groups in the proportions of patients who responded, based on each endpoint included (based on data in Table 2). This is the denominator in the ICER calculation.

The paricalcitol-based treatment was less expensive and more effective than the cinacalcet-based treatment, regardless of which effectiveness measure we examined. In pharmacoeconomic terms, this means that paricalcitol was 'dominant', compared with cinacalcet. In each case, the ICER was negative. For example, for the primary endpoint (an iPTH level within the recommend range of 150–300 pg/mL), the ICER was –US\$25,389. Because negative ICERs are difficult to interpret, the common practice is just to report that the treatment is 'dominant' (as shown in Table 4) rather

than to report the negative ICER value. The 95 % confidence interval for the ICER of the primary endpoint, derived from the bootstrap replicates, was –US\$133,121 to –US\$5,820. Note that the interval does not include zero. The final column in Table 4 provides additional results from the bootstrap analysis—specifically, the proportion of bootstrap replicates in which paricalcitol was dominant. For the primary endpoint, paricalcitol was dominant in 99.1 % of replicates. For all of the other endpoints, paricalcitol was dominant in 100 % of replicates.

Figure 1 is a scatterplot of all 1,000 bootstrap replicates, with the *x*-axis representing the incremental cost and the *y*-axis representing the incremental effectiveness of the paricalcitol-based regimen compared with the cinacalcet-based regimen, where effectiveness is the proportion of subjects reaching an iPTH level of 150–300 pg/mL. All replicates fell within two quadrants of the cost-effectiveness plane. The lower right quadrant, where paricalcitol was both less expensive and more effective than cinacalcet (i.e. dominant) contained 99.1 % of the replicates. The lower left quadrant, where paricalcitol was less expensive but less effective, contained 0.9 % of replicates. For each of the secondary endpoints, the scatterplots (not shown) contained 100 % of bootstrap replicates in the lower right quadrant—where paricalcitol was dominant.

Table 4 Incremental cost-effectiveness results

Effectiveness measure	Difference in costs ($C_p - C_c$) [US\$] ^a	Difference in effectiveness ($E_p - E_c$) ^b	ICER ($C_p - C_c$)/($E_p - E_c$)	Probability that paricalcitol is dominant [%] ^c
Primary endpoint				
iPTH level 150–300 pg/mL ^d	−5,814	0.23	Dominant	99.1
Secondary endpoints				
≥30 % reduction in iPTH level ^e	−5,814	0.35	Dominant	100
≥50 % reduction in iPTH level ^f	−5,814	0.43	Dominant	100
Calcium level 8.4–10.5 mg/dL ^g	−5,814	0.39	Dominant	100
iPTH level 150–300 pg/mL and calcium level 8.4–10.5 mg/dL ^h	−5,814	0.36	Dominant	100

C_c cost in the cinacalcet group, C_p cost in the paricalcitol group, E_c effectiveness in the cinacalcet group, E_p effectiveness in the paricalcitol group, *ICER* incremental cost-effectiveness ratio, *iPTH* intact parathyroid hormone

^a Difference in the total annualized drug cost between treatment groups [i.e. the cost in the paricalcitol group (C_p) minus the cost in the cinacalcet group (C_c)]. This is the numerator of the ICER. Note that the difference is the same regardless of which measure of effectiveness is analysed

^b Difference in the effectiveness endpoint between treatment groups [i.e. the proportion of patients achieving the endpoint in the paricalcitol group (E_p) minus the proportion of patients achieving the endpoint in the cinacalcet group (E_c)]. This is the denominator of the ICER

^c Derived from the bootstrap analysis

^d Proportion of subjects achieving a mean iPTH level of 150–300 pg/mL during the evaluation period (weeks 21–28)

^e Proportion of subjects achieving ≥30 % reduction in the mean iPTH level during the evaluation period compared with baseline

^f Proportion of subjects achieving ≥50 % reduction in the mean iPTH level during the evaluation period compared with baseline

^g Proportion of subjects with a mean calcium level of 8.4–10.5 mg/dL during the evaluation period

^h Proportion of subjects achieving both a mean iPTH level of 150–300 pg/mL and a mean calcium level of 8.4–10.5 mg/dL during the evaluation period

