Cost-Effectiveness of Lanthanum Carbonate in the Treatment of Hyperphosphatemia in Chronic Kidney Disease Before and During Dialysis

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A B S T R A C T

Objectives: Hyperphosphatemia is a common and harmful condition in patients with chronic kidney disease (CKD). We determined the cost-effectiveness of the noncalcium-based phosphate binder lanthanum carbonate (LC) as second-line treatment of hyperphosphatemia after therapy failure with calcium-based binders (CB). **Methods:** Two CKD populations were modeled: 1) predialysis CKD patients and 2) incident dialysis patients. Patients not responding to CB with a serum phosphate (SP) level >5.5 mg/dl received a trial with LC. Patients not responding to LC (SP >4.6 mg/dl) returned to CB treatment. Patient-level data were obtained from clinical trials in predialysis and dialysis. Time-dependent, life-long Markov models (discounting at 3.5% annually) were developed, using a UK National Health Service perspective. **Results:** The health gains with second-line LC treatment compared to CB treatment were 44 and 56 quality-adjusted life-years (QALYs) for the predialysis and incident dialysis populations, respectively. Second-line LC was a cost-saving strategy in the predialysis population because of

the cost-savings of delayed CKD progression. Second-line LC was cost-effective at £6900 (90% probability interval: £5800–£8300) per QALY gained in the dialysis population. Results were robust to plausible variations in other model parameters; inclusion of future unrelated dialysis costs had a large influence on cost-effectiveness estimates. **Conclusions:** Second-line treatment with LC is associated with considerable clinical benefits and good value for money in CKD, irrespective of dialysis status. These results support Kidney Disease Outcomes Quality Initiative guidelines to treat CKD patients with hyperphosphatemia irrespective of dialysis status.
Keywords: chronic kidney disease, cost-effectiveness, end-stage renal disease, hyperphosphatemia, lanthanum carbonate, phosphate binders.

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Introduction

Hyperphosphatemia is an electrolyte disturbance characterized by an excess of serum phosphorus in the blood. It is a common and harmful condition in patients with chronic kidney disease (CKD), irrespective of dialysis status [1] CKD is a continuous process [2], and deregulation of serum phosphate (SP) levels can occur at any point in this process [3]. Increased phosphate levels are independently associated with increased morbidity and mortality in CKD patients on dialysis [4–6] and predialysis across different CKD stages [7–9]. Treatment guidelines issued by the Kidney Disease Outcomes Quality Initiative (K/DOQI) recommend that serum phosphate levels be maintained between 2.7 and 4.6 mg/dl in predialysis patients and between 3.5 and 5.5 mg/dl in dialysis patients [10]. Unfortunately, less than half of the patients actually achieve and sustain these targets [11].

The current first-line drug treatment of hyperphosphatemia in the United Kingdom (UK), as in other countries, in combination with dietary restrictions [10], consists of calcium-based phosphate binders (CBs), in particular, calcium carbonate and calcium acetate [12]. When calcium agents are ineffective or inadequate, a strategy of dose escalation may be inappropriate due to the increased risk of hypercalcemia [13], which is linked to increased mortality [5,14]. K/DOQI guidelines recommend

that total daily intake of calcium, from food and drug treatments, should not exceed 2000 mg [10].

Lanthanum carbonate (LC) is a noncalcium-based phosphate binding agent licensed for hyperphosphatemic dialysis patients [15,16] and recently also for CKD patients not yet on dialysis [17,18]. Treatment with LC after therapy failure with calcium carbonate treatment (i.e., second-line LC treatment) was found to constitute good value-for-money in dialysis patients [19]. The cost-effectiveness of LC in predialysis patients, however, has not been assessed. The goal of this study was to determine the cost-effectiveness of second-line LC treatment of hyperphosphatemia in CKD patients before and after dialysis initiation, from a UK National Health Service perspective.

Methods

Cost-effectiveness analysis

The cost-effectiveness of second-line LC treatment was assessed for two CKD populations: 1) a predialysis CKD population and 2) an incident dialysis population. Incremental cost-effectiveness ratios (ICERs) were calculated as cost per life year gained and cost per Quality Adjusted Life Year (QALY) gained. In

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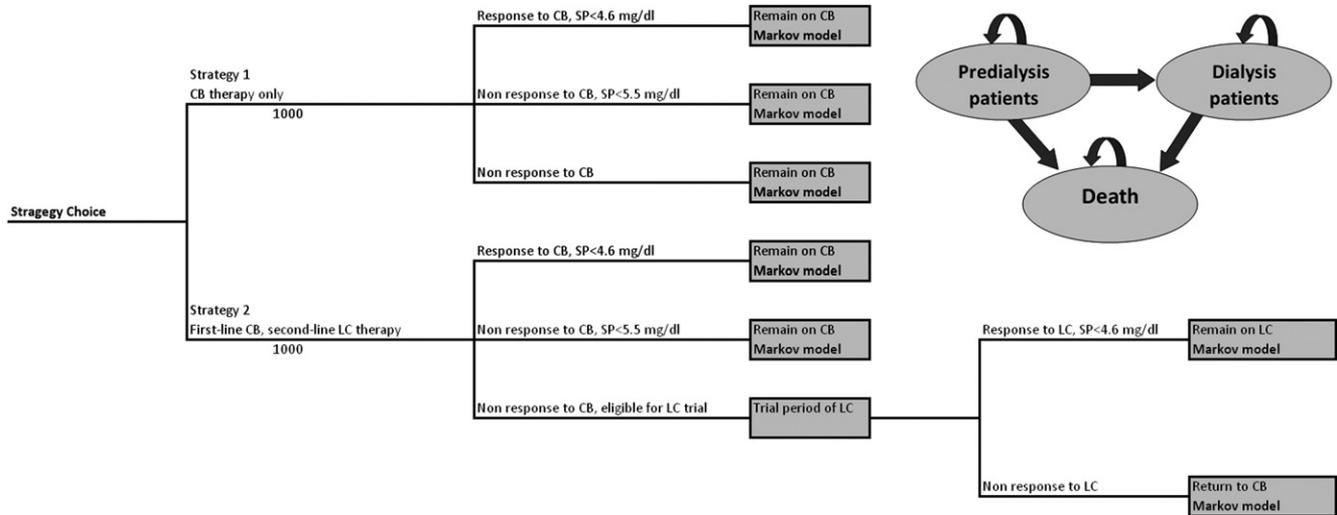E-mail: s.vegter@rug.nl.

Fig. 1 – Decision analytical structure and Markov model (top right corner). CB, calcium-based binder; LC, lanthanum carbonate.

addition, the Net monetary benefit of LC over the comparator at a decision-maker willingness-to-pay threshold of £30,000 per QALY was evaluated [20]. Outcomes were rounded to the nearest £100. The SP level upon which LC treatment is indicated for use is >5.5 mg/dl [21]; the target SP level is ≤4.6 mg/dl for predialysis patients and ≤5.5 mg/dl for dialysis patients [10]. Choice of therapy initiation and evaluation of treatment response were modeled according to these guidelines, shown in Figure 1. Second-line LC treatment was considered for nonresponders to CBs with SP levels exceeding 5.5 mg/dl. Response to LC was evaluated within an 8-week drug trial period; patients not achieving target SP levels during this drug trial were switched back to calcium agents.

Economic model

A decision analytical structure was developed and linked to a time-dependent Markov model [22]. Markovian modeling is a commonly used technique in decision analyses to handle the complexity of multiple interconnective, possible long-term consequences. The health states were predialysis, dialysis, and death; dialysis patients were not allowed to return to a predialysis state. The number of patients in each health state was determined by yearly cycles; a half-cycle correction was applied to account for the fact that events may occur at any point during the year. For the cost-effectiveness analysis irrespective of dialysis status, the model was populated with cohorts of 1000 simulated predialysis patients; for the analysis in dialysis patients, cohorts of 1000 incident dialysis patients were used. An overview of all model parameters is shown in Table 1. The model structure and parameter assumptions were discussed with two UK clinical experts who were consulted for this study.

Drug efficacy

Patient-level data were obtained from two randomized clinical trials, one in predialysis patients (n = 56 treated with LC) [17], and one in dialysis patients (n = 123 treated with LC and n = 257 treated with CBs) [23]. Because of the relatively limited data available for predialysis patients, the base-case drug efficacy for predialysis patients was based on pooled data of predialysis and dialysis patients. Only data from dialysis patients with comparable baseline SP levels as predialysis patients, however, were used to calculate drug efficacy in predialysis. The assumption

that the efficacy of drug intervention in dialysis patients with SP levels comparable to those of predialysis patients is transferable was verified as reasonable and appropriate by the clinical experts consulted for this study. Long-term response to LC was modeled using patient-level data [23] with a previously reported method [19] and was assumed to be the same for predialysis and dialysis patients.

Clinical efficacy and adverse events

Mortality rates according to patients' SP level were derived from epidemiological studies in 3490 predialysis patients [8] and 40,538 dialysis patients [5]. Baseline expected survival was estimated using long-term observational data for almost 28,000 predialysis patients [24] and more than 66,000 dialysis patients [25]. CKD progression rates were based on data for 4231 CKD stage 4 patients [26]. The baseline survival and CKD progression rates were adjusted for patients' average SP levels before applying SP-specific relative risks [19].

In the trials used for this analysis, vomiting was significantly increased with LC compared to CB in predialysis patients (4.0%) [17] and dialysis patients (7.2%) [23]. Duration of vomiting was estimated to be 7 days [19]; during this period, patients were assumed to be prescribed an antiemetic drug (domperidone, 40 mg/day).

Costs and utilities

A third-party payer (UK National Health Service) perspective was adopted for cost estimates. Drug doses of lanthanum carbonate and calcium agents were based on the mean actual daily dose from the trials in predialysis patients [17,27] and dialysis patients [23]. Drug costs were based on the British National Formulary [28]. The costs of dialysis were based on a weighted average [29] of UK cost estimates for hemodialysis and peritoneal dialysis [30]. Dialysis costs in added life-years as a consequence of the more effective phosphate binder strategy were classified as unrelated future costs because prolonged dialysis care is exclusively related to the extended life of treated patients and not directly to the choice of phosphate binder [31,32]. Following previous pharmacoeconomic analyses, these future unrelated dialysis costs were excluded from the base-case analysis but included in sensitivity analysis. All costs were updated to 2009 values. Quality of life (QoL) estimates were identified

Table 1 – Model parameters.