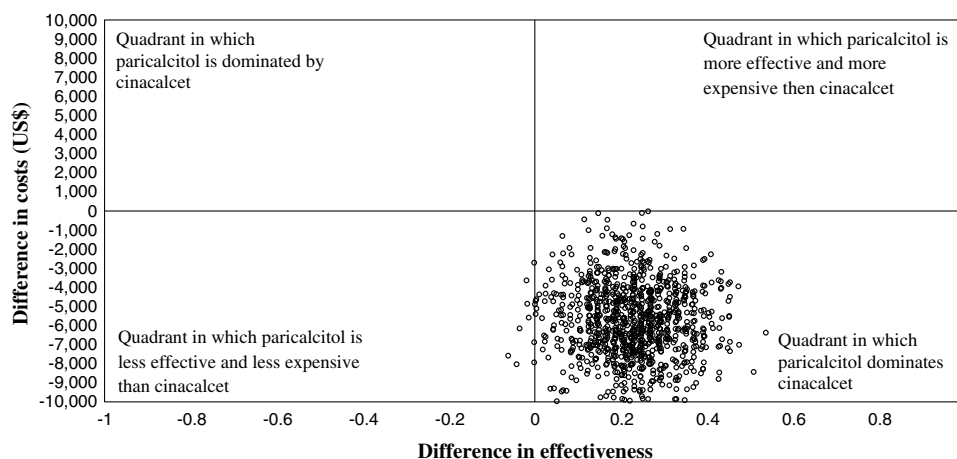


Fig. 1 Scatterplot of 1,000 bootstrap replicates showing the incremental cost and incremental effectiveness of the paricalcitol regimen compared with the cinacalcet-based regimen, where effectiveness is the proportion of subjects reaching an intact parathyroid hormone (iPTH) level of 150–300 pg/mL (the primary endpoint). All simulation results fell within two quadrants of the cost-effectiveness plane:

(1) the lower right quadrant, where the paricalcitol regimen is both less expensive and more effective than cinacalcet (i.e. dominant), containing 99.1 % of the replicates; and (2) the lower left quadrant, where the paricalcitol regimen is less expensive but less effective, containing 0.9 % of the replicates

4 Discussion

In this secondary analysis of US patients enrolled in the IMPACT SHPT study, we found that intravenous

paricalcitol-based therapy with or without supplemental cinacalcet was more cost effective than the combination of cinacalcet and low-dose vitamin D in the management of iPTH and calcium levels in patients with SHPT requiring

haemodialysis. Whether effectiveness was measured in terms of the proportions of patients meeting the iPTH target of 150–300 pg/mL (the primary outcome), or in any of several other ways (the proportions of patients with ≥ 30 or ≥ 50 % reductions in iPTH levels, the proportions of patients who were normocalcaemic, or the proportions of patients who were normocalcaemic and also met the iPTH target), the paricalcitol-based regimen was more effective than the cinacalcet-based regimen. Similarly, when considering both the cost of the study drug and the phosphate binders, the paricalcitol-based regimen was less expensive. As a result, the paricalcitol-based regimen was dominant, compared with cinacalcet.

We used bootstrap analysis to provide a measure of the degree of error around our ICER point estimates. In over 99 % of bootstrap replicates, regardless of the effectiveness endpoint incorporated into the denominator of the ICER, our result remained dominant for paricalcitol over cinacalcet. These results provide a high degree of confidence about the precision of our results.

Our findings are consistent with those of other studies. Using data from all patients in the multinational IMPACT SHPT study, and including those who received either intravenous or oral regimens of paricalcitol or cinacalcet, we previously found that the annualized mean total drug costs (based on 2011 data) were €5387 in the paricalcitol group and €6870 in the cinacalcet group (a difference of €1492, $p = 0.0395$) [21]. Similarly, a post hoc analysis of the ACHIEVE study found that the average medication costs were 48 % higher (data from 2006) in patients treated with cinacalcet plus low-dose vitamin D than in those receiving either paricalcitol or doxercalciferol (US\$5,501 versus US\$3,709 in each group, respectively) [23]. Though not a cost-effectiveness analysis, the only other study that examined costs in paricalcitol- and cinacalcet-treated patients focused on costs related to parathyroidectomy—which occurred less frequently in those treated with paricalcitol [25].