	Predialysis value (95% CI)		Dialysis value (95% CI)		PSA	Ref.
Clinical pathways						
Treatment initiation in mg/dl	>5.5		>5.5			[21]
Target level in mg/dl	<4.6		<5.5			[10]
Drug efficacy, %						
First-line response rate to CB	45.6	(40.5–50.9)	62.2	(59.0–65.4)	Binomial	[23,27]
Second-line response rate to LC	18.8	(16.0–21.6)	44.6	(40.0–48.5)	Binomial	[17,23]
Long-term response to LC	$\lambda = 0.55$	(0.46–0.65)	$\lambda = 0.55$	(0.46–0.65)	Weibull	[17,23]
	$\gamma = 0.92$	(0.78–1.05)	$\gamma = 0.92$	(0.78–1.05)		
Mortality and CKD progression						
Baseline yearly mortality	5.6%	(5.2–5.9)	$\lambda = 0.21$	(0.15–0.26)	Normal/Weibull	[24,25]
			$\gamma = 0.87$	(0.76–0.99)		
RR of mortality by SP level, in mg/dl						
<2.5	0.95	(0.69–1.32)	1.00	(0.96–1.24)	Normal	[5,8]
2.5–3.0	1.00	(1.00–1.00)	1.00	(0.96–1.24)		
3.0–3.5	1.15	(0.95–1.39)	1.00	(0.93–1.07)		
3.5–4.0	1.32	(1.09–1.61)	1.00	(0.93–1.07)		
4.0–4.5	1.34	(1.05–1.71)	1.00	(1.00–1.00)		
4.5–5.0	1.83	(1.33–2.51)	1.00	(1.00–1.00)		
5.0–5.5	1.90	(1.30–2.79)	1.07	(1.01–1.14)		
5.5–6.0	1.90	(1.30–2.79)	1.00	(1.01–1.14)		
6.0–7.0	1.90	(1.30–2.79)	1.25	(1.17–1.34)		
7.0–8.0	1.90	(1.30–2.79)	1.43	(1.31–1.54)		
8.0–9.0	190	(1.30–2.79)	1.67	(1.51–1.86)		
>9.0	1.90	(1.30–2.79)	2.02	(1.76–2.27)		
Baseline yearly CKD progression	14.3%	(13.6–15.0)	NA		Poisson	[26]
RR CKD progression (per mg/dl in SP)	1.19	(1.10–1.29)	NA		Normal	[26]
Quality of Life						
Quality of life	0.71	(0.69–0.73)	0.61	(0.57–0.65)	Beta	[34,35]
Utility decrement vomiting	0.14	(0.08–0.20)	0.14	(0.08–0.20)	Beta	[36]
Adverse events						
Increase of vomiting for LC, %	4.0	(3.0–5.0)	7.2	(5.4–9.0)	Triangular	[17,23]
Duration of vomiting in days	7	(5.3–8.8)	7	(5.3–8.8)	Triangular	[19]
Drug costs, £						
Yearly drug price of LC	1198	(1047–1347)	1540	(1454–1625)	Log normal	[28]
8-wk LC trial	177	(153–200)	224	(212–235)	Log normal	[28]
Yearly drug price of CC	56	(29–83)	85	(77–96)	Log normal	[28]
Yearly drug price of CA	40	(21–60)	NA		Log normal	[28]
Dialysis costs, £*	NA		34,100	(28,120–42,230)	Log normal	[30]
Discounting rate, %	3.5		3.5			[20]

CA, CC, CB, calcium-based binder; CI, confidence interval; CKD, chronic kidney disease; LC, lanthanum carbonate; NA, not applicable; PSA, probabilistic sensitivity analysis; RR, relative risk; SP, serum phosphate.

* Weighted by prevalence of dialysis modalities (hemodialysis: 24.4%, home hemodialysis: 1.1%, satellite hemodialysis: 18.6%, automated peritoneal dialysis: 3.8%, continuous ambulatory peritoneal dialysis: 5.2%) [29].

using a recent systematic review [33]. Using a weighted average of studies identified in this review, a QoL utility of 0.71 was used for predialysis patients and 0.61 for dialysis patients [34,35]. A utility decrement of 0.14 was assumed for a vomiting episode, derived from a published study [36].

Sensitivity analysis

Parameter uncertainty was handled by performing a probabilistic sensitivity analysis (PSA) [22]. In the PSA, joint parameter uncertainty was handled by specifying a probability distribution for each of the parameters [22], shown in Table 1. For parameters based on patient-level data as well as literature review, probability distributions as suggested by health economics guidebooks were used [37]. No probability distribution could be adopted for adverse event rates; therefore, a triangular distribution was used. To explore the sensitivity of the results to uncertainty in individual parameters, scenario analyses were performed using alternative literature sources and variations in

structural pathway decisions. In one scenario, future unrelated dialysis costs were included.

Time horizon and discounting

A lifelong model was adopted, following all patients until death or a maximum follow-up of 40 years, with shorter time horizons explored in sensitivity analysis. Costs and health effects were discounted at an annual rate of 3.5% in line with standard UK guidance [20].

Statistics and software

Baseline characteristics were compared using the Student t test or chi-square test, where appropriate. A P value of <0.05 was considered statistically significant. The cost-effectiveness model was developed and built in Excel; the PSA to calculate 90% probability intervals (PIs) was performed with the Excel

Table 2 – Cost-effectiveness of second-line LC treatment in predialysis and dialysis.		
	Predialysis value (90% PI)	Dialysis value (90% PI)
Therapy response		
Additional LC responders in predialysis	43 (34–53)	NA
Additional LC responders in dialysis	79 (69–89)	168 (151–185)
Total additional LC responders	122 (109–135)	168 (151–185)
Health effects		
Life-years gained	69.4 (53.6–85.9)	91.9 (70.7–117.8)
Dialysis-free years gained	21.3 (15.4–28.2)	NA
QALYs gained	44.1 (34.1–54.2)	55.8 (42.6–72.3)
Costs, £		
Additional drug costs	387 (333–451)	386 (338–446)
Dialysis costs	−726 (−1020–509)	NA
Total costs	−339 (−634 to 129)	386 (338–446)
Cost-effectiveness		
Cost per LY gained, £	Dominating	4200 (3400–5300)
Cost per QALY gained, £	Dominating	6900 (5500–8800)
Net monetary benefit, £*	1700 (1200–2200)	1300 (900–1700)

LC, lanthanum carbonate; LY, life-year; NA, not applicable; PI, probability interval; QALYs, quality-adjusted life-years.

* At a threshold willingness-to-pay of £30,000 per QALY.

add-on @RISK. Statistical tests and graphs were produced using the statistical program R.

Results

Baseline characteristics

Age, sex, and baseline SP were similar between LC- and CB-treated patients, both for predialysis and dialysis patients. Age and baseline SP did not differ significantly between the predialysis patients and the subset of SP-matched dialysis patients used for pooling; there were, however, slightly more females in the predialysis population (50% vs. 36%, P = 0.04).

Drug efficacy

In predialysis patients, first-line response rate to CBs was 45.6%. Hence, in the simulated cohort of 1000 CKD predialysis patients, 544 patients (54.4%) did not achieve SP targets with first-line CB treatment. In the LC strategy, 230 of these 544 nonresponders had an SP level >5.5 mg/dl and therefore received an 8-week trial of LC treatment. Of these, 43 (18.8%) showed therapy response to LC, the remaining 187 patients returned to CB treatment. On entering the dialysis health state, the target SP treatment level recommended by international guidelines changed from ≤4.6 mg/dl for predialysis patients to ≤5.5 mg/dl in the dialysis population [10]. Because of this change in target SP level, more patients treated with LC were classified as therapy responders. An incremental 79 patients responded to second-line LC treatment compared to CB after reaching dialysis.

In the population of incident dialysis patients, the first-line CB response rate was 62.2%. Thus, in the 1000 incident dialysis patient cohort, 378 patients (37.8%) did not achieve SP targets with first-line CB treatment. In the LC strategy, 168 patients (44.4%) showed therapy response to LC; the remaining 210 patients returned to CB treatment. The total number of therapy responders in the two CKD populations is presented in Table 2.

Health outcomes

Median survival of predialysis patients predicted by our model was 6.5 years; the median survival of incident dialysis patients was 3.5 years. The increase in therapy response with second-line LC treatment resulted in additional life-years and QALYs in both

CKD populations (Table 2). In predialysis patients, 21.3 (15.4–28.2) additional dialysis-free years were gained with second-line LC treatment due to delayed CKD progression. The total clinical benefit of second-line LC treatment was 44.1 QALYs (33.4–54.2) in the predialysis population and 55.8 QALYs (42.6–72.3) in the dialysis population.

Cost-effectiveness

For the predialysis patient population, second-line LC treatment was a dominating strategy compared to only CB treatment (i.e., second-line LC resulted in cost-savings as well as clinical benefits). Because SP levels influenced CKD progression in the model, improved SP control with second-line LC treatment resulted in considerable prevention and delay of end-stage renal disease. Indeed, the cost savings in predialysis patients were mainly due to prevented or delayed dialysis care costs. The net monetary benefit for a willingness-to-pay of £30,000 per QALY gained was £1700 (90% PI £1200–£2200). For the incident dialysis patient population, the cost-effectiveness was £6900 per QALY (90% PI £5500–£8800 per QALY), with a net monetary benefit of £1300 (90% PI £900–£1700), shown in Table 2.