The implications of our results are important for patients, health care providers and payers. Under recent Medicare rules, the reimbursement of care for dialysis patients is capitated. By 2016, both oral and injectable medications will be included in a single ‘all-inclusive bundle’ payment to providers. Under this scenario, providers are incentivized to prescribe the most cost-effective therapies. Our results suggest that a paricalcitol-based regimen is more cost effective than cinacalcet, and this may mean both improved outcomes for patients and reduced costs for providers and payers.

Our findings should be interpreted with an understanding of the limitations of our analysis. This was a post hoc analysis of data from the randomized, open-label, phase 4, multinational IMPACT SHPT study. The limitations of the

IMPACT SHPT study have been described elsewhere [20, 24]. Here, we focus primarily on limitations that may have influenced the cost-effectiveness analysis. First, both the cost and effectiveness estimates we incorporated into our analysis were influenced by the IMPACT study protocol. For example, although they were based on approved labelling, the dosing of study drugs and phosphate binders in the IMPACT study may not have reflected actual practice for all patients in the USA. Further, like most clinical trials, the IMPACT SHPT study was short-term (28 weeks). Actual treatment of SHPT in patients on haemodialysis is longer term. We attempted to account for this by using a 1-year time horizon for our cost-effectiveness analysis. We annualized costs on the basis of the evaluation period, where dosing had stabilized. We also made the assumption that effectiveness did not change once dosing was stabilized. It is important to note that in the IMPACT study, patients who dropped out before reaching the evaluation period were not included in the analysis. However, the dropout rates were low for a clinical trial (approximately 20 % in the intravenous paricalcitol group and 30 % in the intravenous cinacalcet group).

The actual drug costs included in our analysis were not part of the IMPACT SHPT study data, but instead were estimated post hoc on the basis of the dosages used by each patient. We estimated the costs of the study drugs and phosphate binders by applying unit costs derived from an external database. This approach may have resulted in slightly different estimates than would have been obtained with actual costs. However, it is not likely that such differences would have changed either the direction or the magnitude of our results.

It is important to note that our cost analysis was restricted to study drugs and phosphate binders reported in the IMPACT SHPT study. An advantage of our analysis was that all of the cost and effectiveness results were from the same set of patients. Many cost-effectiveness studies, particularly those that involve modelling, use heterogeneous sources of data for costs and effectiveness and, because of that, they may be subject to bias. However, a limitation of our approach was that certain costs were not included, because they were not collected or recorded in the IMPACT SHPT study. For example, the utilization of laboratory tests, frequency of hospitalizations or physician office visits, and other health care utilization costs were not included. Inclusion of such costs could provide a more complete understanding of the cost effectiveness of paricalcitol and cinacalcet, particularly since we assumed a payer perspective. These additional costs are generally associated with differences in treatment effectiveness, adverse effects or monitoring. However, in the IMPACT SHPT study, the paricalcitol-based regimen was more effective than the cinacalcet-based regimen, and while the reported serious and

severe adverse events were no different, adverse events leading to treatment discontinuation in patients receiving intravenous therapy were significantly less common in the paricalcitol group than in the cinacalcet group [20]. Moreover, there is no evidence that monitoring requirements are different between cinacalcet and paricalcitol. Therefore, it is unlikely that the direction of our results would have changed if those costs had been included.

One last potential limitation of our analysis relates to the generalizability of the population studied. A slightly higher percentage of US patients who enrolled in the IMPACT SHPT were Black or Hispanic, compared with the general population of ESRD patients. Data from the United States Renal Data System (USRDS) suggests that 36.1 % of ESRD patients in the USA are black and 15.1 % are Hispanic [26]. Across both groups in the IMPACT SHPT study, 44.9 % of US patients were black and 24.5 % were Hispanic. While this difference is small, because the response to therapy may differ by race and ethnicity, it should be considered.

5 Conclusion

On the basis of dosing and effectiveness data from US patients in the IMPACT SHPT study, we found that a regimen of intravenous paricalcitol was more cost effective than cinacalcet plus low-dose vitamin D in the management of iPTH in patients with SHPT requiring haemodialysis.

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