Sensitivity analyses

The results were robust to plausible variations in model parameters, both in the predialysis population (Fig. 2) and in the dialysis population (Fig. 3). Using alternative discounting rates or literature sources for CKD progression [38,39] or varying the frequency of adverse events did not influence the cost-effectiveness outcome. Using an alternative source for dialysis mortality [4] increased the incremental cost-effectiveness ratio (ICER) in the dialysis population to £22,300 per QALY. Of note, not using pooled data for drug efficacy in predialysis patients (i.e., using data of predialysis patients only) had no considerable influence on the cost-effectiveness for LC in this population with an ICER of £1500 per QALY (90% PI £900–£2300), Figure 2. Including unrelated future dialysis costs, however, had a large influence on LC cost-effectiveness. When unrelated future dialysis costs were included, the ICER increased to £48,600 per QALY gained in the predialysis population and £63,000 per QALY gained in the dialysis population.
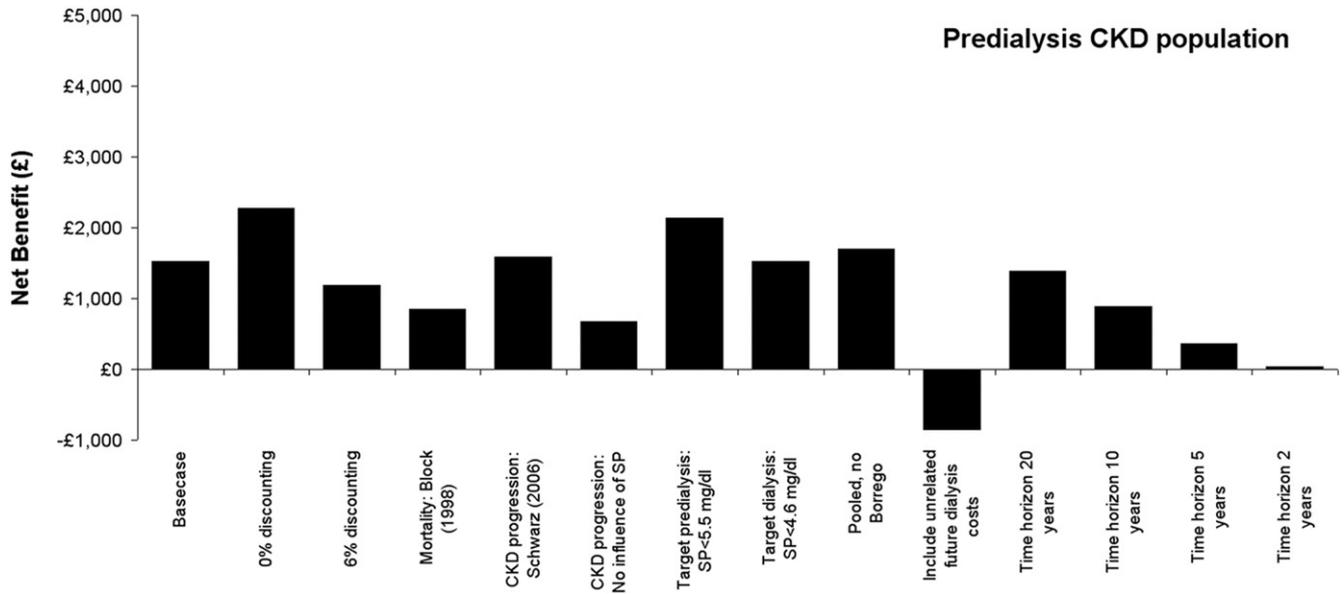
Fig. 2 – Sensitivity analysis in predialysis. CKD, chronic kidney disease.

Discussion

Although the efficacy of calcium and noncalcium-based phosphate binders is similar in a treat-to-target setting [40,41], calcium agents are less expensive and often prescribed as first-line therapy. Noncalcium-based phosphate binders, such as lanthanum carbonate and sevelamer, may be prescribed after therapy failure or other contraindication for calcium agents. Our model demonstrated that second-line use of LC was cost-effective irrespective of dialysis status. In a 1000-predialysis patient cohort, a total of 70 life-years and 44 QALYs were gained by second-line LC use, as well as 21 dialysis-free years. In addition, cost savings of £339 per patient were seen, resulting in second-line LC use *dominating* the comparator strategy. In the 1000 incident dialysis patient cohort, a total of 92 life-years and 56 QALYs were gained by second-line LC use and the ICER was £6900 per QALY, within the acceptable UK thresholds of cost-effective treatments.

One of the main cost-effectiveness drivers in our model was the rate of CKD progression in predialysis patients. Dialysis costs are high, and therefore delaying dialysis initiation can lead to large cost savings. Indeed, earlier studies have found that treatments that delay CKD progression are cost saving [42,43]. Improved SP control with second-line LC treatment [26,38,39] resulted in considerable prevention and delay of end-stage renal disease. By monetizing these clinical benefits, our model predicted overall cost savings for second-line LC treatment, despite the higher drug costs of LC compared to calcium agents. In our model, the median survival of predialysis and dialysis patients was 6.5 and 3.5 years, respectively. The external validity of our model is supported by observational data of 335 Canadian CKD predialysis patients (median survival of 6.4 years) [44] and more than 3000 Scottish incident dialysis patients (median survival of 3.2 years) [45].

The results were robust to plausible variations in model parameters, including discounting rate and data sources for CKD
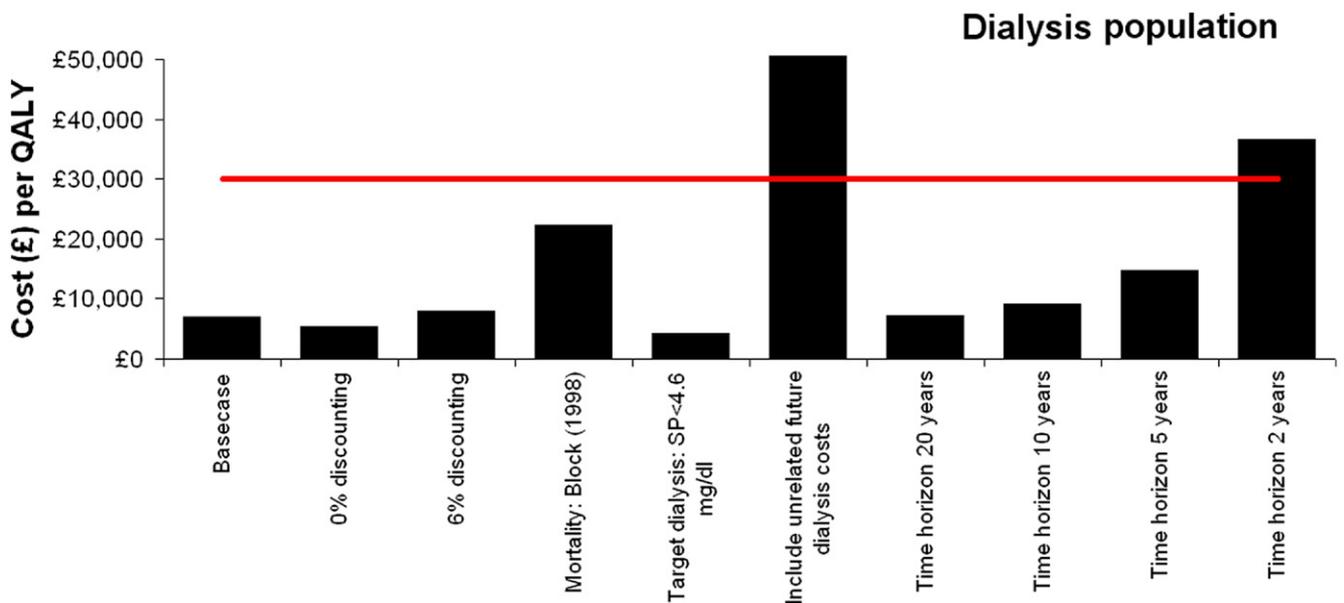

Fig. 3 – Sensitivity analysis in dialysis. QALY, quality-adjusted life-years.

progression and mortality. Unrelated future dialysis costs, however, had a large influence on the ICER. Unrelated future costs were excluded from the base-case analysis. The inclusion or exclusion of unrelated future costs is the topic of a long-standing and as-of-yet unresolved discussion [31,32]; in fact, dialysis has been center stage in this discussion [46,47]. Our results add to this discussion by demonstrating, in sensitivity analysis, that positive cost-effectiveness outcomes were largely dependent on the exclusion of future unrelated costs.

This study, to the best of our knowledge, is the first to analyze the cost-effectiveness of phosphate binders in CKD patients before dialysis initiation. A previous cost-effectiveness analysis in dialysis patients reported an ICER of second-line LC of £25,000 per QALY [19]. The previous analysis used data from a 1998 observational study of Block et al. [4]. In contrast, our model used a larger (40,538 versus 6,407 patients), more recent (2004 vs. 1998), and with longer follow-up (2.0 years vs. 1.5 years) study by the same authors [5]. Several other model parameters were updated as well, including drug costs and QoL estimates.

Our model had some limitations. Data on LC and CB efficacy were derived from 56 and 28 predialysis patients, respectively [17,27]. Although a lack of data in predialysis also applies to other noncalcium phosphate binders [48], we tried to overcome this limitation by pooling predialysis patients with a subset of dialysis patients. Dialysis patients with an SP level comparable to that of predialysis patients were selected for pooling to reduce heterogeneity. Indeed, population characteristics between the two populations were found to be similar. Furthermore, sensitivity analysis showed that results were similar when dialysis patients were excluded from the pooled data set. Therefore, the use of pooled efficacy data enhanced the robustness of our results without biasing the cost-effectiveness outcome. Another limitation of our study was that in the predialysis population, the majority of LC-treated patients were phosphate binder naive [17], thereby not accurately modeling second-line LC treatment.

Several conservative model assumptions were made for this analysis. Patients treated with noncalcium-based binders experience fewer hypercalcemic events compared to CB-treated patients [49]. Hypercalcemia has been linked to increased mortality in dialysis [5,14] and predialysis [50,51]; a causal link between binder choice and mortality, however, was not confirmed in a recent meta-analysis [49]. Therefore, we conservatively did not model any influence of hypercalcemic events in our analysis. LC reduces pill burden compared to calcium agents, which has been associated with higher QoL and patient preference [52,53] and improved drug compliance [53]. Quantitatively useful data for model inclusion of these parameters were not available; therefore, we conservatively did not model any influence of pill burden on QoL or drug efficacy. Finally, lowering SP reduces the risk of bone disease and nonfatal cardiovascular events, reflected by a decrease in hospitalizations [5,54]. This was not included in the model due to a lack of available data.

In conclusion, the use of LC as second-line treatment for hyperphosphatemia after first-line use of CBs, results in considerable health benefits and is cost-effective, using a UK National Health Service perspective, irrespective of dialysis status. The results of this study strengthen K/DOQI recommendations to treat CKD patients with elevated serum phosphate levels irrespective of dialysis status [10]. Furthermore, our results suggest that second-line treatment with LC after therapy failure with CBs may be considered in CKD patients irrespective of dialysis status.

Acknowledgments

REFERENCES

[1] Albaaj F, Hutchison A. Hyperphosphataemia in renal failure: causes, consequences and current management. Drugs 2003;63:577–96.

[2] Eknoyan G, Levin A, Levin NW. Bone metabolism and disease in chronic kidney disease. Am J Kidney Dis 2003;42:1–201.

[3] Tonelli M, Sacks F, Pfeffer M, et al. Relation between serum phosphate level and cardiovascular event rate in people with coronary disease. Circulation 2005;112:2627–33.

[4] Block GA, Hulbert-Shearon TE, Levin NW, et al. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. Am J Kidney Dis 1998; 31:607–17.

[5] Block GA, Klassen PS, Lazarus JM, et al. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J Am Soc Nephrol 2004; 15:2208–18.

[6] Menon V, Greene T, Pereira AA, et al. Relationship of phosphorus and calcium-phosphorus product with mortality in CKD. Am J Kidney Dis 2005;46:455–63.

[7] Covic A, Kothawala P, Bernal M, et al. Systematic review of the evidence underlying the association between mineral metabolism disturbances and risk of all-cause mortality, cardiovascular mortality and cardiovascular events in chronic kidney disease. Nephrol Dial Transplant 2009;24:1506–23.

[8] Kestenbaum B, Sampson JN, Rudser KD, et al. Serum phosphate levels and mortality risk among people with chronic kidney disease. J Am Soc Nephrol 2005;16:520–8.

[9] Voormolen N, Noordzij M, Grootendorst DC, et al. High plasma phosphate as a risk factor for decline in renal function and mortality in pre-dialysis patients. Nephrol Dial Transplant 2007;22:2909–16.

[10] K/DOQI. Clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis 2003;42:S1–201.

[11] Urena P, Jacobson SH, Zitt E, et al. Cinacalcet and achievement of the NKF/K-DOQI recommended target values for bone and mineral metabolism in real-world clinical practice--the ECHO observational study. Nephrol Dial Transplant 2009;24:2852–9.

[12] Hutchison AJ. Improving phosphate-binder therapy as a way forward. Nephrol Dial Transplant 2004;9(Suppl 1):i19–24.

[13] Locatelli F, Cannata-Andia JB, Drueke TB, et al. Management of disturbances of calcium and phosphate metabolism in chronic renal insufficiency, with emphasis on the control of hyperphosphataemia. Nephrol Dial Transplant 2002;17:723–31.

[14] Kalantar-Zadeh K, Kuwae N, Regidor DL, et al. Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients. Kidney Int 2006;70:771–80.

[15] Curran MP, Robinson DM. Lanthanum carbonate: a review of its use in lowering serum phosphate in patients with end-stage renal disease. Drugs 2009;69:2329–49.

[16] Sprague SM. A comparative review of the efficacy and safety of established phosphate binders: calcium, sevelamer, and lanthanum carbonate. Curr Med Res Opin 2007;23:3167–75.

[17] Sprague SM, Abboud H, Qiu P, et al. Lanthanum carbonate reduces phosphorus burden in patients with CKD stages 3 and 4: a randomized trial. Clin J Am Soc Nephrol 2009;4:178–85.

[18] Scaria PT, Gangadhar R, Pisharody R. Effect of lanthanum carbonate and calcium acetate in the treatment of hyperphosphatemia in patients of chronic kidney disease. Indian J Pharmacol 2009;41:187–91.

[19] Brennan A, Akehurst R, Davis S, et al. The cost-effectiveness of lanthanum carbonate in the treatment of hyperphosphatemia in patients with end-stage renal disease. Value Health 2007;10:32–41.

[20] Guide to the Methods of Technology Appraisal. London: National Institute for Clinical Excellence, 2001.

[21] Shire Pharmaceuticals. European public assessment report (EPAR) Fosrenol - Summary Product Characteristics (SPC). 2010.

[22] Berger ML, Bingefors K, Hedblom EC, et al. Health Care Costs, Quality, and Outcomes - ISPOR Book of Terms. Lawrenceville, NJ: International Society of Pharmacoeconomics and Outcomes Research (ISPOR), 2003.

[23] Hutchison AJ, Maes B, Vanwalleghem J, et al. Efficacy, tolerability, and safety of lanthanum carbonate in hyperphosphatemia: a 6-month, randomized, comparative trial versus calcium carbonate. Nephron Clin Pract 2005;100:c8–19.

[24] Keith DS, Nichols GA, Gullion CM, et al. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. Arch Intern Med 2004;164:659–63.

[25] US Renal Data System, USRDS 2010 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2010.

[26] Levin A, Djurdjev O, Beaulieu M, et al. Variability and risk factors for kidney disease progression and death following attainment of stage 4 CKD in a referred cohort. Am J Kidney Dis 2008;52:661–71.

[27] Borrego J, Perez del BP, Serrano P, et al. [A comparison of phosphorus-chelating effect of calcium carbonate versus calcium acetate before dialysis]. Nefrologia 2000;20:348–54.

[28] British Medical Association and the Royal Pharmaceutical Society of Great Britain. British National Formulary. 58th ed. UK: BMJ Publishing Group. 2009

[29] UK Renal Registry 2009. 12th Annual Report of the Renal Association. Nephron Clin Pract 2010;115(Suppl 1)

[30] Baboolal K, McEwan P, Sondhi S, et al. The cost of renal dialysis in a UK setting–a multicentre study. Nephrol Dial Transplant 2008;23:1982–89.

[31] Rappange DR, van Baal PH, van Exel NJ, et al. Unrelated medical costs in life-years gained: should they be included in economic evaluations of healthcare interventions? Pharmacoeconomics 2008;26:815–30.

[32] Lee RH. Future costs in cost effectiveness analysis. J Health Econ 2008;27:809–18.

[33] Dale PL, Hutton J, Elgazzar H. Utility of health states in chronic kidney disease: a structured review of the literature. Curr Med Res Opin 2008;24:193–206.

[34] Davison SN, Jhangri GS, Feeny DH. Evidence on the construct validity of the Health Utilities Index Mark 2 and Mark 3 in patients with chronic kidney disease. Qual Life Res 2008;17:933–42.

[35] Gorodetskaya I, Zenios S, McCulloch CE, et al. Health-related quality of life and estimates of utility in chronic kidney disease. Kidney Int 2005;68:2801–8.

[36] Osoba D, Zee B, Warr D, et al. Effect of postchemotherapy nausea and vomiting on health-related quality of life. The Quality of Life and Symptom Control Committees of the National Cancer Institute of Canada Clinical Trials Group. Support Care Cancer 1997;5:307–13.

[37] Briggs A, Claxton K, Sculpher M. Decision Modelling for Health Economic Evaluation. Oxford: Oxford University Press, 2006.

[38] Norris KC, Greene T, Kopple J, et al. Baseline predictors of renal disease progression in the African American Study of Hypertension and Kidney Disease. J Am Soc Nephrol 2006;17:2928–36.

[39] Schwarz S, Trivedi BK, Kalantar-Zadeh K, et al. Association of disorders in mineral metabolism with progression of chronic kidney disease. Clin J Am Soc Nephrol 2006;1:825–31.

[40] Finn WF. Lanthanum carbonate versus standard therapy for the treatment of hyperphosphatemia: safety and efficacy in chronic maintenance hemodialysis patients. Clin Nephrol 2006;65:191–202.

[41] Suki WN, Zabaneh R, Cangiano JL, et al. Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients. Kidney Int 2007;72:1130–7.

[42] Ruggenenti P, Pagano E, Tammuzzo L, et al. Ramipril prolongs life and is cost effective in chronic proteinuric nephropathies. Kidney Int 2001;59:286–94.

[43] Vegter S, Perna A, Hiddema W, et al. Cost-effectiveness of ACE inhibitor therapy to prevent dialysis in nondiabetic nephropathy: influence of the ACE insertion/deletion polymorphism. Pharmacogenet Genomics 2009;19:695–703.

[44] Devins GM, Mendelssohn DC, Barre PE, et al. Predialysis psychoeducational intervention extends survival in CKD: a 20-year follow-up. Am J Kidney Dis 2005;46:1088–98.

[45] Sawhney S, Djurdjev O, Simpson K, et al. Survival and dialysis initiation: comparing British Columbia and Scotland registries. Nephrol Dial Transplant 2009;24:3186–92.

[46] Manns B, Meltzer D, Taub K, et al. Illustrating the impact of including future costs in economic evaluations: an application to end-stage renal disease care. Health Econ 2003;12:949–58.

[47] Winkelmayer WC, Weinstein MC, Mittleman MA, et al. Health economic evaluations: the special case of end-stage renal disease treatment. Med Decis Making 2002;22:417–30.

[48] Ketteler M, Rix M, Fan S, et al. Efficacy and tolerability of sevelamer carbonate in hyperphosphatemic patients who have chronic kidney disease and are not on dialysis. Clin J Am Soc Nephrol 2008;3:1125–30.

[49] Jamal SA, Fitchett D, Lok CE, et al. The effects of calcium-based versus non-calcium-based phosphate binders on mortality among patients with chronic kidney disease: a meta-analysis. Nephrol Dial Transplant 2009;24:3168–74.

[50] Kovesdy CP, Kuchmak O, Lu JL, et al. Outcomes associated with serum calcium level in men with non-dialysis-dependent chronic kidney disease. Clin J Am Soc Nephrol 2010;5:468–76.

[51] Tomiyama C, Higa A, Dalboni MA, et al. The impact of traditional and non-traditional risk factors on coronary calcification in pre-dialysis patients. Nephrol Dial Transplant 2006;21:2464–71.

[52] Mehrotra R, Martin KJ, Fishbane S, et al. Higher strength lanthanum carbonate provides serum phosphorus control with a low tablet burden and is preferred by patients and physicians: a multicenter study. Clin J Am Soc Nephrol 2008;3:1437–45.

[53] Chiu YW, Teitelbaum I, Misra M, et al. Pill burden, adherence, hyperphosphatemia, and quality of life in maintenance dialysis patients. Clin J Am Soc Nephrol 2009;4:1089–96.

[54] Collins AJ, St Peter WL, Dalleska FW, et al. Hospitalization risks between Renagel phosphate binder treated and non-Renagel treated patients. Clin Nephrol 2000;54:334–41.